Asia Partnership Conference of Pharmaceutical Associations (APAC)

Analysis Report

ver. 2018

Identification and Clarification of the Differences in Regulatory Requirements between Asian Economies

APAC Regulations and Approvals Expert Working Group

April 10, 2018
Tokyo, Japan

Member Associations

HKAPI	Hong Kong Association of the Pharmaceutical Industry
IPMG	International Pharmaceutical Manufacturers Group
IRPMA	International Research-Based Pharmaceutical Manufacturers Association
JPMA	Japan Pharmaceutical Manufacturers Association
KPBMA	Korea Pharmaceutical and Bio-pharma Manufacturers Association
KRPIA	Korean Research-based Pharmaceutical Industry Association
OPPI	Organization of Pharmaceutical Producers of India
PhAMA	Pharmaceutical Association of Malaysia
PHAP	Pharmaceutical and Healthcare Association of the Philippines
PhIRDA	Pharmaceutical Innovation and Research Development Association
PReMA	Pharmaceutical Research & Manufacturers Association
RDPAC	China Association of Enterprise with Foreign Investment R&D-based Pharmaceutical Association Committee
SAPI	Singapore Association of Pharmaceutical Industries
PG	Pharma Group (Vietnam)

Abbreviation

Abbreviation	Description
A.O.	Administrative Order (Philippines)
ACTD	ASEAN Common Technical Document
ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
ARs	Adverse Reactions
ASEAN	Association of South-East Asian Nations
B.E.	Buddha Era
BA	Bioavailability
BE	Bioequivalence
BLA	Biologics License Application
BP	British Pharmacopoeia
BPOM	Badan Pengawas Obat dan Makanan
BPOM	(Indonesian national agency of drug and food control)
BSE	Bridging study evaluation (Taiwan)
CDCR	Control of Drugs and Cosmetic Regulation (Malaysia)
CDE	Center for Drug Evaluation
CDFS	Council on Drug and Food Sanitation(Japan)
CDRR	Center for Drug Regulation and Research (Philippines)
CDSCO	Central Drugs Standard Control Organization (India)
CEP	Certification of Suitability to the monographs of the European Pharmacopoeia
CFDA	China Food and Drug Administration
CFDI	Center for Food and Drug Inspection
cGMP	current Good Manufacturing Practice
Ch.P.	Chinese Pharmacopoeia
CHGRAO	China Human Genetic Resources Administration Office
CIOMS-I	Suspect Adverse Reaction Report Form (CIOMS Form I)
CIRB	Centralised Institutional Review Board (Singapore)
c-IRB	Central IRB
CMC	Chemistry, Manufacturing and Control
CMO	Contract Manufacturing Organization
CoA/COA/CA	Certificate Of Analysis
CoI	Co-principal Investigator
CPC&SC	The Communist Party of China & State Council
CPO	Contract Pharmaceutical Organization.
CPP	Certificate of Pharmaceutical Product
CRC	Clinical Research Centre
CRF	Case Report Form
CRM	Clinical Research Materials Notification
CRMC	Clinical Research Management Committee
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Clinical Trial
CTA	Clinical Trial Application
CTA	Clinical Trial Authorization
CTA	Clinical Trial Approval
CTC	Clinical Trial Certificate
CTD	Common Technical Document
CTIL	Clinical Trial Import License （Malaysia）
CTN	Clinical Trial Notification
CTRI	Clinical Trials Registry- India
CTX	Clinical Trial Exemption
CV	Curriculum Vitae
DAL	Drug Administlation Law
DAV	The Drug Administration Department of Vietnam
DB	Double Blind
DCA	Drug Control Authority (Malaysia)

DCGI	Drugs Controller General India
DLP	Data Lock Point
DMF	Drug Master File
DMP	Data Management plan（China）
DMR	Data Management Report（China）
DOH	Department of Health
DP	Drug Product
DRGD	Drug Registration Guidance Document （Malaysia）
DRR	Drug Registlation Regulations
DS	Drug Substance
EC	Ethical/Ethics Committee
EMEA/EMA	European Medicines Agency
EP	European Pharmacopoeia
EPAR	European Public Assessment Report
EPW	Empowered Procurement Wing (India)
ERB/ERC	Ethical Review Board/ Committee (Philippines)
EU	European Union
FDA	Food and Drug Administration (U.S.)
FDC	Fixed Dose Combination
FERCIT	Forum for Ethical Review Committees in Thailand
FIH	First in Human
FIM	First in Man
FSC	Free Sale Certificate
FtoF or F2F or FTF	Face to Face
FY	Fiscal Year
GCP	Good Clinical Practice
GDA	Generic Drug Application
GDP	Good Distribution Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GS-1	Global Standard One
GSB	Global Safety Board
GTIN	Global Trade Item Number
HA	Health Authorities
HAS	Health Sciences in Singapore
HGR	Human Genetic Resources
HIV	Human Immunodeficiency Virus
HKD	Hong Kong dollar
HKOP	Hong Kong Office of President
HSA	Health Sciences Authority (Singapore)
HVAC	Heating, Ventilation, and Air Conditioning
IB	Investigator's Brochure
IBD	International Birthday
ICF	Informed Consent Form
ICH	The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH E17	ICH E17 Guideline (Multi-Regional Clinical Trials）
ICH E5	ICH E (Efficacy) 5 Guideline (Ethnic Factors in the Acceptability of Foreign Clinical Data)
ICH E6	ICH E (Efficacy) 6 Guideline (Good Clinical Practice)
ICSR	Individual Case Safety Report (Philippines)
IDL	Import Drug Licence （China）
IDR	Indonesia Rupiah
IEC(EC)	Independent Ethics Committee
IL	Import License
IMCT	International Multi-Center Clinical Trial
IMP	Investigational Medical Product
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
IP	Indian Pharmacopoeia
IRB	Institutional Review Board

JP	Japanese Pharmacopoeia
KOL	Key Opinion Leader
KOMNAS	The Indonesian Human Rights National Commission (Komnas HAM)
KoNECT	The Korea National Enterprise for Clinical Trials
KP	Korean Pharmacopoeia
KRW	Korea won
LOA	Letter of Authorization
LTOC	List of Table of Contents
MAH	Marketing Authorization Holder
MAV	Major variation application
MF	Master File (Japan)
MFDS	Ministry of Food & Drug Safety (Korea)
MHLW	Ministry of Health, Labour and Welfare (Japan)
MHRA	Medicines and Healthcare Products Regulatory Agency
MOH	Ministry of Health of the People's Republic of China
MOH or MoH	Ministry of Health (Malaysia) (Vietnam)
MOPH	Ministry of Public Health (Thailand)
MOST	Ministry of Science and Technology
MRCT	Multi-Regional Clinical Trials
MREC	Medical Research & Ethics Committee (Malaysia)
MTA	Material TransferAagreement
NADFC	National Agency for Drug and Food Control (Indonesia)
NBE	New Biological Entity
NCCR	National Committee for Clinical Research (Malaysia)
NCE	New Chemical Entity
NCO	New Combination
ND	New Delivery system
NDA	New Drug Application
NDAC	New Drug Advisory Committee (India)
NDOS	New Dosage form of Approved New Drug
NF	The National Formulary
NHFPC	National Health and Family Planning Commission (China)
NHG DSRB	National Healthcare Group Domain-Specific Review Board (Singapore)
NI	New Indication
NIBIO	National Institute of Biomedical Innovation (Japan)
NIFDC	National Institutes for Food and Drug Control (China)
NME	New Molecular Entity
NMRR	National Medical Research Register (Malaysia)
NPCB	National Pharmaceutical Control Bureau (Malaysia)
NPRA	National Pharmaceutical Regulatory Agency (Malaysia)
NR	New Route of administration
NRPB	National Research Program for Biopharmaceuticals (Taiwan)
NS	New Strength of Approved New Drug
NSAE	Non Serious Adverse Event
NT	New Taiwan dollar
ODD	Orphan Drug Designation (Taiwan)
OTC	Over-The-Counter
PAL	Pharmaceutical Affairs Law
PBRER	Periodic Benefit Risk Evaluation Report
PD	Pharmacodynamics
PFDA	Provincial Food and Drug Administration (China)
PHREB	Philippine Health Research Ethics Board
PI	Principal Investigator
PI	Package Insert
PIC/S or PIC/s	Pharmaceutical Inspection Convention (PIC) / Pharmaceutical Inspection Co-operation Scheme (PICS)
PIL	Patient Information Leaflets
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PMF	Plant Master File
PMS	Post-Marketing Surveillance/Study

PNHRS	Philippine National Health Research System
PP	Philippine Pharmacopoeia
PRH	product registration holders (Malaysia)
PSD	Product Services Division (Philippines)
PSUR	Periodic Safety Update Report
QOS	Quality Overall Summary
R&D	Research and Development
r-DNA	recombinant DNA
REMS	Risk Evaluation and Mitigation Strategy
RFID	Radio Frequency Identifier
RM	ringgit
RMA	Risk Minimisation Activities
RMB	renminbi = CNY (CHINESE YUAN)
RMP	Risk Management Plan
RRC	Research Review Committee (Malaysia)
Rs	Rupee
RTF	Refuse-to-file (Taiwan)
S&E	Safety & Efficacy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Advance Reaction
SAR	Statistical Analysis Report
SEC	Subject Expert Committee
SG-GCP	Singapore Guideline for Good Clinical Practice
SKU	Stock Keeping Unit
SMF	Site Master File
SMP	Safety Monitoring Program (Thailand)
SMPC/SmPC	summary product characteristics
SOH	(Vietnam)
SOP	Standard operating procedure
STM	Specification & Test Method
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TFDA	Taiwan Food and Drug Administration
TGA	Therapeutic Goods Administration (Australia)
Thai-FDA	Thailand Food and Drug Administration
TOX	Toxicology
UP-PGH	University of the Philippines - Philippine General Hospital
US	United States
USP	United States Pharmacopoeia
WHO	World Health Organization

Survey Results
Data sheets from Each Economy
on the areas of IND, NDA, Clinical Trials and GMP Evaluation System

China	(RDPAC)
China	(PhIRDA)
Hong Kong	(HKAPI)
India	(OPPI)
Indonesia	(IPMG)
Japan	(JPMA)
Korea	(KPBMA)
Korea	(KRPIA)
Malaysia	(PhAMA)
Philippines	(PHAP)
Singapore	(SAPI)
Taiwan	(IRPMA)
Thailand	(PReMA)
Vietnam	(PG)

Item	Contents	Detail or Example	China RDPAC/PhIRDA	Hong Kong HKAPI	India OPPI	Indonesia IPMG	Japan JPMA	Korea KPBMA/KRPIA	Malaysia PhAMA	Philippines PHAP	Singapore SAPI	Taiwan IRPMA	Thailand PReMA	Vietnam PG
IND/CT	Requirements of the applicant	CRO is possible?	**Sponsor (Companies) or regulatory agency (CRO)**	Basically, CRO and doctors who can follow standards of GCP.	Sponsor companies, CROs and doctors who can follow standards of GCP.	CRO, Companies and doctors who can follow standards of GCP.	GCP applies to clinical trials conducted by companies and investigators.	Yes. Company, CRO or doctor, who can follow standards of GCP, can be IND holder.	An investigator, or an authorised person from a locally registered pharmaceutical company/ sponsor/ Contract Research Organisation (CRO) with a permanent address in Malaysia can make the application.	As per A.O. 2014-0034, a license is required for a Contract Research Organization (CRO) and its sponsor, prior to the conduct of clincial trial. Sponsor companies, CROs and doctors who can follow standards of GCP.	Sponsor company should make the application.	**The applicant should own the pharmaceutical license in Taiwan.** CRO can be an applicant if the company also has be registered as a pharmaceutical company in Taiwan.	Drug manufacturing/import license holder or government (applicant can be sponsor or CRO	Sponsor companies, CROs and doctors who can follow GCP standards CPO or CRO
	Clinical trial consultation system	System, Timing, Procedure	"Communication and Exchange of Drug R&D and Technical Evaluation Procedure (No.94 of 2016) was issued by CFDA on Jun 6, 2016. This procedure gives priority to communication and exchange during registration for innovative drugs, drugs with advanced preparation technologies and drugs in urgent clinical demand. 1) Types of meetings: Class I meeting: Meeting for major safety issues during the drug clinical trials, and major technical issues of breakthrough therapy drugs in R&D process; Class II meeting: in the critical stages of research and development of innovative drugs, ①Before PhI, ②After PhII/before phIII, ③Before NDA, ④ Before approval for post-marketing risk control; Class III meeting: Other meetings than class I and class II meetings. 2) Timing of the meetings ; I class : within 30 days after submission, II class : within 60 days after submission, III class : within 75 days after submission 3) Meeting form: Face-to-face meeting, record the minutes, CDE video recording 4) other communication ways: Applicants could consult general technical issues with project management personnel in CDE via "Window for applicants", internet consulting platform, telephone, fax, email, mail etc. **On Oct 8, 2017, CPC&SC released the No. 42 to reform CT management to speed up CT, including changing EC review ahead of CT review and streamline CT application. It's a directional policy, still lack of details for operation. CFDA/CDE are working on these detail regulations and may come out in 2018.** **"CFDA announcement on adjusting the review and approval of drug clinical trial (draft)" was released for comments on Dec.14,2017. In normal case, applicant can request for the pre-IND meeting with CDE prior to the submission of IND application. In case that meet the following circumstances, IND application can be submitted without pre-IND meeting: technical guide is precise, there is much mature experience in the clinical trials of drug, and the Applicant can guarantee the quality of application dossiers, or the application for international multi-center clinical trials of international synchronous research & development has been approved in the countries and regions with well-developed supervisory system to implement the clinical trials.**	No	Non-formal consultation is possible. Pre-screening of the application is done at DCGI office before accepting our application. 1. IND- For phase 1 trials of NCEs application is referred to IND committee scheduled to meet every quarter. For molecule discovered outside India FIM studies are not permitted. 2. Other IND application -The application is referred to Subject Expert Committee(SEC) for review. Post review, the Sponsor/CRO is invited to a face to face meeting with SEC where they need to present & defend the proposal.	The consultation with Head of evaluator **& Assistant Director by email and appointment before discussed.**	Various Clinical trial consultations are provided on new drugs and biological products by PMDA. （e.g., pre-PhI/ Pre-PhIIa/Pre-PhIIb /End of PhII study, Pre-application, Quality, Safety, etc）	Official pre IND consultation can be held **30 days (working day)** before expected consultation meeting and it should be requested in written form. Meeting minutes will be issued 10 days after the meeting by MFDS (Ministry of Food and Drug Safety). Pre-review system covers IND preparations. F2F meeting 14~24 days after primary review result.	A formal and structured consultation system is currently not in place but consultation may be requested on an informal basis.	For company-initiated local trial, the proposed clinical trial protocol is prepared by the medical department in consultation with a physician-specialist who becomes a co-author. The protocol is then submitted to the GSB and regional Safety Department & Regulatory Department for approval. The final approval comes from the FDA. For investigator-initiated trials, the proposed protocol is written by the authors subject to the approval of the medical dept of HI-Eisai. (see FDA Circular 2012-007)	No. But for first-in-human trials, HSA would prefer if company has a pre-submission consultation about 2 months before submission.	Regulation consultation service is available for all phases of product development. **In 2018 the reasonable consultation fee will be charged to the applicant and this kind of service will be with legal binding. For more detailed information please refer to the following website. http://www.cde.org.tw/eng/consultation_services/**	Can consult at FDA (Such as direct contact, telephone)	There is no official consultation in place however, sponsor can send letter to **Administration of Science Technology and Training under Ministry of Health** in order to request consultation.

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IND/CTA	Flow of clinical trial notification, IND application and IRB permission	Flowchart	**"CFDA announcement on adjusting the review and approval of drug clinical trial (draft)" was released for comments on Dec. 14, 2017.** **IND approval system will be changed to the "60 WDs' implied permission" system that means applicant is allowed to start the clinical trial if no defined or questioned opinion received from CDE within 60 WDs from the acceptance date of application.** **Actually clinical trial can be initiated after IND permission, IRB permission, and human generic resource approval (MOST).** **CPC &SC released the "Opinions on the deepening the review and approval system and encouraging the innovation of drug and medical device" on Oct. 8, 2017.** **IRB permission of leading site will be recognized by member sites, no repeated IRB permission in each site (It is still in transition period, no real case as yet).** **IRB permission of leading site is the pre-condition of submitting the IND application.** **IND permission related document and IRB permission letter should be submitted for human generic resource approval.** **For BE study, notification system is applied from Dec.01,2015 and for other studies, CTA system is applied.**	Approval by DOH is required. IRB approval is also required.	Clinical trial on new drug shall be initiated after authorization by CDSCO (NOC:No Objection Certificate from DCGI) and approval of respective EC. In case of parallel applications, CDCSO will grant conditional approval and note that the trial should start after Ethics approval	Flow Chart of Clinical Trial Notification See Annex 1, Flow Chart of Post Marketing Clinical Trial See **Annex 2**	A clinical trial is conducted based on notification, not on application. Contracts with clinical sites should be signed after 30 days from the clinical trial notification (14 days from the second trial onwards)	There is no clinical trial notification system, and only IND approval is available. Clinical trial should be conducted within 2 years after IND approval. (See the flow chart at Annex 3)	A Clinical Trial Import Licence (CTIL) authorising the licensee to import a product for purposes of clinical trials is required. The sponsor/ investigator shall not start the clinical trial until the ethics committee/ Institutional Review Board has issued a favourable opinion and approved by the Drug Control Authority (DCA). All the clinical trials that require CTIL/ CTX (Clinical Trial Exemption) must be registered with NMRR (National Medical Research Register). NPRA will only accept favourable opinion/ approval issued by EC that is registered with the DCA.	We now have a central ethical review board in the FDA. This board reviews the protocol. Once approved, the CT may proceed. Centers where the clinical trial is to be conducted is notified. Please see FDA Circular 2012-007 (p. 6 &8)	Under the Health Products Act and its subsidiary legislation, the Health Products (Clinical Trials) Regulations, and require either Clinical Trial Authorisation (CTA) or acceptance of Clinical Trial Notification (CTN) prior to initiation of the clinical trial. There are three clinical trial submission routes (CTC, CTA and CTN) Clinical trials of therapeutic products (e.g. pharmaceutical drugs and biologics) require clinical trial authorisation (CTA) or acceptance of clinical trial notification (CTN) before the trial can be initiated or conducted. Such clinical trials must be conducted in compliance with the Health Products (Clinical Trials) Regulations and the ICH E6 Good Clinical Practice guidelines. Clinical trials of medicinal products (e.g. cell, tissue and gene therapy products or complementary health products) require a clinical trial certificate (CTC) before the trial can be initiated or conducted. Such clinical trials must be conducted in compliance with the Medicines (Clinical Trials) Regulations and ICH E6 Good Clinical Practice guidelines. For clinical trials that require clinical trial authorisation (CTA) or a clinical trial certificate (CTC), the clinical trial application may be submitted concurrently to HSA and the relevant IRB. For clinical trials that require clinical trial notification (CTN) to HSA, the submission should be made only after having received IRB approval for the clinical trial. (See Annex 4)	Some IRBs need to sign the contract before get approval letter.	Same. **Only minor changes as defined in Notification of Thai FDA Re: Regulations on Import or Order the drug into the Kingdom for Clinical Research on 20 Mar 2017** **Moreover, Ministry of Public Health has released an announcement with immediate effect on implementation plan align with PM section 44 to allow MoPH to collect submission and review fee as a maximum fee within 5 years.**	In short: Clinical trial notification, then Hospital IRB permission, IND application and MOH IRB approval. Clinical trial should be submitted to Site level first. After receiving IRB/EC approval at site level (For some Hospitals under Department of Health, the hospital should get approval from SOH and People's Committee before submit to HA), we can continue submission to health authority (HA). The CT can be initiated after getting HA, in this case the Ministry of Health, approval. Import License (IL) in only obtained after having HA approval.
	Time required for clinical trial notification, IND application and IRB permission obtainment	Official timeline: (working days) Timeline based on actual experience	**According to timeline survey 2017 benchmark is 14-18m for IDL-CTA, and 7~11 m for IMCT.** **"CFDA announcement on adjusting the review and approval of drug clinical trial (draft)" was released for comments on Dec.14,2017.** **Initial IND permission will be 60WDs.** **IND for new indication permission will be 40WDs.** **According to the Drug Administration Law (Updated) issued by CFDA on 2017, IRB permission will be mandatorily required for IND application so it may delay the submission time of IND application. For innovative new drug, Pre-IND communication is required, and CDE comments and Sponsor responses are necessary for IND submission. (it will be no more than 3 months for Pre-IND meeting procedure)** **Human genetic resource approval process was streamlined, and the approval time was shortened about 1~2 months.** **Currently, Applicant should start clinical trial study within 3 years after getting IND approval. The expiry date will be updated in new DRR in 2018 yr.**	4 months	IND review: 6-8 months EC review: 2-4 months	Timeline for evaluation is 20 working days for protocol & amendment of clinical trial after NADFC stated the protocol & amendment complete	The rule of "after 30 days from the first clinical trial notification" for drugs containing new active ingredients, new ethical combination drugs and drugs with a new administrative route. The clinical trial can be started after 14 days from clinical trial notification for the second trial onwards (for the same product).	IND application official timeline based on the results of the consultation: 30 working days Timeline based on actual experience: Given 1 time query by MFDS during their IND review period, it takes 2-3 months. According to sites, IRB review will be held every 2 weeks to every 2 months depending on the sites. Totally, for initial 3 months, we can get IND approval & IRB approval in parallel. **Based on individual application (level of document), the requirements of query, expected period and additional document can vary.**	Official Timeline for CTIL/CTX: 45 working days for phase I trial, clinical trial involves biological/ biotechnological, cell therapy product and gene therapy product as well as herbal product. For Others: 30 working days The IRB/IEC should review a proposed clinical trial within a reasonable time. Ethics approval: complete submission without queries can be approved within 4 to 8 weeks. (Re Edition 6.1 Malaysian Guideline for Application of CTIL & CTX, NPRA)	No specific timelines for trial notification. (Basically not more than 60 days from submission)	The timing will depend on which of the three clinical trial submission routes (CTC, CTA and CTN). Clinical Trial Certificate (CTC) and Clinical Trial Authorisation (CTA): 30 working days. Note: 60 working days for cell and tissue products Clinical Trial Notification (CTN): 5 working days. Clinical Research Materials Notification (CRM): Immediate	The time for (CTA-Clinical Trial application) will be within 30 **calendar** days. General IND application procedure will review protocol in detail by CDE and may request to revise protocol based on their review result. **The outcome of review comment can be obtained in around 45 calendar days.** If the protocol is simultaneous submission in A10 countries with same protocol number, fast track review is available so that the overall review time can be reduced as short as **15 calendar days. IRB review timeline depends on each IRB review meeting frequency.** The approval time may take around **1-4** months.	Trial product import license official timeline: Chemical - 20 WD Biological - 60 WD IRB : (each study site or EC of MOPH) - institute EC 2-3 months/ EC-MOPH 6 months. **In addition, HA has established timeline for notification and amendment approval – 20 WD**	Time required for clinical trial notification: 1 month; Hospital IRB: 1.5-3 months; IND application and MOH IRB permission obtainment: 2-3 months

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IND/CTA application materials	Application form	Requirements and language	Yes : application form (in Chinese) "New Document Submission Requirements based on New Registration Classification of Chemical Drugs (No.80 of 2016)" was issued by CFDA on May 4, 2016.	Application form for Certificate for Clinical Trial	Yes (Form 44, in English)	There is a checklist requirement	Yes: Clinical trial notification form (in Japanese)	Submission system were changed to the internet-based system.	Application form for CTIL/CTX (Clinical Trial Import Licence/ Clinical Trial Exemption). In English or Bahasa Malaysia	Yes, in English. Please see FDA Circular 2012-007	Application for Clinical Trial Authorisation, Clinical Trial Notification or Clinical Trial Certificate to HAS. IRB has no form.	Application form is needed and it can be in English. But the format is in Chinese.	Local form (in Thai)	Yes, in Vietnamese
	A statement regarding the reason why the sponsoring of the proposed clinical trial is scientifically justified	Requirements and language	Yes (in Chinese)	No	Yes (in English) and vernacular language	Yes	Yes (in Japanese)	Yes (in Korean)	No	Please see FDA Circular 2012-007 (p.4)	No	Yes, the official letter to indicate the sponsoring of proposed clinical trial is needed.	Cover letter (have template in Thai)	No
	Protocol	Requirements and language	Yes (in Chinese)	Yes, in English	Yes (in English)	Yes	Yes (in Japanese)	Yes (in Korean)and all data **In case of Phase 1 study, The English protocol could be accepted.**	Yes, in English or Bahasa Malaysia Malaysian Guideline for Application of CTIL & CTX, Edition 6.1 September 2015) and all data must be in English or Bahasa Malaysia	Yes, in English	Yes, in English	Required. Both Chinese or English version are acceptable. **The Chinese synopsis is requested.**	See detail in guideline, can be in Thai or English	Protocol is mandatory in VNM and ENG. MOH EC members refer to ENG version to verify information.
	IB	Requirements and language	Yes (in Chinese)	Yes, in English For Ph IV trials, HK registered pack insert can be used.	Yes(in English)	Yes,(in Indonesian or English)	Yes (in Japanese)	Yes (English acceptable) **Korean document may be required as a query.**	Yes, in English or Bahasa Malaysia. For content and format of the IB, reference is made to section 7, current version of Malaysian Guideline for GCP.	Yes, in English	Yes, in English	Required. Chinese or English version are acceptable.	See detail in guideline (for unregistered drug in Thailand)	In English and Vietnamese. It is also accepted for submission of English and summary in Vietnamese
	CRF (sample)	Requirements and language	**No**	Yes, in English	Yes(in English)	Yes, (in Indonesian or English)	No, if the description of CRF is to be read by PC.	Yes (English acceptable) **For MFDS approval, CRF is not needed.**	Yes, in English or Bahasa Malaysia	Yes, in English	Yes, in English	Required. Chinese or English version are acceptable.	No requirement	ENG mandatory; VNM optional
	Informed consent	Requirements and language	Yes (in Chinese)	Yes, in English or Chinese	Yes- ENGLISH to be submitted to DCGI. ICF in local regional languages has to be submitted to Ethics committee for EC approval. (in a language that is non-technical and understandable by the study subject.)	Yes,(in Indonesian or English)	Yes (in Japanese)	Yes (in Korean)	Requirements as in 1. Malaysian Guideline for Good Clinical Practice, section 4.8 Informed Consent of Trial Subjects: 2. Malaysian Guideline for Application of CTIL and CTX, section 4.4.12 Informed consent form (Initial version only): The informed consent form (ICF) provided can be in either English or Bahasa Malaysia	Yes, in English	Yes, in English	ICF checklist is required upon ICF amendment, and the comparison table is also required.	Yes, in Thai	Yes, in Vietnamese and English (both are mandatory)
	Investigator's CV	Requirements and language	No	CV of PI	Yes (in English)	Yes, (in Indonesian or English)	No	No	The GCP certificate and CV for investigator/ PI of each trial site should be provided. The GCP course should be recognised/ approved by National Committee for Clinical Research (NCCR), Ministry of Health Malaysia. The requirement is in accordance to the current version of Malaysian Guidelines for GCP. in English or Bahasa Malaysia	Yes, in English	CV of PI, in English	Required for both PI and Co-I. Chinese or English version are acceptable.	No requirement	Yes, in Vietnamese or English
	Overall requirement on content		**After Dec 1, CFDA carry out centralized acceptance. New requirements released by CDE according to No. 42 and related effective reforming regulations, such as API filing, lab testing, etc, which may rise new issues.** **"CFDA announcement on adjusting the review and approval of drug clinical trial (draft)" was released for comments on Dec. 14, 2017.** **IND application materials shall refer to "Technical Guideline of Phase I Clinical Trial Application of New Drug (Draft, Mar. 29, 2017).** **Also will submit the PV system situation, name list of relevant parties involving in the trial, IRB permission related documents, Pre-IND meeting related documents.**											

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IND/CTA application materials	Non-clinical summary	Requirements and language	Yes (In Chinese) **Will refer to the "Technical Guideline of Phase I Clinical Trial Application of New Drug (Jan. 25,2018,[2018]No.16)**	No	Yes (in English)	Yes, (in Indonesian or English)	No Non-clinical information is included in IB	Yes (in Korean)	Investigator's brochure in English or Bahasa Malaysia	Yes, in English	No	No separate document is required. Referred to IB.	including in IB	Not applicable (often included in IB) If provided, Vietnamese/English
	Non-clinical report	Requirements and language	Yes (in Chinese) **Will refer to the "Technical Guideline of Phase I Clinical Trial Application of New Drug (Jan. 25,2018,[2018]No.16)**	No	Yes (in English)	Yes, (in Indonesian or English)	No	Yes (English acceptable)	Investigator's brochure in English or Bahasa Malaysia	Yes, in English	No	No separate document is required. Referred to IB.	including in IB	Not applicable (often included in IB) If provided, Vietnamese/ English
	Clinical summary	Requirements and language	Yes (in Chinese) **Will refer to the "Technical Guideline of Phase I Clinical Trial Application of New Drug (Jan. 25,2018,[2018]No.16)**	No	Yes (in English)	Yes, (in Indonesian or English)	No Clinical information is included in IB	Yes (in Korean)	No	Yes, in English	No	No separate document is required. Referred to IB.	including in IB	NA If provided, Vietnamese/ English Clinical summary is often included in Protocol and IB.
	Clinical report	Requirements and language	Yes (in Chinese) **Will refer to the "Technical Guideline of Phase I Clinical Trial Application of New Drug (Jan. 25,2018,[2018]No.16)**	No	Yes (in English)	Yes, (in Indonesian or English)	No	Yes (English acceptable) **Summary data can be submitted first and full report can be requested by MFDS.**	Published clinical data in English or Bahasa Malaysia	Yes, in English	No (for HSA, every 6 monthly, status report of the trial to be submitted; for IRB usually annually)	Can refer to IB	including in IB	NA. it is often included in IB
	CMC summary	Requirements and language	Yes (in Chinese) **Will refer to the "Technical Guideline of Phase I Clinical Trial Application of New Drug (Jan. 25,2018,[2018]No.16)**	No	Yes (in English)	Yes, (in Indonesian or English)	No	Yes (in Korean)	Yes	Yes, in English	No	CMC data should be provided	See detail in guideline (for NCE)	Yes (IMPD, CoA, SmPC, label…) English/Vietnam
	CMC report	Requirements and language	Yes (in Chinese) **Will refer to the "Technical Guideline of Phase I Clinical Trial Application of New Drug (Jan. 25,2018,[2018]No.16)**	No	Yes (in English)	Yes, (in Indonesian or English)	No	Yes (English acceptable)	Yes	Yes, in English	No	CMC data is required either in English or Chinese	See detail in guideline (for NCE)	Same as CMC summary
	GMP certificate of the investigational drug	Necessary or Unnecessary	For IND of IMCT, GMP certificate is not required. **For IND of domestic drug, GMP certificate is not required neither.** But a statement that investigational products are formulated in accordance with GMP should be submitted; For CTA of import drug, CPP with GMP statement is required; For CTA of domestic drug, hard copy of GMP certificate of manufacturing plant is required.	Yes	YES	Yes, (in Indonesian or English)	No	Necessary **If GMP certificate is not available, QP declaration letter can be used instead of GMP certificate.**	Yes, necessary	Yes, in English	No (HSA application, to provide GMP certificate of the Drug Product site of Investigation drug, during CTC application)	GMP certificate of the investigational drug is NOT mandatory.	Necessary	Necessary
	Sample of the investigational drug (for IND review)	Requirements and language	**CPC &SC released the "Opinions on the deepening the review and approval system and encouraging the innovation of drug and medical device" on Oct. 8, 2017.(No.42)** **Sample of the investigational drug will be required to submit to CFDA.** **In Drafted DRR of 2017, the sample testing during IND/CTA application testing Is not mandatory, but could be done upon CDE technical review need. The final new DRR may be issued in 2018 yr.**	Yes, proposed label and COA also.	Samples of reference standards and finished product (equivalent of 50 clinical doses or more, if requested by the Authority), with testing Protocol/s, full impurity profile and release specifications. DCGI normaly asks the applicant to submit the samples of the drug product along with reference standard to the government laboratory (Central Drug Testing Laboratory or Indian Pharmacopoeial commission Laboratory). The Applicant needs to submit the samples in the quantity sufficient for three fold analysis	Product Information of investigational drug, CoA of investigational drug, Summary Batch protocol (Three consecutive batch)→ only for Vaccine, Lot release only special for vaccine. **(Annex 5)**	No	No	No, COA only	Yes, in English	No	Not required.	No requirement	No. Minimal required is label mockup. Dossier still can be submitted without pictures.

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NDA	Acceptance of CTD format	CTD or ACTD or Others ?	According to "New Document Submission Requirements based on New Registration Classification of Chemical Drugs (No.80 of 2016)", full CTD + Chinese Module 1 + China unique requirements (such as SAP, SAR, DMP, DMR etc.) are acceptable. **The drafted DRR has new requirement of NDA submission, Chemical drug is same to NO.80. The final new DRR will be issued in 2018 yr.**	Not specified. CTD can be accepted.	ICH-CTD is acceptable. However, it is not indicated in document issued by HA.	ACTD format	CTD format.	**All of the submission should be submitted as CTD format as of 20th, March, 2016.**	All applications are made in ASEAN CTD format.	Application data for new drugs have to be handled by the ASEAN CTD format. There is flexibility on the use of ICH dossier as per FDA Adoption of ACTD.	ACTD or ICH-CTD	All new drug applications including generic application should be submitted in ICH CTD format after 1-July-2014.	Effective from 1 Jan 2016 (with 6 months grace period), the application for NCE and New Biologics/Vaccine for human use have to be in eCTD format. For other classification, the document has to be in ACTD. The ICH-CTD may be acceptable with mapping to ACTD.	ACTD and ICH-CTD format, or CTD for NCE For NCE: ACTD or ICH-CTD is accepted. For the rest: only ACTD is accepted.
	Category of NDA	ex. NCE, Generic, Supplemental,	New registration categories for chemical drugs are issued on Mar 04,2016. 1.Innovative drugs not marketed in and outside China. Drug substances and their preparations containing new compounds with definite structure and pharmacological actions and possessing clinical value. 2.Improved new drugs not marketed in and outside China 2.1 Drug substances and their preparations containing optical isomers with known active ingredients made through such methods as resolution or synthesis, or esterification of known active ingredients, or saltification of known active ingredients (including salts containing hydrogen bond or coordinate bond), or the alteration of the acid radicals, basic groups or metal elements, or the formation of other non-covalent bond derivatives (complex, chelate or clathrate) and possessing significant clinical advantages ii. Preparations of new dosage forms containing known active ingredients (including new administration systems), new formulation and manufacturing processes, new routes of administration and possessing significant clinical advantages. 2.2 Preparations of new dosage forms containing known active ingredients (including new administration systems), new formulation and manufacturing processes, new routes of administration and possessing significant clinical advantages. 2.3 New compound preparations containing known active ingredients and possessing significant clinical advantages. 2.4 Preparations of new indications containing known active ingredients 3.Drugs generic to original drugs marketed overseas yet not marketed in China 4.Drugs generic to original drugs marketed in China 5.Applications of drugs marketed overseas for marketing in China 5.1 Applications of original drugs marketed overseas (including drug substances and their preparations) for marketing in China 5.2 Applications of non-original drugs marketed overseas (including drug substances and their preparations) for marketing in China	Two categories: 1. New Chemical Entity (NCE); 2. Generic (i.e. drug substance already registered at Department of Health (DOH))	New Drug: 1) New Chemical Entity (NCE), 2) New indications, dosage, dosage form and route of administration 3) Fixed Dose Combination (FDC) (See 122E of the Drugs and Cosmetics Rule) Note: all vaccines and Recombinant DNA (r-DNA) derived drugs shall be new drugs unless certified otherwise by the Licensing Authority	A. New Registration consist of : a. Category 1: New Drug and Biological Product registration including Biosimilar Product. b. Category 2: **branded generic** drug / generic product. c. Category 3: Registration of other dosage form. B. Registration of drug variation, consist of : a. Category 4: Major variation registration (VaMa) b. Category 5 : Minor variation registration that needs an approval (VaMi-B) c Category 6.: Minor variation registration with notification (VaMa-A) C. Renewal a. Category 7: Renewal **Annex 6, 7, 8, 9**	Regulatory filing for ethical drugs is required in the CTD format. As for generic drugs this requirement **is** as a basic rule, beginning on March 1, 2017. The new requirement **is** excluded **cell therapy products etc.**	<Chemical> (1) New Drug 1) New chemical structure (NCE) 2) Combination drug including NCE (2) Data requiring drug (Drug for supplementary data submission) 1) Drug with new salt or isomer, etc. 2) Drug with a new indication 3) New dosage drug - Increase/Decrease amount of API - New combination drug 4) Drug with a new administration route 5) Drug with a new dosage and administration 6) Enzyme, yeast, microorganism derivated drug with new origins 7) Drug with a new formulation(same route of administration) <Biologics> (1) Drug containing new molecular entities 1) DNA recombinant drug and Cell culture drug 2) Biologics - Vaccine, antitoxins - Blood products - Biologics other than above (therapeutic antigens, botulinum products, etc). (2) Data requiring drug(Drug for supplementary data submission) 1) Biologics : strains and manufacturing methods are different from authorized biologics 2) Recombinant DNA products: hosts, vectors, or methods to obtain DNA is different from authorized biologics 3) Cell culture derived products: same cell line, but different cell culture or purification methods from authorized biologics 4) Cell culture derived product: cell line is different from authorized biologics 5) When final bulk is the same, but the site for manufacture is different 6) New dosage forms with the same route of administration 7) Biosimilar product(recombinant DNA) 8) Total plasma and component preparations 9) Others not separately classified	Drug Registration Guidance Document (DRGD) Section A, 1.2 Categories Of Product : 1) New Drug Products a) New Chemical Entity (NCE)/ Radiopharmaceutical Substance b) New Combination Product c) Supplemental Product 2) Biologics 3) Generics 4) Health Supplements 5) Natural Products	(1) Drugs containing new active ingredients (2) New ethical combination drugs (3) Drugs with a new administration route (4) Drugs with a new indication (5) New dosage form drugs (6) New dosage drugs (7) Follow-on biologics (8) Drugs supplied in an additional dosage form (9) Similar ethical combination drugs (10) Other drugs	NDA-1 for the first strength NCE and biological entity. NDA-2 for new combination, new dosage form, new route of administration or new indication of registered chemical entities. NDA-3 for subsequent strengths of a new drug product. GDA-1 for the first strength of a generic chemical product. GDA-2 for subsequent strenths of the generic chemical product.	New Drug I : (1) New chemical entity (2) New indication (3) New combination (4) New administration route New Drug 2 (1) New dosage form (2) New usage dose (3) New unit dose	1) Chemical drugs 1.1) New Drugs (NCE, NI, NCO, ND, NR, NDOS, NS) 1.2) New Generic (NG) 1.3) Generic (G) 2) Biological Products *NCE = New Chemical Entity, NI = New Indication, NCO = New Combination, ND = New Delivery system, NR = New Route of administration, NDOS = New Dosage form of Approved New Drug, NS = New Strength of Approved New Drug **Change category of biological to be:** **1. New biologic or stand alone** **2. Biosimilar** **3. Vaccine** **4. Blood products**	**Acc.to Pharma La (effective 1 Jan 2017) and Decree 54:** **1. First time registration NDA (First time application) includes: NCE, line extension (new strength, new dosage form), generic** **2. Extension registration** **3. Registration of change, supplementation**

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NDA	Requirement of CPP	Timing of submission. ex. at NDA, before approval Number of required CPP. Source country. ex. Manufacturing/exporting country, Marketing country (FSC)	**CFDA issued "Decision on adjusting import drug registration administration" on Oct.10, 2017.(CFDA[2017]No.35) For new Cat. 1 and 2 import chemical drug and innovative therapeutic biological product (not marketed in china and overseas), CPP is not requested in the whole process of NDA.** For new Cat.5.1 CPP should be submitted at the submission of CTA and NDA. Both CPP granted by manufacturing country or marketing country are acceptable.	To be submitted at the time of application No. of CPP required: NCE: 2 ICH countries Generic: 1 (source country only)	CPP or Free sale certificate (FSC) issued by country of origin is required at NDA. The CPP and FSC should be notarised and apostilled or legalised by Indian embassy of the country of origin.	Copy CPP is submitted during pre-registration. The original CPP should be present at the submission of NDA. CPP only required for imported product. The product with one CPP will be evaluated within 300 working days. The product with three CPP + two Assessment Report from Other Health Authority (one CPP from manufacturing country , two CPPs from EU, US, AUS, UK, Japan) will be evaluated within **120** working days. **With three CPP as long as having similar indication it can proposed to follow Reliance System. (No need expert KOMNAS for discuss Clinical Study). → Sakigake Japan**	Not required	Imported new drugs: CPP submission is mandatory (Issuance date of CPP should be less than 2 years based on the submission date) Others except imported new drugs: Exemption of CPP submission(if there is any GMP certificate issued by the MFDS) Drugs listed in the pharmacopeia of the US, Japan, UK, Germany, France, Italia and Canada: CPP can be replaced by specific documents both signed by a person in charge of drug manufacturer and authenticated by competent authority. Timing : Before approval Number : One original document or legalized (apostilled) copy Source : Manufacturing country/Marketing country (For the manufacturing country, the GMP certificate can replace the CPP.)	Category 1 & 2: CPP required at time of application; Category 3: CPP required at time of application but not required for locally produced generics; CPP from the competent authority in the country of origin; or GMP Certification/ Manufacturing License for the manufacturer from the relevant competent authority, together with CPP from the country of the product owner; or CPP from country of release, if CPP from the country of the product owner is not available)	Timing of submission is at NDA. Number of required CPP is 1 from Source country e.g. ex. Manufacturing/ exporting country, Marketing country (CPP or FSC/GMP) or any reference country	Submission of CPP is not compulsory and depends on type of submission. In case a bridge of NDA product, proof of approval by any drug regulatory agency is required.	CPP(s) are required before NDA approval. 2 CPPs from 10 advanced countries are required for NCE/BLA approval if no clinical studies in Taiwan. At the time of filing, NCE/BLA can be submitted without CPP. When approaching approval time, if Taiwan participates two global clinical trials (Ph1+Ph3 or Ph2+ Ph3) with designate numbers of Taiwan subjects enrolled, (Clinical development in Taiwan in earlier) then CPP can be waived. NCE/BLA can be approved with one CPP in one of 10 advanced countries but also need one clinical trial in Taiwan (Ph1 or Ph2 or Ph3) with designate number of Taiwan subjects enrolled into the study. 1 EMA CPP accounts for approvals in 5 advanced countries. Product has to be launched in source country or 10 advanced countries.	CPP is required at the timing of submission. 1 CPP from manufacturing country (with marketed status). The product detail has to be supplemented to the CPP i.e. manufacturing sites for all steps to be supplied for Thailand i.e. DP manufacturer, primary and secondary packager and batch releaser. The full composition is also needed to be presented on the CPP.	Provide upon submission 1 CPP from manufacturing or reference countries (ICH, Australia) for each dossier Switzerland is accepted as belongs to ICH
	Approval can be obtained by utilizing foreign clinical trial data.	Requirement of bridging data/report and global clinical trial data/report. Necessity of PK study in local population.	Global / MRCT clinical data for chemical drugs are acceptable, but Chinese P3 and PK data is indispensable. There are also Chinese samples size requirements at the same time. For biologicals, global / MRCT clinical data is acceptable. For imported pediatric drugs in clinical needs and already marketed in the United States, the European Union and neighboring regions of China, relevant clinical trial data completed overseas may be used for the drug registration applications in China.(from CFDA opinion on implementing priority review and approval to resolve the backlog of drug registration applications on Feb 26, 2016.) **CFDA issued "Decision on adjusting import drug registration administration" on Oct.10, 2017. (CFDA[2017]No.35) "3 submissions and 3 approvals "policy was cancelled. IMCT data can be used to support NDA submission directly.** **CFDA issued "Technical requirements on accepting overseas clinical trial data (draft)"on Oct. 20, 2017, which specifies the requirements of accepting overseas clinical trial data on integrity, qualify, basic technical requirements, and also 3 levels of acceptance.**	The overseas clinical trial data is acceptable. Bridging data are not required.	Clinical data in Indian population is required except few life saving therapeutic categories which is at the discretion of the regulatory agency. However now a days, DCGI has become very strict and insists for local clinical trial data for every new drug.	Overseas clinical trial data is acceptable, as long as it is aligned with ICH and/or WHO guideline. Local regulatory trials is required for TB program and drug for family planning program	The overseas clinical trial data is accepted in accordance with ICH E5. The drugs approved by using a bridging strategy or global clinical trial data have increased. But Japanese PK data is indispensable. Discussion of ICH E17 **is reached Step4.**	Only for New Drugs, bridging data is needed additionally. (See figures at Annex 10)	Overseas clinical trial data is acceptable, as long as it is aligned with ICH and/or WHO guidance, and accepted by the major reference countries. Local regulatory trials are not required.	The overseas clinical trial data is accepted.	Overseas clinical trial data is acceptable	BSE is mandatory for **NDA and** BLA such as gene-engineering drugs, vaccines, new molecular of plasma preparations and allergenic preparations.	Not required	Global clinical trial data/report. Since the new Pharma Law takes effect (1 Jan 2017), Vietnam is drafting legislations guiding clinical trials requirements for registration, including criteria for local clinical trial exemption.

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NDA	Application fees	Fees necessary for applying for approval as for NME drug with full data (Category (1))	Registration fee for category 1 and 2: NDA: 432,000 RMB (local drug) 593,900RMB (import drug) Registration fee for category 5: NDA: 502,000RMB (import drug) Authorities comment: Application fee gap between the import drug and local drag are due to the difference in the inspection cost.	Application fee: HKD 1100 License fee: HKD 1370 Renewal fee (every 5 years): HKD 575	Structure remains the same, but draft proposal to increase the same by 3 to 4 times has been proposed. Application fees: NDA: INR 50000 (include MAA fee) Import License: Rs 1000 and at the rate of Rs.100/- for additional drug. Registration Certificate (for import drug): 1500USD for one manufacturing site or its equivalent in Indian currency and 1000USD for one drug or its equivalent in Indian currency. An additional fee at the rate of one thousand US dollars for each additional drug. Duplicate Registration certificate: three hundred US dollars shall be paid for a duplicate copy of the Registration Certificate, if the original is defaced, damaged or lost. Inspection Fee: The applicant shall be liable for the payment of a fee of five thousand US dollars for expenditure as may be required for inspection or visit of the manufacturing premises or drugs, by the licensing authority Test License:The fee of import licences for test and analysis of a drug has been kept Rs. 100 for a single drug and at the rate of Rs. 50/- for each additional drug	Application fee : Pre-Registration : 1 Million IDR (MIDR) Registration fee for : Category 1 : new product & Biological Product : 30 MIDR, new indication : 20 MIDR Category 2: Branded generic product 7.5 MIDR, copy product with BA/BE data: 12.5 MIDR, **generic product 1 IDR** Category 3 : other product: 7.5 MIDR Category 4: VaMa : 2 MIDR for each dosage form/packaging Category 5: VaMa-B : 2 MIDR for each dosage form/packaging. Category 6: VaMi-A : 1 MIDR for each dosage form/packaging. Category 7: renewal : 5 MIDR For pre-inspection GMP document: 7.5 MIDR. For GMP site inspection: **50 MIDR + Accomodation (Ticket+hotel + Lunch, dinner, Pocket money)** **For CAPA : 5 IDR**	The fee of application was revised on Apr.1, 2017. Application fees of drugs containing new active ingredients **(in case of not orphan drug)** To Government : 533,800 yen To PMDA for review : **28,545,700** yen for paper-based compliance inspection : **8,096,400**yen for GCP inspection : domestic **3,361,200** yen, overseas **3,717,600** yen +Travel expense for GMP inspection : domestic **875,000** yen, overseas **1,104,200** yen +Travel expense	Application fee was increased on 30th, November, 2016(Based on mail application. For electronic application, 10% discount) <STM review + S&E review + GMP review> (1) New drugs (including biologics): KRW 6,828,150 (2) Orphan drugs : KRW 3,755,850(Fee can be discounted to KRW 1,877,920 when clinical study report is attached after conducting clinical trial according to the Pharmaceutical Affairs Act) (3) Others: KRW 2,218,650 * There can be discount when review is excluded Cf. Generics(BE, CMC, GMP review included) : KRW 1,707,300 For GMP/GCP inspection(around 7,500,000KRW/person (overseas)) : This one is the travel expense for inspectors, so if GMP inspection would be waived, no more fee is needed. **GMP inspection fee will be decided based on location, period, and number of inspectors.**	Fees are required and details are given in the DRGD Appendix 1: Fees. These are according to product categories, number of active ingredients, types of applications etc.	NCE: 900 USD Initial Registration: 340 USD (1USD= 45 PhP) * above rates are current; however these may change pending implementation of proposed new revised fees.	Registering a product – NDA & GDA a) Screening (Payable upon submission) (i)Abridged/Verification Dossier (NDA & GDA) $550 (ii) Full Dossier (NDA)* $2,750 b) Evaluation (Payable upon acceptance) (i) NDA Abridged Dossier (Chemical Drugs & Biologics) -NDA-1 & NDA-2 $11,000 - NDA-3 $5,500 (ii) NDA Verification Dossier (Chemical Drugs & Biologics) - NDA-1 & NDA-2 $16,500 - NDA-3 $5,500 (iii) NDA Full Dossier* $82,500 (iv) GDA Abridged Dossier - GDA-1 $3,850 - GDA-2 $2,200 (v) GDA Verification Dossier - GDA-1 $10,000 - GDA-2 $5,000 (vi) GDA Verification Dossier (CECA Scheme) - GDA-1 $10,000 - GDA-2 $5,000	NDA: Application fees ("Fee-Charging Standards for the Registration of Western Medicines and Medical Devices") 1. Product registration of a new drug which is of new active pharmaceutical ingredient(s), including new biological drugs / genetical engineering drugs: NT800,000. 2. Product registration of a new drug which is of new combination or new administration route: NT300,000. 3. Product registration of a new drug which is of a new dosage form, new strength with new indication, new dose unit, or controlled release dosage form, new strength of the same therapeutic compound(s) and the same administration route: NT150,000. GMP Inspections for Western Medicines: 1. GMP Inspections for domestic pharmaceutical manufacturers which is new establishment, relocation, expansion, resumption of operations, or addition of a new active pharmaceutical ingredient, dosage form, process operation, medicinal product: NT120,000; Additional fee of NT20,000 will be charged whenever there is an additional dosage form, biological drug, or active pharmaceutical ingredient. 2. GMP Inspections for foreign pharmaceutical manufacturers 1. Review of a Plant Master File (PMF) of an foreign pharmaceutical manufacturer: NT120,000; Additional fee of NT20,000 will be charged whenever there is an additional dosage form, biological drug, or active pharmaceutical ingredient. New foreign manufacturing site overseas on-site inspection: NT700,000 or above.	**Effective 4 Aug, 2017, new fee is applied to all types of applications**	NDA: 250 USD
	Other requirements		**CFDA issued "Decision on adjusting import drug registration administration" on Oct.10, 2017. (CFDA[2017]No.35) "3 submissions and 3 approvals "policy was cancelled. IMCT data can be used to support NDA submission directly.**		Application for Import License is required after marketing approval and Registration Certificate	Specific country requirement on product labeling on product package, example: generic name, retail price, symbol of prescription drug, the name of importer. Site Master File is requested for non registered overseas factories at submission. Inspection may be conducted against overseas factories if necessary		For the NDA of a New Drug, i) Safety & Efficacy ii) Quality (including Specification and Test Method) iii) GMP iv) DMF reviews are mandatory For new drugs and orphan drugs, Risk Management Plan is mandatory. **RMP is required for new composition of effective ingredient, only change on contents, new administration route and new indication.**		Reference Standard Sample (at least 300 mg) subject to FDA advise	For GDA, the reference product must be the registered product with Singapore HSA			Sample, **Site master file***, Labeling, Package Insert, COA for Drug Substance and Drug Product, Trademark… Registration certificate for trademark in Vietnam is required if there is ® symbol on labeling ***: Decree 54/2017/ND-CP requires Evaluation on following good manufacturing practice (GMP) of MFR.**

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NDA application materials	CMC summary	Requirements and language	Yes (Chinese)	for NCE only (document in English)	Yes, in English	Yes (in Indonesian or English as in part II Quality)	Yes (in Japanese as M2 in CTD)	Yes (M2 in CTD, Korean)	Yes (Part 2 in ACTD) - in English or Bahasa Malaysia	Yes,ACTD Part II in English	Yes (in English)	Yes (In English as M2 in CTD) For the new drug application, TFDA requires to include the API information in detail. API DMF is required.	In addition to ACTD on Quality Part II (or ICH CTD Module 2.3), the Certificate of Analysis for Finished product (3 batches), API (for 3 batches from API manufacturer and DP manufacturer) and Excipients (at least 1 batch from Excipients' manufacturer and DP manufacturer).	QOS of DS, DP Vietnamese or English
	CMC report/body of data	Requirements and language	Yes (Chinese)	for NCE only (document in English)	Yes (English is acceptable as M3 in CTD)	Yes (in Indonesian or English as in part II Quality)	Yes (English is acceptable as M3 in CTD)	Yes (M3 in CTD, English is acceptable, but spec. and test methods for DP and DS with non-pharmacopeial spec. should be prepared in Korean in Application package.)	Yes - in full (Part 2 in ACTD) - in English or Bahasa Malaysia	Yes,ACTD Part II in English	Yes (in English)	Yes (In English as M3 in CTD) For the new drug application, TFDA requires to include the API information in detail.	In addition to ACTD on Quality Part II (or ICH CTD Module 3), the Certificate of Analysis for Finished product (3 batches), API (for 3 batches from API manufacturer and DP manufacturer) and Excipients (at least 1 batch from Excipients manufacturers and DP manufacturer).	Vietnamese or English - Drug substance (S): General Information (S1); Manufacture (S2); Characterization (S3) and Control of Drug Substance (S4), Reference Standards or Materials (S5); Container Closure System (S6) and Stability (S7); - Drug product (P): Description and Composition (P1); Pharmaceutical Development (P2); Manufacture (P3); Control of Excipients (P4); Control of Finished Product (P5); Container Closure System (P7). Reference Standards or Materials (P6); Stability (P8) and Product Interchangeability Equivalence evidence (P9).
	Non-clinical summary	Requirements and language	Yes (Chinese)	for NCE only (document in English)	Yes, in English	Yes (in Indonesian or English as in part III Non Clinical Data)	Yes (in Japanese as M2 in CTD)	Yes (M2 in CTD, Korean)	Yes (Part 3 in ACTD) - in English or Bahasa Malaysia	Yes,ACTD Part II in English	Only for full dossier, in English	Yes (In English as M2 in CTD)	ACTD on Non-Clinic Part III or ICH CTD Module 2	Vietnamese or English 1. Table of content 2. Non-clinical written summary 3. Non-clinical tabulated summaries
	Non-clinical report	Requirements and language	Yes (Chinese) Usually synopsis or abstract of each report in Chinese is required, attached with source report.	for NCE only (document in English)	Yes (English is acceptable as M4 in CTD)	Yes (in Indonesian or English as in part III Non Clinical Data)	Yes (English is acceptable as M4 in CTD)	Yes (M4 in CTD, English is acceptable)	Yes (Part 3 in ACTD) - in English or Bahasa Malaysia	Yes,ACTD Part II in English	Only for full dossier, in English	Yes. (In English as M4 in CTD)	ACTD on Non-Clinic Part III or ICH CTD Module 4	Vietnamese or English. Letter 72/QLD-DK dated Jan 5, 2018 and ACTD guidelines on Non-Clinical data mention that Non-clinical summary is enough. Non-clinical report is only required when VN authority wants to double check the summary. In that case, the content of Non-clinical report includes: 1. Pharmacology 1.1 Primary Pharmacodynamics 1.2 Secondary Pharmacodynamics 1.3 Safety Pharmacology 1.4 Pharmacodynamic Drug Interactions 2. Pharmacokinetic 2.1 Analytical Methods and Validation Reports 2.2 Absorption 2.3 Distribution 2.4 Metabolism 2.5 Excretion 2.6 Pharmacokinetic Drug Interactions 2.7 Other Pharmacokinetic Studies 3. Toxicology 3.1 Single dose toxicity 3.2 Repeat dose toxicity 3.3 Genotoxicity 3.4 Carcinogenicity 3.5 Reproductive and Development Toxicity 3.6 Local Tolerance 3.7 Other Toxicity Studies
	Clinical summary	Requirements and language	Yes (Chinese)	for NCE only (document in English)	Yes, in English	Yes (in Indonesian or English as in part IV Clinical Data)	Yes (in Japanese as M2 in CTD)	Yes (M2 in CTD, Korean)	Yes (Part 4 in ACTD) - in English or Bahasa Malaysia	Yes,ACTD Part IV in English	Yes (in English)	Yes. (In English as M2 in CTD)	ACTD on Clinic Part IV or ICH CTD Module 2	Vietnamese or English 1. Summary of Biopharmaceutic Studies and Associated Analytical Methods 2. Summary of clinical pharmacology study 3. Summary of clinical efficacy 4. Summary of clinical safety 5. Synopses of Individual Studies
	Clinical report	Requirements and language	Yes (Chinese) Usually synopsis or abstract of each report in Chinese is required, attached with source report.	for NCE only (document in English)	Yes (English is acceptable as M5 in CTD)	Yes (in Indonesian or English as in part IV Clinical Data). Indonesia required full clinical study report	Yes (English is acceptable as M5 in CTD)	Yes (M5 in CTD, English is acceptable)	Yes (Part 4 in ACTD) - in English or Bahasa Malaysia	Yes,ACTD Part IV in English	Yes (in English)	Yes. (In English as M5 in CTD)	ACTD on Clinic Part IV or ICH CTD Module 5	Vietnamese or English Letter 72/QLD-DK dated Jan 5, 2018 and ACTD guidelines on Clinical data mention that Clinical summary is enough. Clinical report is only required when VN authority wants to double check the summary. In that case, the content of Clinical report includes:1 Reports of Biopharmaceutic Studies 2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials 3 Reports of Human Pharmacokinetic (PK) Studies 4 Reports of Human Pharmacodynamic (PD) Studies 5 Reports of Clinical Efficacy and Safety Studies 6 Reports of Post-marketing Experience 7 Case Reports Forms and Individual Patient Listing

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NDA application materials	Other required documents	Requirements and language	Application form **Self-checklist of application documents** Summary part of application dossiers: (1) Name of the drug (2) Certified Documents, including CPP **if needs, certification document of drug generic name nomenclature, if apply for brand name, provide trademark inquiry sheet or trademark registration certificate** etc. (3) Objectives and basis for development (4) Self-evaluation report (5) Information about the holder of the drug marketing approval (6) Information about the reference listed drug (7) packaging insert and its reasons, and latest references (8) artwork and labeling	Needs to be in English. General requirement for product registration: 1. Authorization letter from manufacturer – to authorize HKOP register, import and market the product 2. Manufacturer license – original 3. CPP- original 4. Information on the manufacturing facilities and practices of the manufacturer & GMP Certificate which meets PIC/S GMP standards 5. Registration sample – color photos/scanned image to show the product and sales pack/container appearance. 6. Proposed sales pack – color prototype 7. Proposed pack insert - prototype - The following document(s) to support the proposed indication(s), dosage, route of administration and other contents of the package insert (if any): a. a copy of reputable reference b. documentary evidence showing that the package insert has been approved by one of the listed countries 8. Master formula (Batch formula not accepted) - Non-proprietary names of ingredients, colour Index number or E-number for all colourants used should be provided 9. Finished product specifications 10. Method of analysis 11. COA of a representative batch 12. Stability data 13. Bioequivalence data for anti-epileptic drugs The BE studies should be conducted in accordance with World Health Organization guidance on the “Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability” or other international guideline. 14. Safety documents for ingredients with animal origins Additional requirements for NCE registration 1. 2 ICH country approvals 2. expert evaluation reports on the safety, efficacy and quality of the product. CV of experts who draft the report. 3. EU-RMP and/or US-REMS, if applicable. Information on whether any risk management plan activities and mitigation strategies will be implemented in HK. 4. clinical and scientific documentation substantiating the safety and efficacy of the product.	AS described in Schedule Y of the Drugs and Cosmetics Rules 1945 1.1 Comprehensive table of contents (Modules 1 to 5) 1.2 Administrative information 1.2.1 Application in Form 44 and Treasury Challan (fee) 1.2.2 Legal and statutory documents 1.2.3 Coordinates related to the application 1.2.4 General information on drug product 1.2.5 Summary protocol of batch production and control 1.2.6 List of countries where MA or import permission for the said drug product is pending and the date of pendency. 1.2.7 List of countries where the drug product has been licensed and summary of approval conditions. 1.2.8 List of countries where the drug product is patented 1.2.9 Domestic price of the drug followed in the countries of origin in INR 1.2.10 A brief profile of the manufacturer’s research activity 1.2.11 A brief profile of the manufacturer’s business activity in domestic as well as global market. 1.2.12 Information about the expert(s)/ Information regarding involvement of experts, if any 1.2.13 Environmental risk assessment 1.2.14 Samples of drug product	See regulation **BPOM No.24** regarding the Criteria and Procedure of Drug Registration **See Annex 11**	CTD Part I (Module 1) in Japanese 1.1 Table of Contents 1.2 Approval application (copy) 1.3 Various certificates 1.4 Information on patent matters 1.5 Data concerning the origin or background of development 1.6 Information on the use of the drug in foreign countries 1.7 List of similar products from the same therapeutic category with the same efficacy 1.8 Package insert 1.9 Documents pertaining to the non-proprietary name of the drug 1.10 Summary of data pertaining to the designation as a poisonous drug, etc 1.11 Master plan for post-marketing surveillance 1.12 List of attached data 1.13 Other data	Module 1 1.1 Table of contents of Module 1 1.2 Application form or approval application(Copy) 1.3 Signature of the person in charge of preparation of CTD, His/Her information(career) 1.4 Certificate of translator 1.5 Information on the use of the applied drug in foreign countries 1.6 Information on comparison with other similar products available in the Korean market and properties of the applied drug 1.7 Various documents related to Regulations on Safety of Pharmaceuticals Article 4 (1) 1.7.1 Bioequivalence test data/ Dissolution test data 1.7.2 CPP 1.7.3 GMP data 1.7.4 DMF data 1.8 A contract(In case any process during manufacturing, QC test would be outsourced) 1.9 LTOC 1.10 Package insert(draft) 1.11 Other data	In English or Bahasa Malaysia: ACTD Part I :Administrative Data And Product Information Section A: Product Particulars Section B: Product Formula Section C: Particulars Of Packing Section D: Label (Mockup) For Immediate Container, Outer Carton And Proposed Package Insert Other admin doc: CPP, LOA, CA, GMP CE	The following documents as ACTD part I (FDA Circular 2013-019) Sec.A Introduction Sec.B Table of Contents Sec.C Administration data and Product Information 1 Application Form 2 LOA 3. Certificates For import product, a. License of pharmaceutical industry b.CPP c. SMF 4. Labeling 5. Product information 5.1 Package Insert 5.2 SmPC 5.3 PIL	Module 1 (or ACTD Part Ⅰ) documents e.g, Letter of authorizations Declaration Artwork of packaging material GMP certificate Patent declaration Reference country/product approval and approved package insert, if applicable	CTD Module 1 (Taiwan Specific) CTD format was announced in July 2012 and became mandatory for NCE products since Nov. 01, 2012. New Drugs other than NCE, as well as generic products also need to be submitted in CTD format starting from July 01, 2014. **Legalized API GMP certificate from API sourcing country should be provided before NDA approval.**	e-Submission for NCE and new biologics / Vaccine for human use.	CoPP, GMP, Label mockup, Manufacturing profile(a brief format of Plant Master File, following DAV template) Vietnamese or English **- For Site master file: Decree 54/2017/ND-CP requires Evaluation on following good manufacturing practice (GMP) of MFR.** **- For filing dossiers: besides instruction in Cir. 44, letter 72/QLD-DK dated Jan 5, 2018 regulates as follows:** **-Each part should be filed certainly in one or some files and arranged according to the following order:** **+ Part I, Part II** **+ Part III, Part IV** **+ BE/BA report** **+ Evaluation on following GMP of MFR.** **- BA/BE report: should include 01 extra package insert.** **- Part III, Part IV: should be submitted 01 copy of package insert, SmPC, and both soft copy (in USB) and hard copy with same content. Data in soft copy should be written as searchable PDF. Dossier code, dossier type, product name, applicant name should be written on package of USB.**

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NDA Approval review	Review organization	Review organization, Decision organization, Advice committee	Review CDE (Center for Drug Evaluation) Decision CFDA (China Food & Drug Administration) Inspection **CFDI of CFDA (Center for Food and Drug Inspection)**	Review: Drug Office, DOH Approval: Pharmacy and Poisons Board	CDCSO/DCGI (Drug Control General of India) Twelve New Drug Advisory Committees (NDAC) were newly constituted to examine the applications for permissions for clinical trials and approvals for new drugs.	1. Committee of Safety-Efficacy Evaluation with the task of evaluating the safety and efficacy aspect to be discussed in the periodic meeting of National Committee/ KOMNAS. 2. National Committee on Drug Evaluation with the task of discussing formulating, giving consideration and decision of the results of drug evaluation through a periodic forum meeting. 3. Committee of Quality Evaluation with the task of evaluating the quality aspect. 4. Committee of Product Information Labeling Evaluation with the task of evaluating in the aspects of Product Information and Labeling.	Review PMDA (Pharmaceutical and Medical Device Agency) Decision MHLW (Ministry of Health, Labour and Welfare) Advice CDFS (Council on Drug and Food Sanitation)	**In 2017, all the work of review moved to NiFDS and now regional MFDS can also review generic drugs.**	National Pharmaceutical Regulatory Agency (NPRA): Receive and review applications; NPRA's Review Committee will finalise and propose it to the Drug Control Authority (DCA) for approval/rejection. DCA: decide on registrations & licenses, and new/revised regulatory requirements	Philippines FDA Department of Health Food and Drug Administration	HSA (Panel of internal and external reviewers.)	Review center is composed of TFDA and CDE. Drug Advisory Committee provides consultation during the review and further endorses the CDE review if there are special issues. Decision organization is TFDA.	Thai FDA	Review organization: Drug Administration of Vietnam (under the Ministry of Health); expert from Institutions national wide. Decision organization, Advice committee: Drug Committee with members include Ministry of Health, KOLs from Universities and Institutions.
		Number of reviewers ex. Clinical, Non-clinical, CMC, Chemical/Biological	**<As of Jun 2017> All staffs: 650 Including the following review related staff: Traditional Chinese drug: CMC 24, Clinical 13 Chemical drug: CMC 142, Clinical 34 Biological product: CMC 31, Clinical 19 Pharmacology and toxicology: 39 Biostatistics and clinical pharmacology:30 Review administration (including project management): 66** <2020 personnel plan> CDE: 1600 in total	Undisclosed	CDSCO total manpower 327 (as of 2009). No detailed information.		All staffs: **906** Review Dept. : **578** Safety Dept. : **190** (As of **Apr. 1, 2017**) Pharmacology : 384 Medical doctors and Dentists : 42 Engineering : 44 Veterinarian and Toxicity : 25 Biostatistics : 13 Science and agriculture, etc. : 63 Clerical work : 101 (As of April 1, 2012)	MFDS Chemical Administration **- Pharmaceutical Policy : 34** **-** Drug management: **21** **- Narcotics Policy : 10** **- Narcotics Management : 10** **- Pharmaceutical Quality : 21** - Clinical Trials Management : **18** **- Pharmaceutical Approval and Patent Management : 7** **- Pharmaceutical Safety Evaluation : 14** Bio Administration - Biopharmaceutical Policy : **17** **-Biopharmaceutical Quality Management : 15** **- Herbal Medicine Policy : 12** **- Quasi-Drug Policy : 11** NiFDS - Drug Review Management : **47** - Pharmaceutical Standardization : **20** - Cardiovascular and Neurology Products : **17** - Oncology and Antimicrobial products: **18** - Gastroenterology and Metabolism products: **17** - Bioequivalence Evaluation: **16** - Biologics: **16** **- Recombinant Protein Products : 15** - Cell & Gene Therapy: **13** - Herbal medicines: **12** and Regional KFDAs	Total NPRA staff: ~500 Centre for Product Registration: ~120	All staffs : 400 FDA employees		Division of Medicinal Products under TFDA, which is responsible for all drug products, has around 100 active staff including administrative, drug safety and regulation build-up. Among the manpower, about 40-50 staff belongs to new drug, generic drug and clinical trial reviewing force.	See Attached sheet-Number of reviewers (Annex 12) i.e. 2 external reviewers for each section of Clinical, Non-clinical and CMC.	5 Groups, with 3 experts/reviewers in each Group (Administration, quality control, pharmaceutical, pharmacology, clinical)

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NDA Approval review	Review process	Append the flow of the review of applications for new drug with the attached paper.	**CDE acceptance staff receives the ND package and complete the format checking within 5 working days. Application is transferred to CDE system after acceptance, and** then CDE reviews and evaluates in 150 working days after the application enter reviewing plan. **If CDE gives a green light,** CFDA approves it in 30 work days. **CFDA issued "Decision on adjusting import drug registration administration" on Oct.10, 2017.([2017]No.35) "3 submissions and 3 approvals "policy was cancelled. IMCT data can be used to support NDA submission directly.**	Undisclosed	DCGI accept the application in Form 44 and then it is forwarded to NDAC for expert review.	Pre-registration review document until complete documents --> Payment of pre-registration fees-->submit pre-registration --> Evaluation--> Approval Pre-Registration Registration review document --> Payment of registration fees --> Submit registration documents --> Clock start of registration review /Evaluation → Approvable Letter → submit data Commercial Product (copy importation/other data, CoA, Mock up product, sample) → evaluation → Approved Registration Number See Annex 13 Note: * Only NCE/Biological Product Non-Clinical & Clinical were evaluated through Committee of Safety-Efficacy evaluation and National Committee then continue with Committee of Quality Evaluation, and Committee of Product Information. *Others (Generic & variation) were evaluated with Committee of Quality Evaluation, and Committee of Product Information. **Now start with e-reg, pre-NDA & NDA**	See Annex 14	See figures at Annex 15	See Annex **16** (Re DRGD 8. FLOW OF REGISTRATION PROCESS)	Please see Flowchart_PSD_ revised_Aug 2007 Submit to Center for Drug Regulation and Reseach (CDRR)	(See Annex 17)	For NDA submit to TFDA applied to new review process with Refuse-to-file (RTF) mechanism after 60 days from filing **day** and only one-time comments from TFDA. Annex 18	Review process **should take roughly 20% time reduction from previous system. However, FDA has not yet issued official public manual of the new process at the time of report.**	1. Upon receiving dossier submission, Drug Administration of Vietnam (under Ministry of Health) will review and conclude 2. Drug Committee to review. Different parts will be independently evaluated by different experts. 3. Official announcement by Ministry of Health
	Review time	The standard period of time from acceptance of applications to the approval of new drugs.	**Official timeline of CTA / NDA of import drug from submission to approval: 145 working days. Based on RDPAC timeline survey 2017 benchmark, IMCT 7~11months, CTA 14~18months, NDA (priority) 12~16 months, NDA (non-priority) 30~36 months.**	NCE: 7-10 months Generic: 9-12 months	About 12-15 months for marketing approval and registration certificate. About 3 months for Import License.	Timeline of pre-registration 40 working days after completed documents for category 1,2,3,4,5. Timeline of registration 100 working days after completed documents for: a. New Drug & Biological Product that are indicated for the treatment of serious life-threatening human disease, or classify as Orphan drug, or classify for public health program, or new drug which development by Pharmaceutical industry / research institution in Indonesia b. New registration of generic essential copy drug. c. New registration of copy drug with standard electronically information (Stinel). d.Major variation. Timeline of registration **120** working days after completed documents for a New Drug, Biological Product, major variation with: 3 (three) CPP from countries with known good evaluation, system or approved in the country that has applied harmonized evaluation system (EU, EPAR, EMEA). b. New Registration of Copy Product without Stinel. Time line of registration of 300 working days after completed documents:1 CPP from original country. Timeline Renewal product without variation: 10 working days Timeline Export Product: 7 working days **(See Annex 19, Annex 20)**	Review time of FY **2016** (**70** percentile for Priority review, 70 percentile for Standard review) Priority review products: **8.8** months Standard review products: **11.6** months	**120 days (If there is no more query from the MFDS)**	See DRGD Section 8.4.4 Timeline For Product Registration Eg: NCE/NBE: 245 Working days; Generics: 210 working days, etc	Review time of FY 2012 (Median) Priority review products : 9 months Standard review products : 15 months New lead time: 18 months	Reference to GUIDANCE ON THERAPEUTIC PRODUCT REGISTRATION IN SINGAPORE NOVEMBER 2016 – TARGET PROCESSING TIMELINES. APPENDIX 5 TARGET PROCESSING TIMELINES Screening: 25 working days Evaluation: Full dossier: 270 working days Abridged: 180 working days Verification: 60 working days	NCE NDA & BLA standard review: 360 days Priority review: 240 days Streamlined review: 180 days For the non-NCE NDA with efficacy & safety clinical data, the review timeline in TFDA/CDE will extend from 200 days to 300 days. Attached with new milestone figure.	**No official timeframe announced at the time of this report. However, agreed timeframe for approval of new drug (NCE) and biologics is 220 working days; Vaccine 280working days; Biosimilar: 230 working days; Generic: 95-155 days; Generic biologics: 160 days.**	24-30 months

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NDA Approval review	Priority review system	Presence of priority review system, Content of system, Subject drug for priority review ex. unmet medical needs, for serious life-threatening disease	Special review procedure exists, which is appropriate for following applications of new drugs: 1) Active ingredients extracted from plants, animals or minerals, etc. and their preparations not yet marketed in China, and newly discovered Chinese crude drugs and their preparations; 2) Chemical drug substance and their preparations and biological products not yet approved for marketing in China or abroad; 3) New drugs for the treatment of diseases such as AIDS, malignant tumors and rare diseases, etc. with significant clinical advantages; and 4) New drugs for the treatment of diseases, for which effective therapeutic method is not available. For those drugs specified in items 1) & 2), the applicant of drug registration (hereinafter "the Applicant") may apply for the special examination and approval when submitting the application for clinical trials of the new drugs. For those drugs specified in items 3) & 4), the Applicant may apply for the special examination and approval only when submitting the production applications. Priority review and approval procedure is issued on **Dec.28, 2017(CFDA opinions on encouraging the innovation of drug and implementing priority review and approval.2017 No.126)** Scope of priority review and approval 1. Drug with significant clinical value satisfying following conditions: 1).Innovative medicines not yet launched in domestic and overseas market 2).Innovative new drugs with manufacturing site transferred to China 3).Drugs with advanced formulation technologies, or innovative therapies, or sufficient clinical advantage 4). Clinical trial application for drugs whose originator patent will be expired within 3 years; marketing application for drugs whose originator patent will be expired within 1 year. 5). New drug CTA that applicant simultaneously filed the same application and got permitted to conduct clinical trial in EU or US; Drug NDA **or ANDA** manufactured the product in China, which is undergoing simultaneous filing in EU or US and passed GMP/GCP inspection by EMA/FDA (products manufactured with same production line) 6).Traditional Chinese Medicine with clear clinical therapeutic purpose in prevention and treatment for major diseases. 7).New drug listed in the National Major Science and Technology Projects and National Key R&D Plan 2.For below diseases prevention and treatment and can show significant clinical advantage 1)AIDS; 2)TB;3)Hepatitis;4)Rare disease;5)Malignant tumor;6)Pediatric drug;7)Diseases with high incidence or unique in elderly people 3.thers 1). Post approval manufacturing process change of a generic drug with the aim to meet generic drug quality consistency compared with reference products 2).For ANDAs which had been listed in CFDA GCP self-inspection Notice (CFDA notice No. 117 in 2015), if the applicant withdraw the application and then complete research to show quality and efficacy consistency compared with reference product, the later ANDA submission will be eligible for priority review. 3).Urgent unmet medical needs and drugs in shortage. The List should be provided by NHFPC and Ministry of Industry and Information Technology. The list should also be reviewed by CDE and related agencies/ experts invited by CDE. **4).Obligatory license drug when the public health is seriously threatened. The conditions of serious threat and obligatory license procedure will be made by NHFPC.** The priority review and approval is applicable for both IND, CTA and NDA applications. The purpose of this document is to resolve the application backlog issue**, accelerate the pace of marketing for new drug with significant clinical values and generic drug with urgent unmet medical needs.**	usually no; except official request from Hospital Authority upon urgent situation	There is no formal priority review system. Depends on therapeutic area and unmet requirement.	**Reliance system with 120 working days**	The priority review system exists. Orphan drugs receive priority review automatically. New drugs not designated as orphan drugs which target other serious diseases and which are apparently expected to contribute to the improvement of quality of healthcare may be designated as "non-orphan priority review products" based on overall evaluation of the seriousness of the target disease and medical usefulness of the drugs. Designation is made based on the opinions of external experts if an application is submitted with an application for marketing approval. **Early conditional approval system was effective on Oct 20,2017.**	The priority review system exists in regulation but a specific guidance is under preparation. 1) Drugs which target for life-threatening or serious diseases such as AIDS, cancers etc. 2) Drugs of which is deemed necessary because treatment is not possible with existing therapies due to resistance or other reasons 3) Other drugs such as anti-cancer agents, orphan drug, DNA chip etc : recognized by MFDS minister for patients or industrial development 4) Orphan drugs for unmet medical needs	There is no formal priority review system in place. Priority review status will be provided on case to case basis, based on the applicant's justification. Timeline for Priority Review: 6-9 months	The priority review system exists. For serious diseases and life-threatening conditions and which are apparently expected to contribute to the improvement of quality of healthcare based on overall evaluation of the seriousness of the target disease and medical usefulness of the drugs. Consideration is made based on the opinions of external experts if an application is submitted with an application for marketing approval. Please refer to FDA Circular on Facilitation of Evaluation.	No separate priority review system or pathway. Only if product is submitted via Abridged Evaluation (with 1 reference country approval); and meets the pre-defined criteria in the guide (unmet medical need, etc). Grant of priority review is on case-by-case basis, at discretion of the Agency during Screening. Applicant will be notified at the point of acceptance of application, if request is granted.	Priority review designation should be applied and get approval before NDA submission. If your NDA would like to apply as PR process s, granted TFDA agreement before NDA is mandatory. Streamlined review process: For the product which approval by two of three regions from USFDA, EMA and MHLW/PMDA, assessment reports should be provided, and BSE should be waived upon NDA submission.	Priority Review: for product in need e.g. anti-HIV, anti-cancer or product in need as per endorsed from Thai FDA. Abridged Evaluation: effective from 1 Oct 2015 by referring to the approval & evaluation from one of the reference agencies i.e. US FDA, EMA (Centralized system), MHRA, Swiss Medic, TGA, Health Canada, PMDA. The full assessment report including all response to LoQ are required for Thai FDA consideration whether the application can be reviewed under this route.	The Drug Administration of Vietnam and the Department of Medical Device and Construction (as regards in-vitro diagnostic biologicals) will consider priority review for: a. Drugs for special treatments specified in the list of orphan drugs issued by the Ministry of Health; b. Drugs for treatments in emergencies, natural disasters, epidemics; c. Local drugs manufactured on modern GMP production lines, within no more than 18 months as from the date of issuing the GMP certificate. d) Vaccines pre-qualified by the WHO. The abovementioned authorities will consider issuing registration numbers or release written replies before the standard timeline, based on the request of the relevant applicants.

tem	Contents	Detail or Example	China RDPAC/PhIRDA	Hong Kong HKAPI	India OPPI	Indonesia IPMG	Japan JPMA	Korea KPBMA/KRPIA	Malaysia PhAMA	Philippines PHAP	Singapore SAPI	Taiwan IRPMA	Thailand PReMA	Vietnam PG
	Orphan drug system	Presence of orphan drug system, Criteria for designation, Incentive, etc.	CPC &SC released the "Opinions on the deepening the review and approval system and encouraging the innovation of drug and medical device" on Oct. 8, 2017.(No.42) NHFPC will establish the list of rare disease, and is not published till now. For the drugs approved overseas used for the treatment of rare disease can get conditional approval for early marketing. The draft guideline for conditional approval for drugs with urgent needs (including the approved drugs used for rare disease approved overseas) was just issued for comments on Dec.18, 2017. Priority review and approval procedure is issued on Dec.28, 2017(CFDA opinions on encouraging the innovation of drug and implementing priority review and approval.2017 No.126). Rare disease is one of the priority review and approval conditions	No	The orphan drug system does not exists.	Drugs for rare disease will be evaluated within 100 working days. No regulation establishing	The orphan drug system exists. Designation criteria Number of patients Less than 50,000 in Japan Medical need There are no appropriate alternative drugs or treatment methods. The efficacy and safety are expected to be outstandingly greater than those of existing drugs. Possibility of development There is a theoretical ground for using the drug for the target desease and the development plan is acceptable. Incentives (1) Subsidy payment(The total budget for financial year 2013 was 860 million yen.) (2) Guidance and consultation on research and development activities (MHLW, PMDA, NIBIO). PMDA provides a priority consultation system. (3) Preferential tax treatment (4) Priority review (5) Extension of re-examination period The re-examination period for the drugs will be extended up to 10 years.	The orphan drug system exists. Designation criteria -Prevalence is less than 20,000 in Korea -Drugs to treat diseases for which appropriate therapy and drugs have not been developed or have been significantly improved in terms of safety and/or efficacy, compared to existing alternative drugs - Products which do not meet the criteria above can be designated as an orphan drug if it is acknowledged that the limited supply of product would cause any serious harm to the concerned population or the MFDS minister recognizes it. Also there is orphan drug on the development stage in Korea.	For all categories of products namely new chemical entities/new drugs, biologics and generics (including Non-Scheduled Poison product): i. Application for registration that being submitted to National Pharmaceutical Regulatory Agency (NPRA) will only be accepted/ considered after the products have been designated as orphan products. ii. Application for registration must be submitted via online system and with appropriate processing fee. iii. Upon receipt of complete application, the application will be processed within ninety (90) working days. (NOTE: A draft document on "Malaysian Guideline For The Management Of Orphan Drugs" is being finalized. It is proposed to have a 'Malaysian Rare Disease List' endorsed by the Authority, and an evaluation timeline of 120 working days.	The orphan drug system does not exists but we have a DOH A.O. 4 s. 1992 for Compassionate Special Permit for life-saving drugs. This is the closest that we can get in as far guidelines for orphan drugs are concerned.	For a product with a proposed indication that has been designated as an Orphan Drug by at least one reference drug regulatory agency or a product that has been approved by at least one reference drug regulatory agency via an accelerated/fast-track approval, approval under exceptional circumstances or equivalent approval process, the applicant should consult HSA on the eligibility of such a product through the verification route prior to its submission	2015.9.23 Orphan Drug Designation procedure was issued by TFDA, all ODD should submit technical documents according to application form, and need to provide Orphan Drug safety efficacy tracking protocol execute after approval with periodical report to TFDA for review until NDA approval. Also provide Orphan Drug NDA registration schedule to TFDA.	Even there is an orphan drug regulation in Thailand but the intention of this regulation is for the drug in need for rare & serious disease, low usage with no alternatives and face a problem of shortage nationwide. The drug has to be proposed by prescriber's association and be considered for enlisting in the list considered by Thai FDA Subcommittee. The regulatory requirement for generic drug is applied for orphan drug registration.	Yes. According to new Pharma Law (effective 1 Jan 2017), the Ministry of Health will issue criteria and list of orphan drugs. This will be in the form of a Circular, being drafted by the MOH and expected to be issued in the next few months.
NDA Approval review	approval matters	You may append the approval matters with the attached paper.	Approval number ・Marketing License Holder and its address ・Manufacturer and its address ・Non-proprietary Name ・Brand name in Chinese if applicable ・Active ingredients and Contents or Nature ・Dosage form ・Dosage strength ・Packaging size ・Shelf life ・Specification & test methods ・labeling and artwork ・packaging insert		・Generic Name ・Brand name ・Manufacturing Method ・Dosage and Administration ・Indications ・Storage Methods and Expiration Date ・Specifications and Test Method ・Name of the Manufacturing Site used to Manufacture the Product	Before Marketing Authorization , applicant receive Approvable Letter. In the Approvable Letter, it mentions some data to be submit (PI & packaging for commercial production, copy importation for import product only, if necessary NFADC will do on site inspection for local product before issued Marketing Authorization. The Duration between Approvable letter and Marketing Authorization Letter is two years. NAFDC will evaluate the data(with timeline 20 workdays) as requested before issued Marketing Authorization. The Marketing Holder will attached with Registration Form, Approved Package Insert, Approved Patient Information Leaflet	・Non-proprietary Name ・Brand name ・Ingredents and Contents or Nature ・Manufacturing Method ・Dosage and Administration ・Indications ・Storage Methods and Expiration Date ・Specifications and Test Method ・Name of the Manufacturing Site used to Manufacture the Product, Address, License/Accredetation Category, etc.	1. Product name 2. Classification number and classification (prescription drug or OTC) 3. Drug substance and quantity 4. Appearance 5. Manufacturing method (Locations of a manufacturing site of active ingredient and all manufacturing processes shall be described) 6. Efficacy/effectiveness 7. Administration/dosage 8. Cautions for use 9. Packaging unit 10. Storage method and using (validity) period 11. Specification and test method 12. Manufacturer who has the certificate of manufacturing/distribution item license (declaration), outsourcing manufacturer/distributor, contract manufacturer, and importer (including manufacturer) 13. Condition for license ・Product category: License/Declaration, New Drug/ Orphan drug, etc.,	Upon registration of a product by the Authority, the product registration holder shall be notified by the Authority and a product registration number (i.e. MAL number) shall be assigned to the registered product via the system. . Registration status of a product shall be valid for five (5) years or such period as specified in the Authority database (Re DRGD 8.5 Regulatory Outcome)			TFDA will issue approval letter and 1st TPI review draft after NDA granted approval. TFDA will issue notification letter after TPI finalized within 30 days. Applicants can prepare printed TPI and packaging material samples to collect the drug license (IDL) after receiving License Collection Notification. Drug product can be imported and launched to the market after IDL.	Any change require variation submission and approval is required.	

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NDA Approval review	Other information concerning approval review		**The draft guideline for conditional approval for drugs with urgent needs (including the approved drugs used for rare disease approved overseas) was just issued for comments on Dec.18, 2017.** **China DMF was implemented from Nov. 30, 2017. Drug substance, excipient and packaging material companies should submit the registration documents to CDE directly and get the register number from CDE.** **The review of drug substance, excipient and packaging material will be jointly with the review of drug product.** **The implementation of China DMF might affect the timing of submission, review, approval of NDA.**	N/A		NCE should provide API Drug Master File or Internal Monograph as required in Part II Quality of Drug Substance or CEP of API with attachment & GMP Certificate of API's manufacturer. Approval of SMF should also be considered to get approval of registration number.			As stipulated under the CDCR 1984, Regulation 11(1), the Authority may, at any time reject, as well as cancel or suspend the registration of any product if there are deficiencies in safety, quality or efficacy of the product or failure to comply with conditions of registration.			Biosimilar product updated registration guidance was announced on Jun-2015 **and updated specific guidance for biosimilar monoclonal antibodies was announced in Dec-2015**		
NDA Pre-approval inspection	GCP inspection		**CFDA implemented the centralized acceptance from Dec.1, 2017, that means that acceptance of domestic applications, such as IND,NDA,ANDA some supplemental applications were changed from local FDAs to CFDA.** **After the centralized acceptance, drug clinical trial data inspection will be conducted based on the review's needs, not mandatory. It is applicable for both domestic drug and import drug.** **CDE entrusts CFDI to conduct site inspection of GCP compliance during NDA review per CDE review need**	Not required	DCGI may conduct GCP on-site inspection. DCGI will issue instructions to the CDSCO officers/Inspectors to conduct the inspection identifying the clinical trial site/ facilities to be inspected. CDSCO issued 'GUIDANCE ON CLINICAL TRIAL INSPECTION' in Nov. 2010.	GCP inspection for local clinical study in Indonesia. GCP inspection for import product is not required.	The GCP on-site inspection is executed by PMDA to 2 or 4 medical institutions and applicants.	GCP on-site inspection to sites, company and CROs according to MFDS's plan (Pre-approval inspection for pivotal studies in Korea, Regular inspection).	The Guideline for GCP Inspection is intended to provide comprehensive information on National Pharmaceutical Regulatory Agency (NPRA) inspection programme and covers inspections at the clinical trial sites, clinical laboratories, computer systems, sponsors and/or contract research organisations (CRO), bioequivalence studies and independent ethics committee/ institutional review boards. This guideline is also intended to serve as a guide to the sponsors/CROs, local investigators and others on NPRA inspection procedures. Requirements as given in GUIDELINES FOR GOOD CLINICAL PRACTICE (GCP) INSPECTION	The GCP on-site inspection is executed by FDA to medical institutions and applicants. Frequency not clear.	CT in Singapore Pre-marketing approval application inspections are usually done announced and apply to completed clinical trials. Criteria during GCP Inspections: (i)Protocol (ii)Medicines (Clinical Trials) Regulations (iii)SG-GCP, adapted from ICH E6 on GCP (iv)SOPs for conducting clinical trials	The GCP on-site inspection is executed by TFDA around 4-6 weeks after CSR submitted to TFDA in selected medical institutions (depends on the number of involved site)	No requirement	N/A. Applicable for local clinical trials only. When local clinical trial is conducted, GCP inspection is carried out.

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NDA Pre-approval inspection	GMP inspection	ex. On-site inspection, Document inspection, CPP/GMP certificate from source country accepted	GMP overseas inspections are conducted for some import drugs selected by CFDA during the CDE technical review of drug registration application or after IDL approval. **For domestic drug, pre-approval on-site inspection will be conducted based on the review needs.** **CFDA issued the draft of partial revision of DAL on Oct.23, 2017, for domestic drug, GMP inspection will be combined with pre-approval on-site inspection. Currently not formally enforce.**	Document inspection only, CPP/GMP certificate from source country accepted	GMP inspection of Indian mfg. units will be arranged before granting the manufacturing license and periodic review of the mfg. unit The Licensing authority or by any other persons to whom powers have been delegated in this behalf by the licensing authority of India may inspect the manufacturing premises of mfg. units outside India on need basis	For imported product: Based on evaluation of Site Master File, if necessary GMP inspection site will be request by NAFDC. GMP Inspection Report from PIC/S country will be evaluate and can be consider for Waive on Inspection	Since the amendment of the Pharmaceutical Law (PAL) in April 2005, GMP compliance inspections have become a requirement that must be met for marketing approval. Application for GMP compliance inspections for all manufacturing sites listed in the applications for marketing approval must be submitted to the GMP compliance inspection authority (PMDA or prefectures) by each manufacturing site	GMP inspection can be done for manufacturing sites of drug product and drug substance. Basically MFDS conduct on-site inspection (from 2009). For chemical products, some waiver period for on-site inspection would be allowed (5 years for non-sterile products, 3 years for sterile products). Even in case of on-site inspection waiver, GMP documents should be submitted.	On-site inspection required unless exempted. (NOTE: NPRA will perform GMP Inspections on facilities in non-PIC/S countries. This is effective for New Registrations from 1 July 2016, and for Existing Products upon renewal starting 1 January 2017. Inspection exemption for renewals of sites in non-PIC/s countries may be granted if supported by GMP certification from the listed reference and/or PIC/S countries.)	Since 1989, GMP compliance inspections have become a requirement that must be met for marketing approval. For foreign manufacturer, CPP and GMP certificate is being required	Documentary evidence must be provided to certify that the manufacturer(s) complies with current applicable GMP standards. Applicants must submit a GMP certificate issued by a drug regulatory agency for all drug product manufacturing sites including, but not limited to, bulk product manufacturers, primary packagers and secondary packagers. If the drug product is manufactured by a new overseas drug product manufacturing site not previously registered with HSA before 1st April 2004, a GMP Conformity Assessment will be conducted by HSA. Thus, when applicable, applicants must also submit the application form to request for GMP Evidence Evaluation or for an Overseas GMP Audit with the required documents as stipulated in the Guidance Notes on GMP Conformity Assessment of an Overseas Manufacturer	**Applicants should register biological drug substance manufacturers and drug product manufacturers PMF to TFDA. Only chemical drug substance manufacturers can be registered through DMF paper review.** **PMF can be independent applications with NDA filing and the review can be in parallel with NDA.** **PMF and DMF approval should be acquired prior to NDA approval.** **For PIC/s member countries, PMF registration can be conducted by either paper review or on-site inspection.** **TFDA only accept on-site inspection for non-PIC/s member countries.** If multiple manufacturing sites are involved in different manufacturing process of the product (e.g., semi-product, bulk un-labeled, final packaging...), each of the sites has to be registered.	**GMP accreditation was replaced by GMP clearance. The application require for all product application and sites presented in PⅢ On-site inspection will be required for non-PICs site.**	**- Normally, GMP certificate from source country is accepted. But according to Decree 54, (Article 96, clause 3), Inspection can be conducted in cases of:** **a) MFR has registration dossiers of drug product, drug substance which is modified, or suspected of untrue information, data.** **b) MFR has drug product which is concluded as level 1 of quality violation by MOH.** **c) MFR has submitted a dossier of requesting manufacture condition evaluation, but the dossier is concluded as not matching requirement of GMP by MOH.** **(Annex 21)** **- Mutual recognition, acceptance of inspection, audit outcomes from pharmaceutical regulatory authorities with regard GMP compliance shall be applicable to:** **a) Manufacturers of countries on the MOH-issued list of countries with which Vietnam has international mutual recognition treaty regarding GMP inspection outcomes, ICH countries and Australia, except for the cases stipulated in clause 3 (above).** **b) Manufacturers belonging to ICH member countries, Australia and that are inspected and assessed as in conformity with Good manufacturing practice by US Food and Drug Administration, USFDA, European Union member countries, European Medicines Agency (EMA), Australia (Therapeutic Goods Administration, TGA), Japan (Pharmaceuticals and Medical Devices Agency, PMDA) or Canada (Health Canada), except for the cases stipulated under clause 3 of this Article (above).**
	Other inspections	ex. GLP requirement and evaluation	**Since from Dec.1, 2017, for the NDA newly submitted, drug clinical trial data inspection will be conducted based on the review's needs, not mandatory. It is applicable for both domestic drug and import drug.** **1) For local drugs, GMP certificate is not mandatory for NDA Approval. But the manufacturing plant must get the GMP certificate before the drug sale.** (See "NDA" - GMP inspection). GMP inspection to licensed manufacturer is carried out every five years by on-site inspection. An application for GMP renewal should be submitted 6 months before GMP expiration. 2) For import drugs, GMP on-site inspection started recently. Some selected drugs were inspected at foreign site after license approval.	Not required	N/A	In the GMP inspection site, the Laboratory is inspected by NAFDC. The Laboratory inspected following GLP requirements.	"Paper-based compliance inspections" is executed by PMDA to confirm whether data attached to NDA applications accurately reflect the results of clinical trials and other studies, and whether those are made in accordance with GCP, GLP and reliability standards.	- Laboratory should get the GLP certification GLP inspection will be conducted by MFDS if necessary **and valid GLP certification may be issued.**	NPCB also conducts other inspections including for GLP, GCP, GDP, BE centres.	Paper-based compliance inspections is executed by FDA to confirm whether good distribution practice is being implemented.	Non-clinical studies providing toxicology information to support clinical trials should be conducted in compliance with GLP.	**Business undertakings engaged in wholesaling, importing and exporting pharmaceuticals, shall meet the standard of Western Pharmaceuticals Good Distribution Practice Regulations, and shall obtain the western pharmaceuticals distribution license upon the inspection and approval from the central competent health authority.**	No requirement for GLP inspection	

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Clinical trial	Necessary procedures to start clinical trials	The actual procedures to start clinical trials, for example, IND/CTA => import of investigational drugs => IRB etc.,	**IRB permission/Pre-IND communication (if applicable) => IND submission=> IND permission by CDE => Human Genetic Resource (HGR) approval => start of clinical trial.** Clinical trial should be started within 3 years after obtaining CTA. Ministry of Technology and Science intends to raise the legal position of HGR regulation. All clinical trials with the involvement of foreign investment are required the submission and approval of HGR.	a. IRB approval b. if study medication is required to be imported, then Application of clinical trial certificate (CTC) at Drug Office, Department of Health is required.	Clinical trial on new drug shall be initiated after authorization by CDSCO and approval of respective EC. In case of parallel applications, CDCSO will grant conditional approval and note that the trial should start after Ethics approval. Trials should also be registered with CTRI (Indian Registry) before screening patients.	After receiving Clinical Trial Approval Letter from NAFDC, the Clinical Study can be started.	Notice of claimed investigational new drug exemption to PMDA. Contracts with clinical sites should be signed after 30 days from the clinical trial notification (14 days from the second trial onwards).	Regulatory approval: Obtain IND Approval and IRB approval in parallel. IND approval will be taken 30 **working** days, however it will take about 2-3 months normally including additional data submission. Import approval: After above regulatory approval, obtain import approval on clinical study supply, if necessary, in order to initiate the clinical trials. **Under the MOHW, the KoNECT* deals with clinical trial sites and CRO and related regulations.** **The IND approval for Companion diagnostics is required.** ***http://kiis.konect.or.kr/invoke/mainpage/**	Application to The Research Review Committee (RRC) & The Medical Research Ethics Committee (MREC) required. Also, application to the National Pharmaceutical **Regulatory Agency (NPRA)** for clinical trial import license (CTIL) is necessary. Parallel submission is possible. (Re: Malaysian Guideline for Application of Clinical Trial Import Licence and Clinical Trial Exemption Edition 6.1)	Clinical Trial Protocol approval is required. Please see FDA Circular 2012-007 (flowchart).	Reference to: Guidance on Determination of Whether a Clinical Trial Requires a Clinical Trial Authorisation (CTA), Clinical Trial Notification (CTN) or Clinical Trial Certificate (CTC), 1 Nov 2016 Guidance on Regulatory Requirements for New Applications and Subsequent Submissions, 1 Nov 2016	IND approval by TFDA＋ Import permit of IMP → IND approval by IRB (IND in TFDA and IRB can be parallel) → CTA approval by **IRB** → Payment pay to medical institution completely →Site initiation visit. Since final ICF is approved by TFDA, **it is needed to submit the updated ICF that approved by IRB to TFDA to unify the ICF version between TFDA and IRB.** (Notification:1011410615)	Submission to EC and FDA can be done in parallel 1. We have to submit the EC approval letter within 15 days after the approval letter of last site is available 2. When we submit the EC approval letter, if there is any change to documents we submit earlier (i.e. submit SIIC v.1 in IL package but EC approval shows SIIC v.2), we need to submit the revised documents (SIIC v.2) together with EC approval letter. 3. We can start the trial when we receive both EC approval and IL. 4. IL will be valid for 4 years from the date of TFDA's signature on NYM. If product importation period is more than 4 years, we need to apply for new IL but can refer to document in previous package.	Clinical trial should be submitted to Site level first. After receiving IRB/Ethics Committee approval at site level, we can continue submission to health authority (HA). Import License (IL) is only obtained after having HA approval. The CT can be initiated after getting HA approval.
	Necessary data/ documents/ brochures to start clinical trials	Necessary Tox data for initiation of clinical trials (specify local requirement other than ICH-M3 or S6)	Protocol & IB. Usually TOX data aren't required for initiation of clinical trial because all data have been reviewed by authorities. Because site/IRB always follows CTA.	Please refer to the guidelines (Guidance Notes on the Application for Certificate for Clinical Trial/Medicinal Test)	List of necessary Tox data is shown in APPENDIX III of Schedule Y, the Drug and Cosmetics Rules 1945.	Clinical Trial Documents consist of : UK-1 Form, Protocol, Investigator's Brochure, Informed Consent, Documents of trial drugs, Summary Protocol of Batch Production (for Vaccine and biological products).	Generally necessary data and or documents are followed ICH requirement. Sometimes additional reproductive toxicity tastings are requested before clinical trials.	In May 2011, it was amended and inserted into the Enforcement Regulation of Pharmaceutical Affairs Act and, in March 2013, it was transferred to Regulation on Safety of Pharmaceutical Drugs Etc: Korean Good Clinical Practice (KGCP) of Medicinal Products, Specifications for Clinical Trial Control of Pharmaceutical Drugs **Comment: if the question is regarding necessary document, there is no additional requirement other than ICH-M3.**	Application to The Research Review Committee (RRC) & The Medical Research Ethics Committee (MREC) required. Also, application to the National Pharmaceutical **Regulatory Agency (NPRA)** for clinical trial import license (CTIL) is necessary. Parallel submission is possible. (Re: Malaysian Guideline for Application of Clinical Trial Import Licence and Clinical Trial Exemption Edition 6.1)	Generally follow ASEAN requirement. Please see FDA Circular 2012-007	The sponsor should submit the supporting documents (listed in Table 2) to HSA for CTA, CTN and CTC applications. (See Annex 22)	Investigator brochure is required for clinical trial approval.	ICH E6	IB submission is required.

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Clinical trials	Necessary data/ documents/ brochures to start clinical trials	Are there any necessary documents/ brochures outside IND/CTA dossier	CRF & ICF Contract with site IRB approval Human genetic resource approval Some sites require insurance certificate for the clinical trial IMP Certificate Of Analysis (Some sites require GMP certificate), and PI's CV are required.	Please refer to the guidelines (Guidance Notes on the Application for Certificate for Clinical Trial/Medicinal Test)	As per Schedule Y Registration of clinical trial is mandatory in the ICMR Clinical Trial Registry prior to initiation of the trial.	Informed Consent to the patient	Explanatory materials and consent form used for obtaining informed consent	GMP warranty letter or certificate, Insurance certificate	Submission of Investigator Brochure is required.	Documents needed to get patients' consent. Please see FDA Circular 2012-007. Patient informed consent form is already part of the CTA dossier. Suggest answer should be: clinical trial agreements/contracts	Original declaration document of the principal investigator and sponsor has to be submitted	No extra document requires outside IND/CTA dossier. Only for biosample needs to send out to oversea, the statement from central lab is needed.	Material Transfer Agreement	- Informed Consent - IRB approval - Agreement template - PI CV -IMP related documents - Insurance
		Document Language (acceptability of English document)	In Chinese.	preferably English and patients consent form in English and Chinese/Chinese only	English ICF: neccecary to translated into local language on site	Indonesian or English	In principal all documents have to be described in Japanese	Protocol and consent form should be translated into Korean. **However, Acceptability of the document can vary dependent on reviewers.** Also phase I except FIH can be submitted in English	Re: Malaysian Guideline for Application of CTIL & CTX Edition 6.1:- 4.6.2 Language: Application form must be filled in English or Bahasa Melayu. All data must be in English or Bahasa Melayu and must be legible. In cases where supportive documents is not originally in English or Bahasa Melayu, a copy of the document in its original language, accompanied by authenticated translation in English or Bahasa Melayu shall be submitted. The ICF has to be in English, Bahasa Malaysia, Mandarin and Tamil (where required).	English For study documents to be used by healthcare professionals - English. For patient materials - English, plus any language applicable to the locale, eg Cebuano, Hiligaynon, HAS	English	Protocol synopsis should be in Chinese.	Thai and/or English	Vietnamese
	Requirement of domestic clinical data for NDA application, if there is foreign data	Necessary or Not-necessary -Necessity in PK / healthy sbj. -Necessity in patient data	Usually Chinese patient's data including DB study and PK study are needed, which indicates similarity in drug response (i.e. efficacy and safety) with foreign data.	Not necessary	Necessary waiver for clinical trial in Indian population for approval of new drugs, which have already approed outside India can be considered only in cases of national emergency, extreme urgency, and epidemic and for orphan drugs for rare diseases and drugs indicated for conditions/diseases for which there is no therapy (Office order dated 03.07.2014)	Generally, Indonesian patient's data requested which indicates similarity in drug response (i.e. Efficacy and safety) with foreign data for drug which used for family planning programme and other drugs based on request from Authorized body, for example public health programme for TB, etc	In principal PK in healthy Japanese sbj and P2b data in Japanese patients are requested.	Foreign data is acceptable. But bridging data in Korean should be generated.	Not necessary	Local clinical trial is optional; PSUR submission will be required as part of Post-Marketing Surveillance. Comment: For NDA, there is no requirement in the Philippines.	Not necessary	NCE has to submit Bridging Study Evaluation package before or simultaneously with NDA. If BSE successfully waived and at least 2 of 10R countries has approved (2 CPP), foreign data package can be accepted and no need to perform domestic study. If a bridging study is required, local PK or clinical data is required.	Not-necessary	Not necessary for certain cases. Regulation on criteria for domestic/local clinical trials requirements being drafted by Ministry of Health, expected to be issued in the next few months.
	Acceptance of foreign clinical data for NDA	Is there any conditional requirements, for example similarity in PK/PD?	**According to "Technical requirements on accepting overseas clinical trial data (draft)" issued on Oct. 20, 2017, the clinical data from global studies can be recognized by CFDA when meet required standard.**	Yes (for NCE products) Not required for generic products	Foreign Clinical data can be a supportive document, however Indian data (PhaseIII) is must.	Acceptable if the clinical data following GCP and the result based on evaluation of safety and efficacy is good.	Acceptable if the similarity in PK/PD is indicated.	Acceptable; in case of similarity on S&E or PK/PD **between Korean and foreign data (bridging study).**	Yes	Acceptable if the similarity in PK/PD is indicated.	Yes	The following drug items are subject to a bridging study assessment: 1. New chemical entities (NCE); or 2. Genetically engineered drugs, vaccines, plasma derivatives of new molecular entities, and allergen extracts of new molecular entities	Yes	Yes. Regulation on conditional requirements and criteria for domestic/local clinical trials requirements being drafted by Ministry of Health, expected to be issued in the next few months.

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Clinical trials	Required number (or rate) of local subjects in pivotal clinical studies for NDA approval	Please explain for both local and multination al clinical trials, if necessary. *ex.* totally around 100 *ex.* 1/5 of all subjects in multi-nation al studies	**The total subjects' number is decided by the scientificity of the trial design and meets the needs of statistics. There is no lower limit of total subjects number.** For registration purpose, 100 pairs of Chinese patients in pivotal studies is requested whatever local studies or MRCT. Meanwhile, it is requested to show similarity in drug response and safety profile between Chinese and foreign patients in MRCT. China MRCT guideline was published by CFDA on Jan 30 and effective on Mar 1, 2015	Not specified	P-I: 1-2 centers. At least 2 patients. P-II: 3-4 centers. At least 10-12 patients at each dose level. P-III: a. The drug already approved/marketed in other countries: at least 100 patients distributed over 3-4 centres. b. The drug is a new drug substance discovered in India and not marketed in any other country: at least 500 patients distributed over 10-15 centres. (According to draft guideline on Clinical trials and New Drug Approval 2011 - 2012) However Now a days DCGI asks for 200 patients or more for Phase III studies for the drug approved/marketed in other countries depending on the prevalence of disease and therapeutics area. (According to draft guideline on Biosimilars : Annex 23) There is a provision to consider 100 patients for Phase III and 200 patients for Phase IV trials or a combination of 300 patients for both Phase III + Phase IV trials combined.	Local clinical trial is needed for new drugs for family planning programme, TB drugs, and others drug based on request from Authorized body.	It is requested to show the consistency in drug response between Japanese and foreign patients in multi-regional clinical trials based on **ICH E17**	No definite requirement. For both local and multinational clinical trials, statistically meaningful number of subject is needed.	N/A	There is no required number of local subjects in clinical trials for NDA approval. For PMS studies, it is suggested (but not required) that there should be 3,000 subjects. Comment: PhIV/PMS is still required but number of patients will be set by the type of the drug and the disease set by FDA (FDA Circular 2013-003)	N/A. But in the HSA CTC application, applicant has to declare expected number of subjects to be enrolled from each site.	It is request to show the consistency in drug response between Asia population and Caucasians in multi-national clinical trials. For this purpose, at least 15-20% of all subjects is hopefully to be Asian population. As for NDA approval, it was divided to two situation. Non-CPP: Early clinical development in Taiwan, Ph 1+ Ph 3 or Ph 2+ Ph 3.Taiwan patient No. for Ph1 study :≧10, for Ph 2 study: ≧20, for Ph3 study:≧80. One-CPP: One of Ph 1, Ph2 or Ph3 study in Taiwan. Taiwan patient No. for Ph1 study :≧10, for Ph 2 study: ≧20 or 10%, for Ph3 study:≧80 or 10%, or Multinational Ph3 study: total sample size ≧200 then Taiwan No.≧30 or 5%, total sample size ＜200 then Taiwan No.≧10.	Not-necessary	N/A Given the current legislative developments in Vietnam (new Pharma Law takes effect from 1st Jan 2017, guiding legislations are being drafted and not yet issued), old regulations such as Circular 03/2012/TT-BYT will continue to take effect as long as it does not contradict with the new Pharma Law.
	Practicable number of clinical centers or sites in the country	# of sites with facility of clinical trials Is there any license system for clinical study site?	**CPC&SC issued the "Opinions on deepening the reform and encouraging the innovation of drug and medical device (No.42)" on Oct.8, 2017. Clinical trial site will not get a license from CFDA. The site can record-filing on CFDA website, then conduct the clinical trial. More resources of clinical sites can be used in China, including government/private hospitals, research institute, and university.**	Practicable no. of clinical study sites not specified; No license system for clinical study sites; however, the clinical study sites are usually university or government hospitals.	More than 1000 sites	It around 50 clinical centre.	Clinical trial can be initiated in many study sites. No license system for clinical study site	Certified sites by MFDS: **187 sites(Jan. 2018)**	The CRC has a network comprising of 33 centres in MoH hospitals, collaborations with 5 Private hospitals' and affiliations with 3 University hospitals, plus access to 120 other MoH hospitals	Clinical trial can be initiated in many study sites. Protocols should be evaluated by IRB/EC. Comment: A clinical study site should have an ethics committee that is accredited or is ongoing accreditation procedures by PHREB.	There are 13 public hospitals and 16 private hospitals which can conduct clinical trials.	**Around 126 centers/teaching hospitals** https://www.cims.tw/ch/taiwan_irbs	**19 officially recognized sites (IRB/EC site)**	Practicable no. of clinical study sites not specified; No license system for clinical study sites; however, the clinical study sites are usually university or State hospitals.
	IRB system for clinical trials	Installation of IRB/EC in sites Is there National IRB?	**CPC&SC issued the "Opinions on deepening the reform and encouraging the innovation of drug and medical device (No.42)" on Oct.8, 2017. Regional Ethnic Committee will be established, to guide the EC review work in the sites and entrusted by sites who don't have the EC to conduct the EC review work.**	Yes. An IRB for each cluster of hospitals	Independent Ethical Committee (IEC) & Institutional Ethics Committee No National IRB	There are National IRB system.	Institutional IRB.	There is not the national IRB but the Institutional IRB	Institutional and national IRB (MREC) available depending on sites. There are 13 IRBs/IECs in Malaysia registered with the NPRA. These include the Ministry of Health Medical Research and Ethics Committee (MOH MREC), the Penang Ethics Committee and ethics committees from universities and private hospitals. Clinical trials conducted at these sites have to be approved by the respective IRB/IEC	Institutional IRB/Ethic Committee. The general guidelines on CT may be referenced from the "National ethical Guidelines for Health Research 2011 edition. Another reference is FDA Circular 2012-007 that recognize ERB/ERC for purposes of conducting CT of Investigational Medicinal Products and it also validates the agreement between the FDA and PNHRS or Philippine National Health Research System which includes the establishment of a clinical trial registry. Comment: Sites with its own EC should be accredited by PHREB or are currently undergoing accreditation process this year. For sites that do not have its own EC, the institutional ethics review board of UP-PGH can oversee and perform EC duties for that site.	Singapore has 2 clusters of public hospitals. 1 cluster is under NHG DSRB (National Healthcare Group Domain-Specific Review Board) and the other cluster is under SingHealth CIRB (Centralised Institutional Review Board). For private hospitals, they have their own IRB/EC	C-IRB is composed of 33 hospital IRBs. Some other sites may also take fast track for c-IRB approved trials. J-IRB covers 78 hospitals. (this information is collected from C-IRB website) NRPB-IRB is composed of 20 hospital IRBs. Every medical center has its own IRB. There is different requirement between different IRB.	Available Yes, National IRB or Central IRB.	Yes. There are EC at both Site and health authority level

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Clinical trials	Prevalence of GCP in clinical centers		GCP is observed in all clinical sites.	Yes	Yes. GCP is observed in all clinical sites.	GCP is observed in all clinical studies	GCP is observed in all clinical sites.	**GCP is mandatory**	GCP is observed in all clinical studies. (Local recognized GCP certificate is compulsory for all investigators.)	Yes, GCP is observed in all clinical sites. ICH Guidelines, GCP E6 Comment: Mandatory for the Investigators and the site staff who are directly involved in the ccnduct of the clinical trial.	GCP is observed in all clinical studies	GCP implementation in all clinical trials is mandatory since 1997.	A must	Yes
	Investigators	ex. about 50 physicians have been trained in US/EC	Uncountable number of physicians in China.	Yes	Large pool of trained Investigators in diverse therapy areas	Investigator must have GCP training before the trial and understand the protocol comprehensively in order to conduct the trial in accordance to GCP. No requirement investigator have been trained in US/EC	Uncountable number of physicians in Japan	Uncountable, **lots of investigators in Korea. Mandatory educational systems exists in Korea. However, the number of investigators is not something the government should manage or control.**	The CRC has access to more than 550 clinical investigators.	Uncountable number of physicians. In addition to CVs, IRBs require that investigators undergo GCP training and this should be renewed or refreshed every 2 years.	No info	TFDA regulated necessary training hours needed for GCP and ethical then qualified to conduct clinical trial. No actual number of investigator to get GCP training.	No information (Beware of USFDA blacklist)	N/A
	Investigational drug	Condition of customs procedure	Tax and custom clearance. If imported investigational drugs to be used, CTA is necessary for Customs procedures and clearance.	Application of Import License based on the approved CTC	Permission to import of investigational product shall be obtained by applying for a test license. The application should be made in Form 12.	Sponsor request to import unregistered product was to NAFDC. Approval letter for Importation from NAFDC is used for release product in the customs.		**Import permit should be gotten from Korea Pharmaceutical Traders Association in advance. Also, certification should be given from Regional KFDA as an "investigational drug".**	Clinical trial import license and proper clearance required.	Yes	Reference to Guidance on Clinical Research Materials, 1 Nov 2016	It needs to get import permit that issue from TFDA, then Customs will allow investigational product import into Taiwan within the quantity on the import permit.	Condition of customs procedure - import license, CoA, Air waybill, invoice, License Per Invoice, National Single Window	Application of Import License based on the approved CTC
		Investigational drug labeling (requirements and language)	Chinese label is needed. According to China GCP (2003 version), "only used for clinical trial" should be indicated in the label of investigational drug. In China IMCT guideline, the following information should be included in the label of investigational drug: sponsor name, trial number, kit number, dosage and administration, only used for clinical trial, dosage form, administration way, strength, batch number, storage condition, expiry date etc.	IP name; Strength, dosage, storage condition; manufacturer - English or English and Chinese	• "For Clinical Studies only" • Name or a code number of the study • Name and contact numbers of the investigator • Name of the institution • Subject's identification code	In Indonesia language for clinical trial in Indonesia. In Clinical trial Multicenter / country English language is acceptable.	Japanese label is needed	1. "For clinical trial only" 2. The name of investigational drugs or identification marking (in case of blind design, both study drug and comparator should be indicated in the IP label), if necessary, formulation, administration route, quantity, assay of active ingredient or potency can be included in the label. 3. The lot number or code number 4. Name, address and telephone number of business/person who received the IND approval 5. The expiry period 6. The storage condition 7. "Keep out of reach of children" except when the product is for use in trials where the product is not taken home by subjects. 8. Reference code(clinical trial can be identified) 9. Subject identification number, treatment number, visit number. **Language should be in Korean and also should follow KGCP.**	Refer to CTIL guideline. English acceptable.	Yes, in English Comment: Import license is required for each shipment of Investigational Drug. The government body responsible for issuing this is the Phil FDA.	Reference to Guidance on Labelling of Therapeutic Products and Medicinal Products Used in Clinical Trials, I Nov 2016. Please see page 11. (See Annex 24)	Label has to be prepared in traditional Chinese under PIC/S GMP regulation.	Require product name or random number/subject no., dosage, amount, manufacturer, expiry date and the content of 'this product is used for clinical trial only' in Thai. **Comprehensive list.** **(1) Non-proprietary name or drug code including strengths of active substance(s)** **(2) Study number and/or study title** **(3) Batch number** **(4) In case of self-ministration drug, e.g. home medication, etc., Thai or English instruction on how to use drug, which is understandable by subjects, should be provided** **(5) Name and address of the sponsor** **(6) Expiry date or retest date.** **(7) Storage condition** **(8) Indicate the sentence "for trial use only" in Thai**	Required in Vietnamese. "For clinical trial only".

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Clinical trials	Availability of multi-national CRO	*ex*. local branch, many local CROs	Multi-national CRO is available in China, such as Quintiles, ICON, Covance, ICN, PPD, PRA, RPS etc	Yes (domestic and multi-national companies)	Multi-national CROs like Quintiles, Parexel, PPD, ICON etc are available	Multi-national CRO is available in Indonesian	Multi-regional CRO is available in Japan	**Please refer to KoNECT* site.** ***http://kiis.konect.or.kr/invoke/mainpage/**	8 International CROs And 4 locally incorporated CROs	Multi-national CRO is available in Philippines	Available	Multi-national CRO is available in Taiwan	There are many international CRO in Thailand.	Yes
	Adverse reaction reporting during clinical trial	*ex*. SAE: report to Authority within 7 days etc.,	SAE: it is requested to report to the relevant authority in 24 hours after knowing the event.	Serious and unexpected adverse events - Fatal/life threatening: no later than 7 calendar days; submit report in 8 additional calendar days - Others: 15 calendar days NSAE and serious expected adverse events: - Brief summary at the end of trial	NewGazette GSR889(E) was published on 12 Dec. 2014. The rules of free medical management and financial compensation on 122DAB(30 Jan 2013) was amended. Any report of serious adverse event of death occurring in clinical trial, after due analysis shall be forwarded by the Sponsor to Chairman of the Ethics Committee and Chairman of the Expert Committee constituted by the Licensing Authority as defined under rule 21(b) under Appendix XII with a copy of the report to the Licensing Authority and the head of the Institution where the trial has been conducted within 14 calendar days of occurrence of the serious adverse event. While current provisions require payment of compensation in cases of injury or death of a subject occurring in a clinical trial due to the failure of an investigational product to provide the intended therapeutic effect, the notification changed this clause with adding supplementary item. It is effective from 12 Jun. 2015.	Investigator should report all serious unexpected adverse event to sponsor /CRO as soon as possible after known it, if there are some next adverse event, report a.s.a.p. until end of event. Sponsor should report all serious adverse event in Clinical Trial include death to Head of NAFDC and Ethics Committee within 15 days start from known the event, if there is next event, report it a.s.a.p until end of event.	Case of death by unknown adverse event have to be reported to PMDA within 7 days. Case of death by known adverse event and unknown serious adverse event have to be reported within 15 days.	• Death or life-threatening SUSARs: within 7 days from the moment that the sponsor recognizes (the detail information should be additionally reported within 8 days from the first report) • Other SUSARs: within 15 days from the moment that the sponsor recognizes it	Death or possibly leading to death SAEs within 7 days, other SAEs within 15 days in CIOMS-I Form. Please refer to Malaysian Guideline for Safety Reporting of Investigational Products for more details.	SAE: report to Authority within 3-7 days. Please see FDA Circular 2012-007 (p.9-10) Comment: As per A.O. 2014-0034	Fatal or life-threatening unexpected ADRs: within 7 calendar days. All other serious unexpected ADRs: within 15 calendar days. (See Guidance for Industry: Safety Reporting Requirements for Clinical Drug Trials)	SUSAR: report to Authority within 7 days for death and life threatening case, within 15 days for other cause. It is same as international rule.	To FDA: Only Local SUSAR, death or life-threatening related to study product within 7 days, other local SUSAR within 15 days (from sponsor awareness) To site IRB/EC: Death or life-threatening within 7 days, other SAE within 15 days (FERCIT)	**Acc.to Decision 62/QD-K2DT dated June 2, 2017:** **CRO, and other relevant organization, person have responsibility to report AEs/ SAEs:** **a) AE/SAE occurred in VN territory:** **- For death or life-threatening SAE: urgently reported within 7 working days when having SAE information.** **- Other SAE: within 15 working days when having SAE information.** **- In case of additional information on medical happening of SAE, or happening of patients with SAE, or change of relationship between SAE and investigational product: within 15 working days since the day having additional information.** **b) AE/SAE occurred outside VN territory (VN is one of countries in multi-national CT): All SAEs which makes trial protocol change, or make trial pause in one country member should be reported to Administration of Science Technology and Training- MOH, EC of MOH, National center of ADR and drug information as CIOS form or appendix 1 of the Decision 62.** **- Timeline of report: not more than 15 working days since the day having decision on trial protocol change, or trial pause.**
	GCP site inspection		-GCP inspection There are 30-50 cases per year of Triggered Inspection conducted by CFDA or PFDA which are triggered by complaints/requests from CDE/CFDA. Annual inspection plan-based Routine Inspection conducted by PFDA is also available. -Clinical trial data inspection Since Jul.22, 2015, CFDA conducted clinical trial data inspection for each NDA to improve the clinical trial quality in China. Only pass the inspection, drug can be approved for marketing. The criteria for inspection is not GCP but the key points for clinical trial data inspection (No.228) issued by CFDA. **From Dec.1, 2017, clinical trial inspection was changed to conduct based on the review needs.**	Accredited to the sites by separate parties	Yes.	NAFDC will do GCP site inspection during clinical trial	After NDA, PMDA inspects the applicant and 2-4 medical institutions based on GCP.	**Yes, by the MFDS**	Yes		Will be conducted by the HSA Clinical Trial Branch, on locally conducted clinical trials.	**TFDA will conduct GCP inspection at sites for TW NDA registration purpose studies after CSR is submitted. For oversea GCP inspection, TFDA and industries are still under discussion.**	Yes	Yes GCP inspection is limited to domestic clinical site only.

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Manu -facturing	Acceptance test for Import drug	How the specifications & test methods for acceptance test of import drugs are set in your country?	QC test for 3 batches should be conducted by NIFDC. Specification and test methods should be approved by CFDA at the stage of NDA. **From Dec.1, 2017, QC test, review of specification and test methods by NIFDC were conducted based on the review's needs.**	Based on the approved particulars.	Specifications and test methods are to be set according to registered specifications. Official in pharmacopeia or in-house specifications with validation data are available.	Specification and test methods are following Indonesian Pharmacopeia, USP/NF, BP, EP, JP.	Specifications and test methods are to be set according to JP.	Specification and test methods are usually set in accordance with official compendium or registered in-house specifications.	Both compendial and non-compendial specifications are accepted.	Specifications and test methods are to be set according to registered specifications.	To be tested according to approved specifications & test methods	There is no need to have acceptance test in Taiwan except for vaccine, and plasma produced products. TFDA will provide certification seal after TFDA acceptance test. **TFDA will issue product releasing certificates instead of providing serial sealing label on the individual products.**	Both compendial and non-compendial method are acceptable	Yes. Request sample in first time dossier of NDA. Review based on reference Pharmacopoeia and Vietnamese Pharmacopoeia.
	Pharmacopeia	What is standard pharmacopeia? What is other accepted pharmacopeia? ex. USP/NF, JP, EP	All import drugs and domestic drugs should follow Ch.P2015.	BP, USP, EP and JP. In-house specification for NCE would be accepted by DOH.	If a DP/DS is official in the Indian Pharmacopeia(IP) than must conform to IP if not official in IP than BP/USP/EU Pharmacopeia standards are to be followed	Standard Pharmacopeia: Indonesian Pharmacopeia Other accepted Pharmacopeia: USP/NF, BP, EP, JP	JP (Japanese Pharmacopeia)	Standard: KP Accepted: JP, Ph. Eur(EP), USP(NF), BP, Deutshces Arzneibuch, Pharmaacipee Francaise	The main pharmacopeia references are BP and USP. Others are JP and EP	JP, USP/NF, EP, BP, PP (Philippine Pharmacopoeia)	Pharmacopeias accepted by HSA are Ph. Eur., USP, BP, and JP	USP/NF, EP, JP, and Ch.P. are all acceptable.	USP 34, NF 29 and supplements, BP 2011 volume 1-5 and Addenda, the fourth edition of IP and supplements, Thai-pharmacopoeia II volume I part 1 and supplements, the seventh edition of EP and supplements plus updated revision. **In addition, the latest version of international pharmacopoeia as announced is accepted.**	Standard: Vietnam Pharmacopoeia Reference (USP/NF, JP, EP, BP, USP, Ph.Eur)
	GMP system	What is current GMP requirements? ex. PIC/S	Chinese GMP 2010 version (MOH order 79)	PIC/S has been adopted for local manufacturer and overseas manufacturer.	Indian GMP as outlined in Schedule M of DRUGS AND COSMETICS RULES, 1945 Then, these regulations and guidelines (Schedule M) were revised in order to be based on WHO-GMP in 2003.	PIC/S GMP & **WHO GMP** requirements	Japan has been a member of PIC/S GMP since July in 2014.	As South Korea joined to PIC/S membership in July, 2014, MFDS has been prepared a provision to harmonise the Korea Good Manufacturing Practice (KGMP) of Pharmaceutical Drugs with PIC/s guidelines and issued, MFDS Notification No. 2015-35 in June, 2015. The validation of GMP certificate is for 3 years from the completion of GMP inspection.	The current PIC/S Guide to GMP for Medicinal Products and its Annexes have been adopted as the standard used by NPRA to assess the GMP conformity of manufacturers.	Philippine applied for membership in the PICS (June 2009) --> PFDA has officially adopted the PICs Guidelines for GMP of medicinal products as per AO 2012-0008	PIC/S GMP requirements	Taiwan is one of the PIC/s member countries since Jan 2013. Sourcing country drug substance GMP certificates (original and legalized by Taiwan Embassy) are required in the application of NDA and drug substance post-approval changes (including drug substance license or drug product license), and license renewal. The detail requirements of the qualification of sourcing country GMP certificates, please refer to TFDA website. (http://www.fda.gov.tw/TC/siteListContent.aspx?sid=301&id=9897&chk=666e6379-8ed5-4983-9c21-553c03d00144&param=pn%3d1%26sid%3d301#.WBFY1k3_rIX) Q&A section (http://www.fda.gov.tw/TC/siteContent.aspx?sid=4601#.WBFYqC197IU)	Thai FDA is PIC/s country member effective from 1 Aug 2016.	Current regulation (Circular) on GMP requirements being drafted following the new Pharma Law (effective 1 Jan 2017). Previous regulation: a) Local manufacturer must have the certificate of eligibility for drug trading and "Good Manufacturing Practice" certificate (abbreviated as GMP) according to the schedule of the applicable GMP by Ministry of Health or the certificate of eligibility for drug trading in case the manufacturer must validate the production conditions when being granted the certificate of eligibility for drug trading. b) The foreign drug manufacturers must have the criteria "Good Manufacturing Practice" - GMP equivalent or higher principles and standards "Good Manufacturing Practice" as recommended by the World Health Organization international (WHO-GMP). In case of the certification "Good Manufacturing Practice - GMP" or certificate of pharmaceutical products - CPP doesn't not specify that the manufacturer got GMP-WHO certificate, the applicant must provide the evidence to prove the principle, GMP standard that manufacturer got not less than GMP-WHO standard. For in vitro diagnostic biologicals, manufacturer must get GMP standard or ISO standard or other equivalent certificate. In case of doubt about the condition of production or drug quality, Drug Administration or the Department of Medical device and Construction (for in vitro diagnostic biologicals) will conduct audits manufacturing facility before or after granting the registration number.

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Manu -facturing	GMP system	Please describe GMP evaluation process by the authorities. ex. GMP clearance/ accreditation required before NDA ex. On-site or document inspection ex. Acceptability of GMP certificate from original country	**1) For local drugs, pre-approval on-site inspection will be conducted based on the review needs.** **CFDA issued the draft of partial revision of DAL on Oct.23, 2017, for domestic drug. GMP inspection will be combined with pre-approval on-site inspection. Currently not formally enforce.** 2) For import drugs, GMP on-site inspection started recently. Some selected drugs were inspected at foreign site after license approval.	For overseas manufacturer, inspection is usually not required if the manufacturer complies with the Pharmaceutical Inspection Co-operation Scheme (PIC/S) GMP standards. For local manufacturer, an inspection by pharmacist inspector will be conducted at the company's premises within 2 weeks from the submission of a new application. The application will be considered by the committee. If approved, a license valid for 1 year will be granted.	GMP inspection will be arranged before granting the manufacturing license and periodically The Licensing authority or by any other persons to whom powers have been delegated in this behalf by the licensing authority of India may inspect the manufacturing premises of mfg units outside India on need basis.	The manufacturer which is first time register export product to Indonesia should provide SITE MASTER FILE (SMF) for GMP evaluation. After evaluation of SMF, the NADFC will approve to continue registration process of NDA or request site inspection. Before inspection, the manufacturer should provide Pre-inspection document for preparation of the site inspection. After inspection, the NADFC will issue approved or reject to continue registration NDA. The inspection report from other Authorized Health Authority can be consider for Waive of Inspection to the Manufacturer.	GMP compliance is pre-requisite for obtaining a Product Marketing Approval in Japan (see Pre-approval inspection, GMP). GMP inspection to licensed manufacturer is carried out every five years either by on-site or document inspection.	Pre-approval GMP review: 1) documents (Minimum requirements) -based 2) Site inspection. In case MFDS visits the same site within 5 years for another products and submitting PIC/S country's inspection report (contents should be detail enough to fulfill MFDS requirement), on-site inspection could be waived. (In case of sterile product (DS & DP), waiter within 3 years, In case of biologics, exemption period is maximum 2 years.) Even though MFDS does not visit the site, documents for GMP review should be submitted. **In case a major change for sterile products manufacturing site happens such as reconstruction, extend a building, HVAC change, etc., despite of the same site, pre-approval GMP review is required** 3) Supplementary request after site inspection	NPRA is a PIC/S member and follows the PIC/S Guide to Good Manufacturing Practice for Medicinal Products. PRH must provide acceptable evidence to show that the manufacturer of the product follows an internationally accepted standard of Good Manufacturing Practice (GMP) and recognized by the Authority in Malaysia. NPRA will perform GMP Inspections on facilities in non-PIC/S countries, unless exempted.	GMP compliance (or better yet GMP Clearance) is a pre-requisite for the site registration of the manufacturing site and source into the License to Operate, which then is a requirement in obtaining a Product Marketing Approval in Philippines. Current evaluation for foreign sites is based on documentation review but the FDA may require on-site inspection depending on results of documentation review. GMP inspection of licensed local manufacturer is conducted by local FDA every 2 years, GMP recognition system of overseas manufacturing sites was introduced as per AO 2013-0022.	Domestic manufacturers in Singapore are subjected to licensing and periodic GMP audits by HSA. All new overseas manufacturers will be subjected to a GMP Conformity Assessment by HSA. Refer to GMP CONFORMITY ASSESSMENT OF AN OVERSEAS MANUFACTURER, May 2016	PMF registration: For manufacturing plants located in PIC/s member countries, it can be applied either by documents review or by on-site inspection. For manufacturing plant located in non-PIC/s member countries, it can be applied by on-site inspection. GMP follow-up: It will be taken every 2-4 years depending on the TFDA risk management assessments. Applicants can apply GMP follow-up by document review or on-site inspection (sometime TFDA will proactively request on-site inspection around 1 year before the periodic follow-up). Sourcing country GMP certificates are mandatory documents for PMF registration. PMF registration and NDA are individual applications and their reviews / approvals are in parallel. (PMF approval letters can be supplemented before NDA approval)	**GMP accreditation was replaced by GMP clearance. The application require for all product application and sites presented in PⅢ** **On-site inspection will be required for non-PICs site.**	Current regulation (Circular) on GMP requirements being drafted following the new Pharma Law (effective 1 Jan 2017). Acceptance of GMP certificate from original country.
		Please describe frequency/number of on-site inspections to domestic/overseas manufacturers by the authorities. ex. number of inspections conducted in last year	The overseas manufactures for 34 products of some foreign companies were inspected by CFDI in 2015. 28 products were inspected in 2014. (http://www.cfdi.org.cn/ccdweb/view?oid=menunews&ntyp=D01) The list of products to be conducted overseas GMP on-site inspections by CFDA in 2016 is issued and includes 49 import drugs. (http://www.cfdi.org.cn/ccdweb/main?fid=open&fun=show_news&nid=7210) **In 2017, there are 39 products to be conducted overseas GMP on-site inspections by CFDA, including 11 products in the list of inspection 2016 but not inspected in 2016.**	Since the manufacture license valids for only 1 year, inspection will be made at least on annual basis for local manufacturers	Annually. For overseas, CDSCO started inspection of Pharmaceutical firms for import registration of drugs. Six on-site inspections in 2011 for DS manufacturing site in China, and four China drug manufacturing sites in 2012.	Every month there are on site inspection to domestic and overseas manufacturers by the Authorities. Almost Asia countries are inspected.	Number of on-site GMP inspection to overseas manufacturer in FY **2016 was 79. About 85% are in Asia.**	**Inspection period is every 3 years. MFDS doesn't publicize the number of inspections for internal reasons. Instead, they make open the total number of manufacturers complying with KGMP. As of 2015, there are a total of 412 companies including 273(finished drugs), and 139(raw materials).**	The number of GMP Inspections conducted in **2016** was **470**. Of these, the number of inspections on pharmaceutical premises was **94**.	No details as of this moment. For overseas manufacturing sites, please note that FDA Phils may require conduct of on-site inspection where GMP certificate submitted was issued by a non-PICs member Regulatory Authority.		Overseas inspection in **2017: 22**. No domestic data publication available.	- Domestic: Non-sterile drug: every 3 years Sterile drug: every 1.5 year - Overseas: if needed FDA's plan on inspection: (Note: The FDA is working on the update of this regulation, but not come out yet at time of report) • Routine Inspections ~ 60-70 plants/year • Special inspection in special case • And there will be Follow up Inspection which they are setting on criteria (may be from Risk Assessment). **GMP accreditation was replaced by GMP clearance. The application require for all product application and sites presented in P.3.** **On-site inspection will be required for non-PICs site.**	N/A Current regulation (Circular) on GMP requirements being drafted following the new Pharma Law (effective 1 Jan 2017).

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Manu -facturing	DMF system	Please describe DMF system (or plan for introduction). Is DMF mandatory or optional?	**Yes, China DMF system was established and implemented from Nov.30, 2017.** **Applicable scope is drug substance for drug product with registration cat. 2.2, 2.3, 2.4, 3, 4, 5, and excipient and packaging material for drug product with all registration categories. So it covers both import drug and domestic drug.** **It will have an impact on the submission and review timeline of import drug after the actual implementation of China DMF.** **CDE will issue the explanation document to specify how to implement China DMF, especially for overseas excipient and packaging material used for import drug very soon.**	Not specified	No DMF system exists. (Note: CMC part of application dossier is called DMF, but it does not mean DMF system as in other countries.) API DMF as per ICH CTD is also acceptable.	DMF (open & closed part) of API are needed as mandatory for generic and NCE API.	The submission of MF (Master File) is optional. Drug substance, Intermediate, New excipients, Packaging materials etc. are subjects of MF.	NCE and API for generics should be submitted DMF since 2002. But all APIs should be registered by 2015, but not completed yet. (Every year, MFDS announced the list of APIs which should be registered.) Only drug substance(API) is subject of DMF. API for newly registered sterile injection should be submitted DMF since 2017.	A DMF is required for API registration, and may be replaced by a CEP or full details of Part II S ACTD. API registration is being implemented in phases.	With the adoption of the ASEAN CTD, maintenance of DMF is mandatory based on requirements stipulated on the ASEAN Variations Guideline.	If a Drug Master File is submitted, then a separate declaration letter issued by the applicant must also be provided to state that the DMF submitted to HSA is identical to that submitted to the chosen reference drug regulatory agency. Appendix 11 describes the DMF process and documentary requirements for DMF submission	DMF is only applied to chemical drug substance and their drug products. Drug substance DMF is mandatory for NDA approval. DMF dossier can be reviewed during NDA review process or can be applied as a separated application.	**Only SMF is required for GMP clearance.**	N/A
		Annual or periodical update reporting required?	**Yes, according to the draft of "Jointly review of drug substance, excipient and packaging material with drug product" issued by CFDA for public comment on Dec. 5, 2017, annual report and change report are needed in the future.**	Not specified	N/A	N/A	No annual updated system. Partial change application or notification is required for changes. **ICH Q12 is considering.**	Annual report should be submitted by Jan. 31 every year if the relevant changes are applicable for the subject of annual report	DMF is one of the 3 options for Regulatory Control of APIs. Assessment of APIs data and information include changes and variations submitted by the product registration holder (PRH)/API Manufacturer. Assessment of an API will also be performed for a registered product prior to a product renewal application, which is required every 5 years presently.	N/A As applicable	Applicants are responsible for maintaining and updating the DMF. When a DMF has been updated, the table of summary of changes and the DMF Submission Form must be provided together with the updated sections of the DMF. If there are changes to the DMF that will result in a post-approval variation to the drug product, product registrants must file a post-approval variation – refer to Chapter F of this guidance for more information on the post-approval process.	The DMF approval will be valid for 5 years and combined with NDA drug license. There is no annual update reporting mechanism in Taiwan. Detail post-approval major / minor change classification, please refer to appendix 12 of "Drug Review and Registration Guidance."	Not required	N/A for imported products.

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			RDPAC/PhIRDA	HKAPI	OPPI	IPMG	JPMA	KPBMA/KRPIA	PhAMA	PHAP	SAPI	IRPMA	PReMA	PG
Manu -facturing	Contents of packaging label and language	Please describe required contents of packaging label and language to be used. ex. refer to guidance document	The required contents are described in CFDA order 24. The contents should be written in Chinese	English or English and Chinese, requirements described in Guidelines on the Labelling of Pharmaceutical Products	The required contents are described in rule 96 & Schedule D2 of the Drug and Cosmetic Rules 1945. PI and packaging labels should be written in English	New guideline 2011 for labeling prescription drug: request to provide Package insert (English or Indonesia), Patient Information Leaflet (Indonesian), outerbox should following packaging requirement (name of the product, active substance, volume, indication, contraindication , dosage and administration, storage condition, manufacturing name & address , imported by,) also retail price, Registration number, Harus dengan resep dokter, Logo of prescription drug. In the label, after product name should follow active substance names, Label also following regulation on registration. Guideline for OTC: inner box and all product information should be in Indonesian language	The required contents are described in Article 50 of the Pharmaceutical Affairs Act. The contents Should be written in Japanese	For pharmaceutical products including prescription only, OTC drugs and quasi-drugs, the labelling is the summarized indication of efficacy and safety that must be exactly same to the registered/approved product information by the Korean Health Authority. This is presented through three types of labelling like the following: • Package leaflet • Container • Carton (outer package) The required information including product name, lot number, dosage form, name and address of manufacturer or importer, etc. is defined in Articles 56, 57, 58, 59, 60 and 65 of the PAA and Articles 69, 70, 71, 74, 75, 76 and 77 of the Regulation on Safety of Pharmaceutical Drugs etc.	The labeling content is stated in Drug Regulatory Guidance Document. The labeling for pharmaceutical products are in English or Bahasa Malaysia. Some labelling statements are mandatory in Bahasa Malaysia, eg for “Keep medicine out of reach of children”	The required contents are described in Generic Labeling Law. The contents Should be written in English. (see A.O. 55, series 1988)	Refer to: GUIDANCE ON MEDICINAL PRODUCT REGISTRATION IN SINGAPORE APPENDIX 7 Points to Consider for Singapore Labelling, 1 Nov 2016. The product labels, PI and/or PIL must be in English. If non-English text is included in the labelling, applicants must provide an official statement to declare that the non-English text is complete, accurate and unbiased information and is consistent with the English text. Information provided in the labels should be consistent with the information submitted in the application dossier. Any discrepancies should be highlighted and brought to HSA’s attention	The required package label contents are described in Article 20 of “Regulations for Registration of Medicinal Products.” The contents of outer box should be in English and Chinese. Chinese packaging insert is mandatory while English PI is optional. Any local redressing activities need CMO registration to the drug license and showed CMO information in the package insert.	Follow ASEAN labeling requirements Thai language required for - category of drug - expiration date - special warning package leaflet in Thai.	Vietnamese. New Circular on Labelling no. 01/2018/TT-BYT issued by the Ministry of Health on 18 January 2018. (Annex 25) *Outer package labels (article 7)* For drugs, drug raw materials: 1.1 The outer packaging label of a drug must show the following contents: a) Drug name; b) Dosage form; c) Composition, strength, weight or concentration of pharmaceutical substances, medicinal materials in the drug formulation; d) Packaging specification; d) Indications, method of administration, contraindications; e) Number of certificate of marketing registration or number of import license (if applicable); g) Lot number, manufacturing date, expiry date, quality specification, storage conditions; h) Warnings and precautions; i) Name, address of manufacturer; k) Name, address of importer (in the case o imported drugs); l) Origin of the drug. 2. The outer packaging label of a drug raw material (including medicinal materials, traditional medicinals, semi finished medicinal materials, semi finished drugs) must show the following contents: a) Name of the drug raw material; b) Weight or volume of the drug raw material in the smallest package unit; c) Quality specification of the drug raw material; d) Number of certificate of marketing registration or number of import license (if applicable); d) Lot number, manufacturing date, expiry date, storage conditions of the drug raw material; e) Name, address of manufacturer; g) Name, address of importer (in the case of imported drug raw materials); l) Origin of the drug raw material. 3. Labels of controlled drug raw materials (including semi finished drugs): Apart from the contents stipulated under clause 2 of this Article, raw materials being pharmaceuticals, medicinal material or semi finished drugs containing pharmaceutical substances, medicinal materials belonging to the List of narcotic, psychotropic substances, drug precursors, hazardous drug raw materials, hazardous medicinal materials, radioactive drug raw materials, must have outer packaging printed with the wording "Narcotic raw materials", "Psychotropic raw materials", "Drug precursor raw materials", " Hazardous raw materials", "Hazardous medicinal materials "," Radioactive materials" respectively. The wording "Narcotic raw materials", "Psychotropic raw materials", "Drug precursor raw materials", " Hazardous raw materials", "Hazardous medicinal materials ","Radioactive materials" must be printed in Bold in a textbox and on the label’s facesheet bearing the name of the drug raw materials. 4. Where the contents stipulated in clause 1 of this Article cannot be fitted into the outer packaging label, the contents stipulated in point đ clause 1 of this Article may be summarily presented as follows: indications, contraindications and other information: see enclosed package insert". *Secondary packaging labels (article 8)* 1. The secondary packaging label must show at a minimum the following contents: a) Name of the drug; b) Lot number; c) Expiry date. 2. In cases where the secondary packaging is made of a transparent material that allows for information on the primary packaging label to be seen through, such secondary packaging does not have to be printed with the contents stipulated in clause 1 of this Article.

														Primary packaging labels of drugs, drug raw materials (article 9) 1. Labels of drug primary packaging must show all the following mandatory contents: a) Drug name; b) The quantitative composition, strength, concentration or volume of pharmaceutical substances, medicinal materials in the drug formulation; c) Lot number; d) Expiry date; d) Name of manufacturer. 2. Labels of primary packaging of drug raw materials With regard to drug raw materials that have an outer packaging showing all the contents stipulated in clause 2 and clause 3 Article, unless they are removed from the outer packaging for retailing, labelling on the drug primary packaging shall not be required. 3. With regard to drugs, drug raw materials having no outer packaging, the contents stipulated for outer packaging labels under Article 7 of this Circular must be printed in full on the primary packaging. *Format of supplementary labeling (article 10)* 1. Supplementary labels must show all the mandatory contents in Vietnamese language that are not yet available or still missing from the original label in accordance with the provisions of Article 7 of this Circular. 2. Where the size of supplementary labels is to small to fit all the mandatory contents stipulated under clause 1 of this Article, some of such contents shall be presented as follows: a) Indications, method of administration, contraindications and other information: see enclosed package insert; b) Cross reference of manufacturing date, expiry date, lot number that are presented on the original label; c) Number of certificate of marketing registration or number of import license: may be left blank but number of certificate of marketing registration or import license (if applicable) must be filled in before placing the drug on the market.

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Manu -facturing	Bar code on packaging materials	Please describe requirements of Bar Code on packaging materials and concerned regulations.	CFDA issued the notification that bar code on packaging material was temporarily suspended, then the requirements of bar code are deleted from the revised GSP. Company will take the main responsibility to establish the drug tracing system. Bar code is not mandatory to be used in the future.	For product registration, no concern. For supply to government hospital: GTIN barcode as issued by GS-1	For product registration, no concern. For supply to government hospital: GTIN barcode is required Barcode requirements using GS1 identification standards has been implemented. (reference: The Office Memorandum No: Z-16025/02/08-EPW dated 6th May 2011 by MoHFW). For local Indian market, it is still not made mandatory	**The draft regulation of Jan9th .is made as the foundation of Article 30 stated in the new brown book 2017. There is 7 years grace period, in 2020: in secondary packaginig drug with primary packaging bottle and vial > or similar with 5 ml. In 2025: for all drug packaging and food.**	The contents Should be written in Japanese.	MOHW Notification No. 2013-63 was issued to build the base of distributional information of domestically manufactured or imported pharmaceuticals by determining identification with barcodes/RFID tag. Except several products, all pharmaceutical drugs including the imported products must adhere a barcode since 2009. There are three codes of GS1 system, which can be used on the barcode. **And, serial number is included in the information that barcode contains since 2015.**	Bar code is an optional information.	Barcode is required per SKU. It is a requirement upon submission of new drug applications with effective date on June 2015.	No regulatory requirement on bar code. It is a internal company logistics requirement.	**Barcode requirements implementation temporarily suspended.**	No regulatory requirement for Bar code But some hospitals require barcode	Not a requirement. Organizations and individuals who are responsible for drugs are encouraged to write bar codes or paste anti-counterfeit stamps with confidential, anti-counterfeit information related to their products on drug labels to prevent counterfeits or allow for easy product recognition
Post approval	Renewal system of approved license	Please describe renewal system of marketing authorization or manufacturing license. ex. renewal required every 5 years ex. re-evaluation system	Manufacturing license system is adopted for registration management. So, renewal system is based on manufacturing license. Renewal is required every 5 years, and should be submitted within 6 months before expiration date of license. **"Pilot scheme of the Drug Marketing authorization Holder (MAH) System" would end in advance. It's expected that the MAH System works for all the drug application.in 2018.**	Renewal required every 5 years.	Renewal system has been implemented for the followings. 1) Import license (Every 3 years. Renewal application should be made three months before the expiry of the existing license.) 2) Registration certificate (Every 3 years. Renewal application should be made nine months before the expiry of the existing license.) 3) Manufacturing license (Every 5 years. The license will be expired if the renewal applications not made within six months of its expiry) Marketing Authorization is one time issue, no renewal required.	**Renewal fee is 5 M IDR, Renewal (5 M IDR)+Minor Variation (each items Minor Variation 1 M) Renewal (5M) +Major Variation (each items variation 2 M IDR). For example: Renewal + 2 Minor variation = 7 M IDR**	Not renewal but re-examination system is adopted. Drug monitoring is required for 8 years for NCE drug, 4-6 years for new indication/ administration route and 10 years for orphan drug.	**Below documents should be submitted: 1. Data concerning safety management collected during the Effective Period and action plan a. Data pertaining to the expedited report defined in Article 9 of the「Regulation on Safety Information Control of Medicinal Products, etc.」 b. Data pertaining to the periodic data defined in Article 10 of the「Regulation on Safety Information Control of Medicinal Products, etc.」 2. Data concerning the state of use in foreign countries and the safety-related measures a. Data defined in Article 5.1.7 of the「Regulation on Pharmaceuticals Approval, Notification and Review」collected during the "Effective Period" (but, data defined in Article 6.1.7 of the「Regulation on Biological Drug Approval, Notification and Review」in the case of biological drugs, etc., and data defined in Article 6.1.7 of the「Regulation on Herbal(oriental) Medicine Product Approval, Notification and Review」in the case of herbal drug products (crude drug products) 3. Quality management data collected during the "Effective Period" a. Data falling under „7.3 Product Quality Review"stated in „Attached Table 1. Good Manufacturing Practices(GMP) for pharmaceuticals under Article 48 of the Enforcement Regulation" b. A copy of the effective Certificate of Compliance for each pharmaceutical issued under the provision of Article 48.2 of the Enforcement Regulation (for imported drugs, a copy of the effective manufacturing certificate issued by the production country's government or public institution) 4. Matters pertaining to labeling a. Effective container · packaging and attached documents at the time of Renewal Application under Articles 56 to 58 of the Act b. Data pertaining to the labeling change history stated in Subparagraph 12 of Attached Table 1 set forth in the Enforcement Regulation 5. Data pertaining to actual result of manufacture · import during the Effective Period a. Data of manufacture · import results by year under Article 38.2 of the Act b. Supportive data to confirm the exceptional conditions, for pharmaceuticals falling under Article 21 of the Enforcement Regulation or Article 3.4 of this Regulation 6. Effective certificate of approval or notification of pharmaceutical manufacturing, marketing and import**	Renewal is required every 5 years of a product registration. Renewal needs to be submitted 6 months prior to registration expiry. (NOTE: Pre-renewal requirements eg for stability data at zone IVb, GMP inspection etc must also be fulfilled.)	Renewal system is being implemented. Renewal for products under Monitored Release status is after 3-5 years. Products on regular registration status, i.e. under Initial or Renewal status, renewal is done every 5 years.	Reference to "RETENTION OF THERAPEUTIC PRODUCT ON THE PRODUCT REGISTER TPB-GN-002-000" . All registered therapeutic products will remain on the Register, unless: a) The registration is suspended or cancelled by HSA, or b) The registration is cancelled by the registrant, or c) The registrant has failed to make a payment for an annual retention fee within 60 calendar days after the retention fee due date.	Renewal procedure is required for approved license (every 5 years).	There are 3 kinds of license in Thailand which are Manufacturing license, Import license and Sale license, all of which require annual renewal. Based on current Thai Drug Act, the product license is life-long, no requirement of renewal, except for drug classified as narcotics and psychotropics shall subject to renewal every 5 years. Product license will be automatically withdrawn if no production/import ation every 2 consecutive years.	MA validity is from 3-5 years (3 years: 1st time registered in VN; 5 years: renewals). MA extension is mandatory. **MA renewal is invalid due to regulations in new Pharmacy Law. (effective 1 Jan 2017). Current regulation (Circular 44/2014/TT-BYT) on drug registration is being drafted following the new Pharma Law (effective 1 Jan 2017). Until Jan 17, 2018: still on-going.**

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Post approval	Post marketing surveillance or safety monitoring program	PSUR submission required? Other post-approval safety requirements? ex. Safety monitoring program/ monitored release	Annual PSUR submission is mandatory until the first renewal date, and it becomes every 5 years after the first renewal date. Mandatory special monitoring is performed over drugs within the new drug monitoring period as well as drugs imported for the first time within 5 years. The monitoring results shall be summarized, analyzed, evaluated and reported as required. **On Dec. 28, 2017, CFDA issued" Announcement of MAH submitting ADR report directly (draft)". MAH was asked to report all suspected ADR/AE on CFDA ADR direct reporting system. It's expected to be in operation in Jul. 2018.**	For NCE only. PSUR has to be submitted every 6-monthly for the first 2 years of product registration approval, and annually in the following 3 years.	PSUR submission is mandatory for a period of four years. For new drug, every 6 months for the first 2 years, and annually for another 2 years. May be extended by the authority in the interest of public health. (Reference: Schedule Y of the Drugs and Cosmetics Rules amended in 2005) PSURs due for a period must be submitted within 30 calendar days of the last day of the reporting period. For conditional approval, there is a case where Phase IV crinical trial imposed.	PSUR submission is required only for NCE and certain product if it is required by HA. There is an obligation to report all Adverse Events (unexpected/expected, serious/ non serious in Indonesia or foreign countries) to NADFC	PSUR submission is mandatory every 6 months in first two years and annually after two years. Use-result survey data should be submitted together.	PSUR submission is mandatory every 6 months in first two years and annually after two years. Use-result survey data should be submitted together.	PSUR/BPRER is mandatory for NME: 6 months once in the first 2 years, and 12 months once in the subsequent 3 years.	As per PFDA Circular 2013-004, the post marketing surveillance system was enhanced to cover all registered products. Periodic (minimum on annual basis) submission of PSUR/ PBRER, and AE reports and submission of RMP are required.	Reference to: GUIDANCE FOR INDUSTRY POST-MARKETING VIGILANCE REQUIREMENTS FOR THERAPEUTIC PRODUCTS, 1 Nov 2016 This guidance addresses the types of documents to be submitted at the point of application for product registration, and during the post-marketing phase of the therapeutic products (e.g. during variation application review or when new significant safety issues are identified). Include the following: ・ Records of adverse effects; ・ Serious adverse reaction (SAR) reporting; ・ Risk management plans (RMPs); ・ Periodic benefit-risk evaluation reports (PBRERs); ・ Updates on actions taken by other regulatory authority or company in response to safety issues.	Pharmacovigilance period is first 5 years for NCE drugs. PSUR should be submitted every 6 months in the first 2 years and annually for the rest 3 years. PSUR submission period can be adjusted based on global international birthday (IBD) and its data lock point (DLP) within 3 months of drug license collection.	New drug approval will be with "conditional approval" requiring Safety Monitoring Program for 2 years. After 2 years, the application for "Unconditional approval" (or SMP releasing) is needed. Apart of local data, one of the document required is worldwide safety data and the PSUR for all relevant periods will be used for submission at this step. Actually, there is no PSUR regulation.	Periodic ADR report (PSUR, PBRER, report safety, effectiveness)

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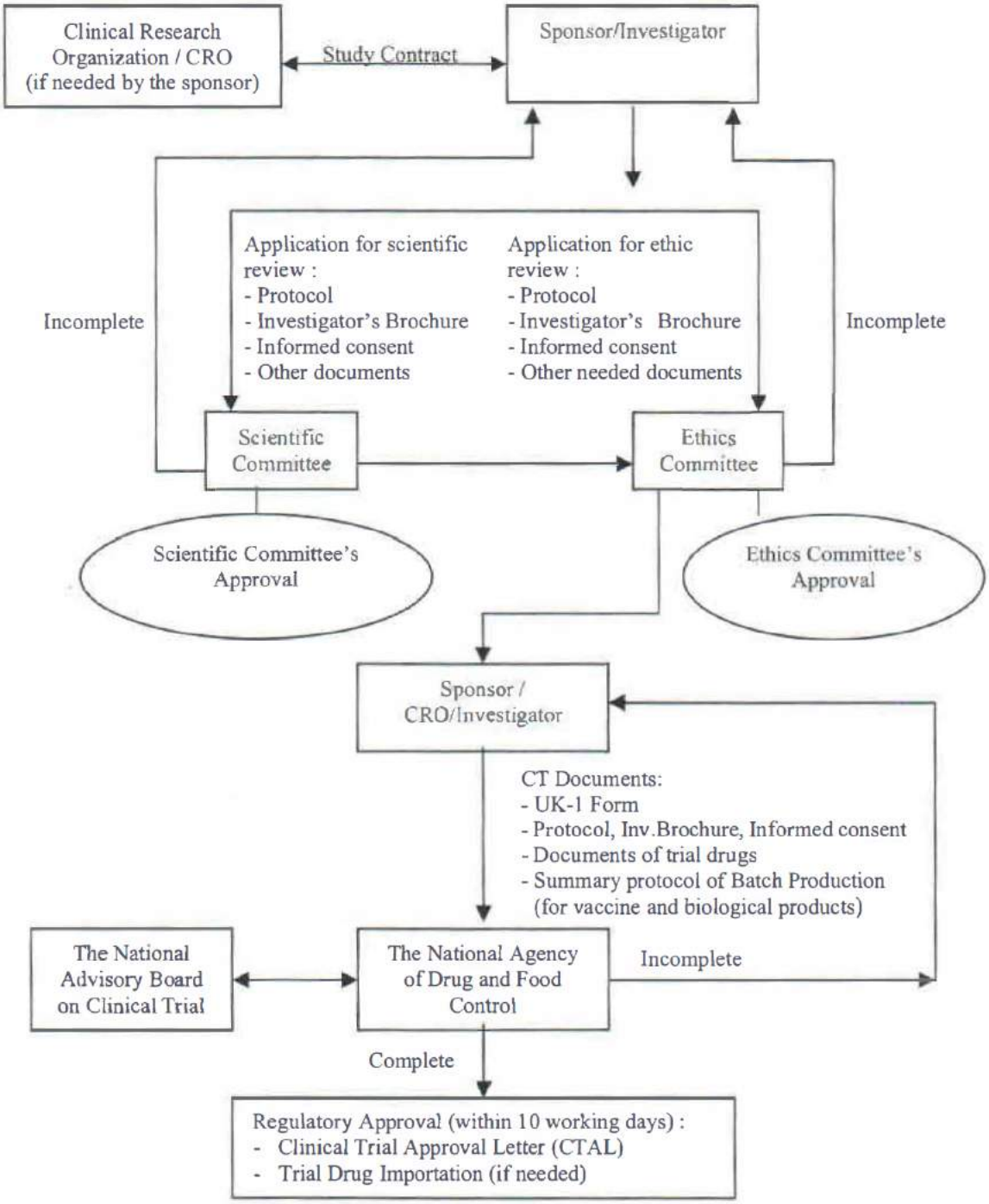
Post approval	Risk Management Plan (RMP)	Please describe requirements of RMP/REMS. ex. Mandatory at NDA, submit up on request from the authorities	Not yet officially implemented. For the product which is accepted for special review procedure, Risk Management and Implementation Plan should be submitted at NDA. **For innovative drugs (new registration category No.1), the RMP should be submitted at NDA.**	One of the mandatory requirements for NCE registration	N/A at present	**Draft RMP under consult public**	RMP document is mandated for NDA as M1.11.	For improved management and control for known or potential risk of post-approved drug product, a risk management plan (RMP) was introduced from 01-Jul-2015. For approval of new drugs and orphan drugs, the Risk Management Plan (RMP) should be submitted with application form in accordance with amendment made by MFDS Notification No. 2015-27. The scope of drugs required to submit the risk management plan will be expanded annually step by step by 2018.	**RMP for New Drug Products/Biologics:** **i. An RMP or an update, as applicable, may need to be submitted at any time during a product's life-cycle.** **ii. RMP or an update will normally be expected, with an application involving a significant change to an existing registered product.** **iii. A significant change in indication is a change of approved indication(s) of a product where the new treatment target population differs materially from the one for which the product was previously approved.** **An updated RMP should always be submitted if there is a significant change to the benefit-risk balance of one or more medicinal products included in the RMP.** **Submission of RMP for Generics and other Products:** **As a general rule, RMPs for these medicinal products are not required to be submitted. But, it is expected that PRH will continue to evaluate the safety of their products on a regular basis and report any new safety information that impacts the benefit-risk balance or the product information. However, a RMP may be requested when there are safety concerns affecting the benefit-risk assessment that require specific risk minimisation activities.**	RMP is required for submission of NDAs (FC-2013 004). There's no local format of RMP.	Reference to "APPENDIX 16 GUIDELINE ON THE SUBMISSION OF RISK MANAGEMENT PLAN DOCUMENTS", 1 Nov 2016. All NDA-1 and biosimilar product applications must have an accompanying RMP submitted. For other application types such as NDA-2 or 3, major variation application (MAV) or generic drug application (GDA), RMP documents may be requested by HSA on a case-by-case basis: ・ For NDA-2, the request for RMPs may be in response to a new safety concern arising from a new route of administration; ・ For MAV, the request may arise as a result of a new safety concern associated with a new indication that may require additional PV activities and/or RMAs ・ For GDA, a RMP may be required if the innovator or reference product has safety concerns that have been identified to require additional local PV activities and/or RMAs.	The necessary of local RMP will be decided by TFDA during the NDA review. RMP protocol will be discussed and finalized between TFDA and NDA applicants.	**On 28 Apr 2017, the Thai FDA announce a guideline on RMP for biological products.**	Not a mandatory requirement. The request could be given following the decision of Advisory Council for the Grant of Drug Registration License. Risk management plan for a drug should include the following information: - Overview of drugs - Safety information -Pharmacovigilance Plan - Plan of Post-marketing studies - Risk minimization activities - Summary of the plan
	Adverse drug reaction reporting after marketing	Please describe reporting requirements of ADR for marketed products.	Reporting is mandatory for ADR observed in post-marketing period including PMS. Reporting period of Serious ADR and unknown ADR are within 15 days and death should be reported immediately (30 days for non-Serious ADR for drugs within the new drug monitoring period or imported drugs within 5 years from the date of initial import permission).	SUSARs have to be reported within 15 calendar days from date of first receipt.	Serious unexpected adverse reactions: must be reported to the licensing authority within 15 calendar days of initial receipt of the information by the applicant. Other: to be reported in PSUR.	Reporting is mandated for ADR observed in post-marketing products. 1. AE Spontaneous serious unexpected in Indonesia, as soon as possible, not more than 15 calendar days. 2. AE spontaneous non-serious unexpected in Indonesia, report every 6 months. 3. AE Spontaneous serious expected in Indonesia, as soon as possible, not more than 15 calendar days. 4. AE spontaneous serious unexpected in froiegn countries, as soon as possible, not more than 15 calendar days	Reporting is mandated for ADR observed in post-marketing products including PMS. Reporting period of Serious ADR is within 15 days (or 30 days for expected ADR).	Reporting is mandated for ADR observed in post-marketing products including PMS. SAE: within 15 days from reported day NSAE: within next year Feb from reported day	The PRH (product registration holders) shall inform the HA immediately of any adverse reaction arising from the use of the registered product. All PRHs must ensure that a pharmacovigilance system is in place by the company and appropriate action is taken, when necessary. PRHs are required to monitor and report any product safety issues that arise locally or internationally to the NPRA as well as comply with all safety-related directives issued by the Authority. The timeline for ADR reporting differs by reporter category. (Malaysian Pharmacovigilance Guidelines 2nd Edition 2016)	Reporting is mandated for ADR observed in post-marketing products including PMS. Reporting period of Serious ADR/AE, ICSR is within 5 days and serious one must be reported promptly.	Reference to "GUIDANCE FOR INDUSTRY POST-MARKETING VIGILANCE REQUIREMENTS FOR THERAPEUTIC PRODUCTS, 1 Nov 2016. Upon becoming aware of any SARs, the company must report the event to the Vigilance and Compliance Branch as soon as possible within 15 calendar days. The regulatory reporting time clock starts as soon as any personnel of the company is aware of the SAR.	**Medical care institutions and pharmacies shall, within seven (7) days upon knowing of the severe adverse reactions (SAEs) of death and life-threatening, make report and copy to pharmaceutical dealers holding permit licenses of medicines. If information of the report is not completed, it should be supplied within fifteen (15) days.** **Medical care institutions and pharmacies shall, within fifteen (15) days upon knowing of the other SAEs except of death and life-threatening, make report and copy to pharmaceutical dealers holding permit licenses of medicines.** **Pharmaceutical dealers holding permit licenses of medicines shall, within fifteen (15) days upon knowing of the SAEs of medicines, make report in accordance with regulations.**	Follow Guidance for Industry Post-marketing Safety Reporting Requirements for Human Drug and Biological Products Including Vaccines (Annex 26)	Follow Ministry of Health guidance for ADR report. - Patient information (Initials, gender, age/date of birth, weight) - Details of AE* Date of onset/latency, concise description of AE (e.g. type of rash), severity Suspected health products Brand name or active ingredient(s), dosage form, strength, manufacturer, batch number, - Administration route - Concomitant health product - Reporter's details Name, profession, place of practice, contact no., email address

Item	Contents	Detail or Example	China RDPAC/PhIRDA	Hong Kong HKAPI	India OPPI	Indonesia IPMG	Japan JPMA	Korea KPBMA/KRPIA	Malaysia PhAMA	Philippines PHAP	Singapore SAPI	Taiwan IRPMA	Thailand PReMA	Vietnam PG
Post approval	Variation guideline	Is there any guideline document for post-approval changes? If yes please show the title.	The variations to be approved or filed are listed in Drug Registration Regulation order 28. Meanwhile, Guideline for Variations of Post-Marketing Chemical Drug Products has been implemented. **CFDA issued the guideline for the study on the variation of manufacturing process of post-marketing chemical drug on Aug. 21, 2017. ([2017]No.140)** **CDE issued the draft guideline for variations of post-marketing biological products for public comments in Sep of 2017, not formally implemented.**	Please refer to the guidelines for Change of particulars (Guidance Notes on Change of Registered Particulars of a Registered Pharmaceutical Product; issued by Drug Office, Department of Health of Hong Kong).	Chemical products: In case major change, approval is needed within 30 days by submission of variation application. For minor change, it should be notified to the authorities within 30 days. (See Drugs and Cosmetics Rules, 1945) Biological products: LEVEL I - Supplements (Major Quality Changes); LEVEL II - Notifiable Changes (Moderate Quality Changes) LEVEL III - Annual Notification (Minor Quality Changes) (See Guidance for Industry: Post approval changes in Biologic Products – Quality, Safety and Efficacy Documents)	Regulation of the Head of National Agency of Drug and Food Control **No 24, year 2017 (Annex 11): Criteria and Procedure of Drug Registration.**	Partial change application should be submitted for approval of changes. For minor changes, notification system can be applied. Scope and handling of these changes are stipulated in the Pharmaceutical Affairs Law and several notices.	**Pharmaceutical Affairs Act, Several notices and Guidelines exist. One of the several Guidelines is "Regulation on Pharmaceuticals Approval, Notification and Review".**	**Malaysian Variation Guideline For Pharmaceutical Products (Apr 2013) This guidance document is adopted from the ASEAN Variation Guideline for Pharmaceutical Products 2012 incorporating Malaysia's specific requirements.** **Malaysian Variation Guideline for Biologics (Jan 2017)**	FDA Circular No. 2014-008: Application Process and Requirements for Post-approval Changes of Pharmaceutical Products, 28 Feb 2014, which was effective on 1 April 2014. Almost the same with "Asean variation guideline", but a country specific request was added.	Reference to "GUIDANCE ON THERAPEUTIC PRODUCT REGISTRATION IN SINGAPORE TPB-GN-005-000"; Chapter F Post-Approval Process.	Please refer "Regulations for Registration of Medicinal Products for post-approval changes application"	As per ASEAN Variation Guideline (AVG).	Yes. As ASEAN harmonization. Current regulation (Circular) on Registration which includes Variation being drafted following the new Pharma Law (effective 1 Jan 2017). Previous regulation: Appendix II issued together with Circular 44 on Drug Registration (Major variation, minor variation and others).

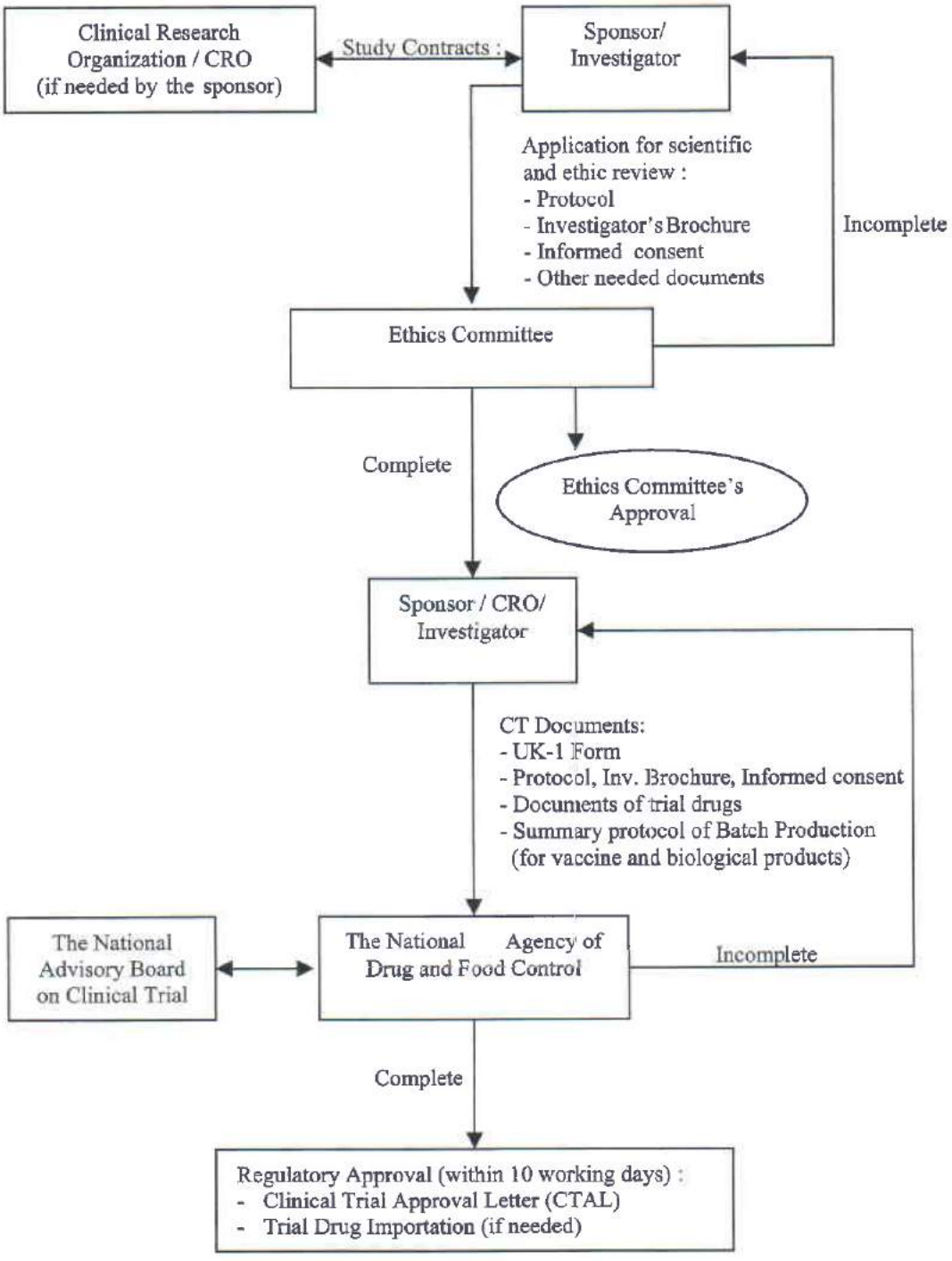
ATTACHMENT IIa
DECREE OF THE HEAD OF THE NATIONAL AGENCY OF DRUG AND FOOD CONTROL
REPUBLIC OF INDONESIA
NO 02002/SK/KBPOM
REGARDING CLINICAL TRIAL PROCEDURE

Flow Chart
Pre-Marketing Trial



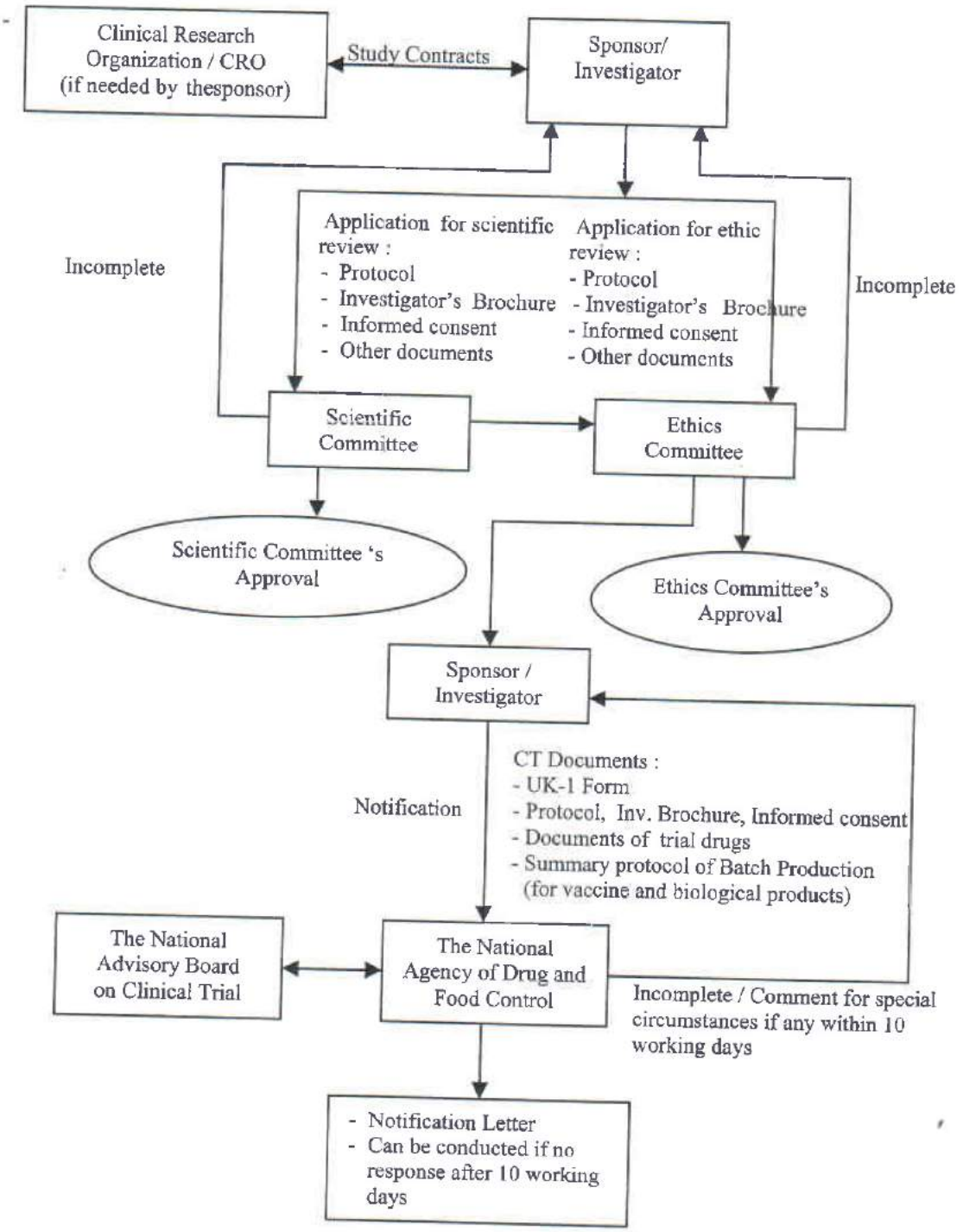
ATTACHMENT IIb
DECREE OF THE HEAD OF THE NATIONAL AGENCY OF DRUG AND FOOD CONTROL
REPUBLIC OF INDONESIA
NO 02002/SK/KBPOM
REGARDING CLINICAL TRIAL PROCEDURE

Flow Chart
Pre-Marketing Trial
(Inseparate Scientific and Ethics Committee)



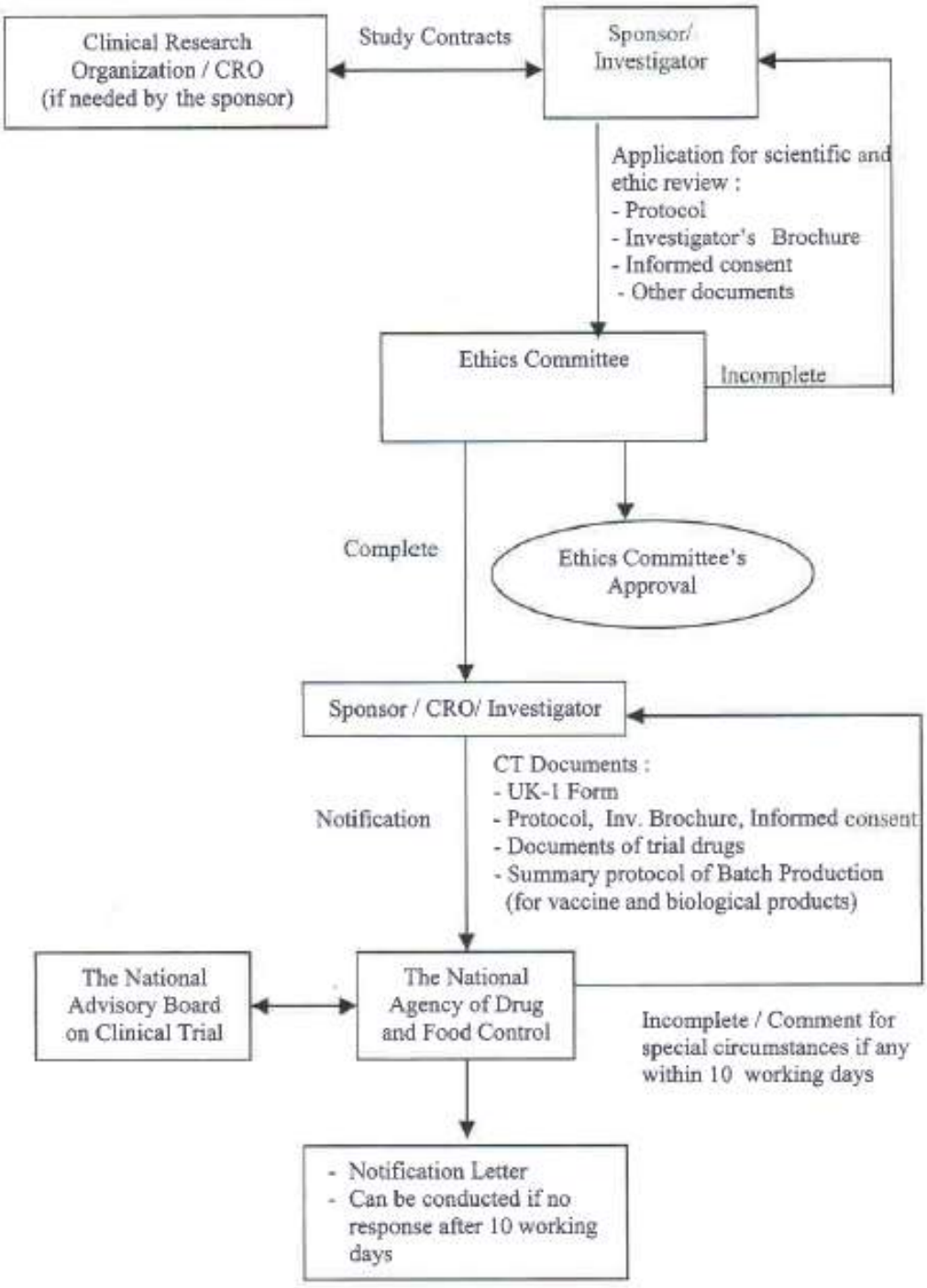
ATTACHMENT IIIa
DECREE OF THE HEAD OF THE NATIONAL AGENCY OF DRUG AND FOOD CONTROL
REPUBLIC OF INDONESIA
NO 02002/SK/KBPOM
REGARDING CLINICAL TRIAL PROCEDURE

Flow Chart
Post-Marketing Trial
(Separate Scientific and Ethics Committee)



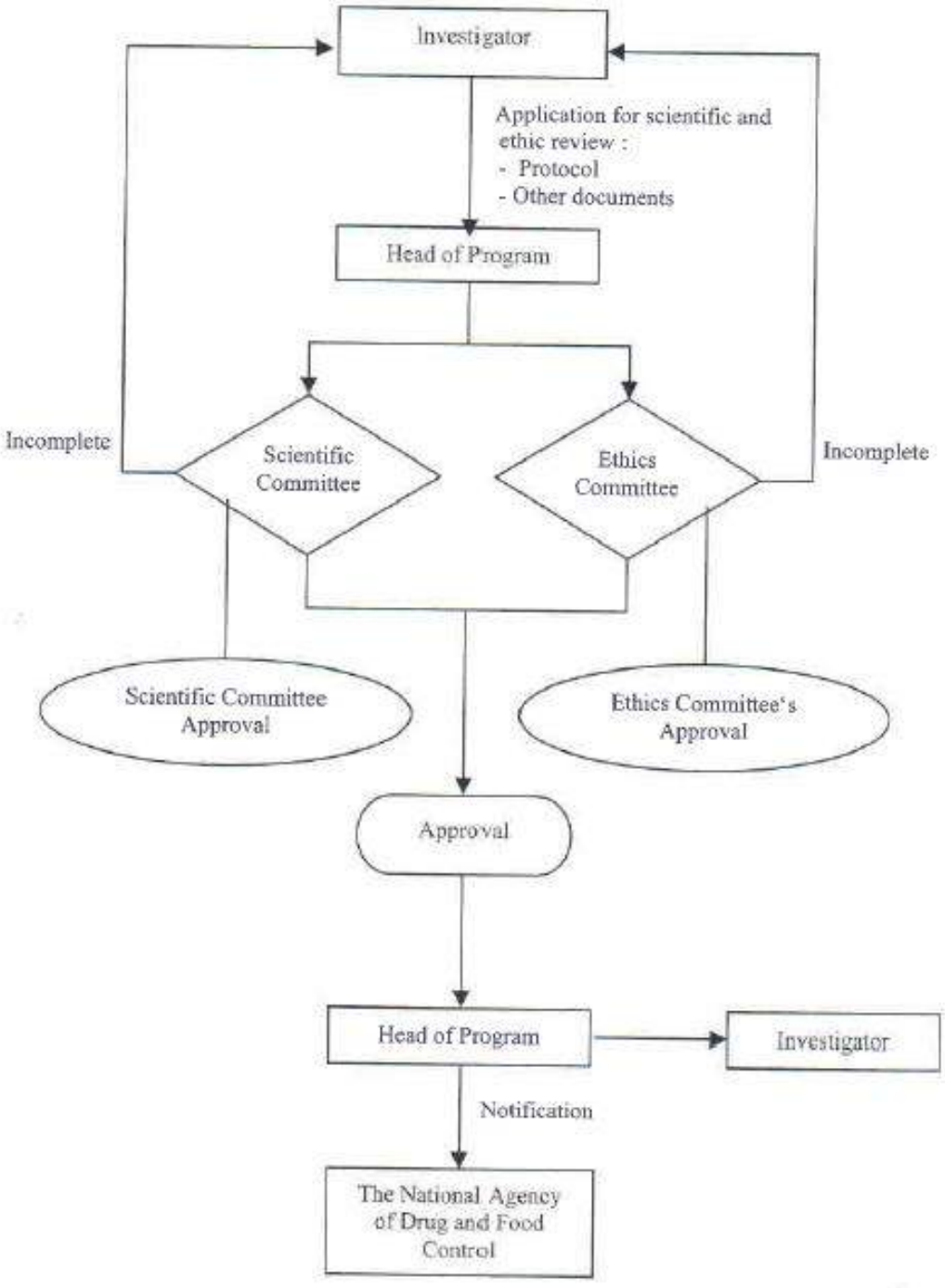
ATTACHMENT IIIb
DECREE OF THE HEAD OF THE NATIONAL AGENCY OF DRUG AND FOOD CONTROL
REPUBLIC OF INDONESIA
NO 02002/SK/KBPOM
REGARDING CLINICAL TRIAL PROCEDURE

Flow Chart
Post-Marketing Trial
(Inseparate Scientific and Ethics Committee)



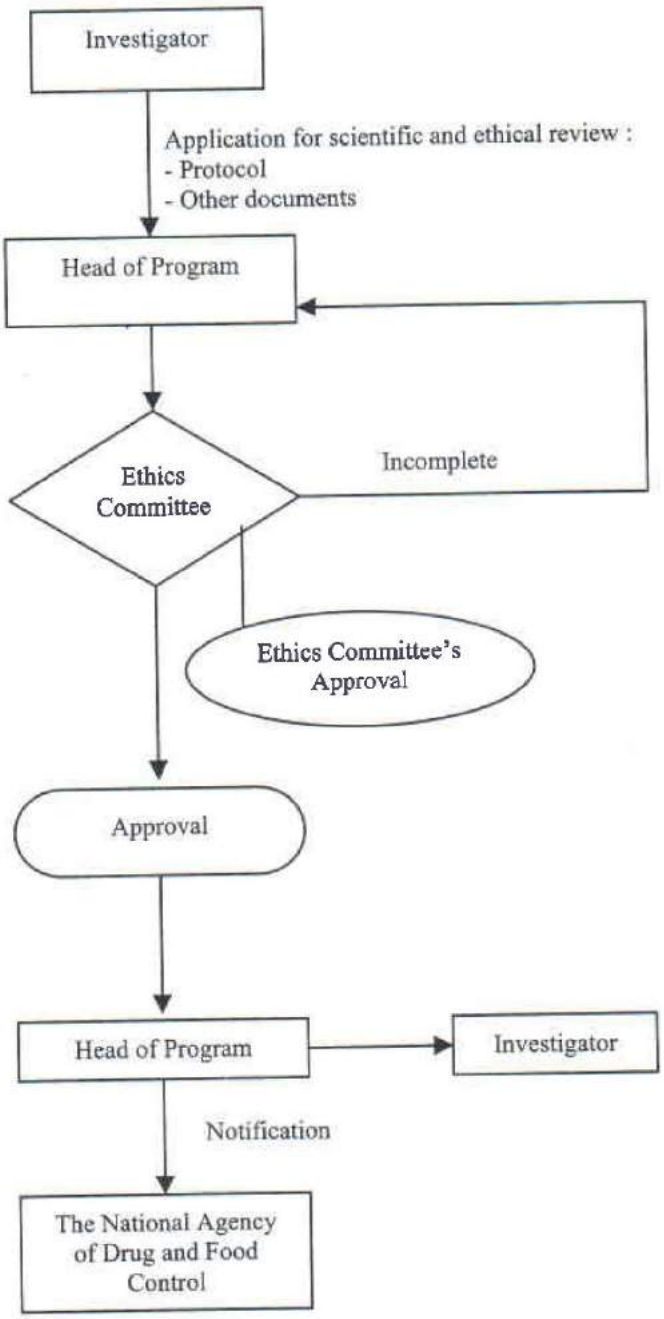
ATTACHMENT IVa
DECREE OF THE HEAD OF THE NATIONAL AGENCY OF DRUG AND FOOD CONTROL
REPUBLIC OF INDONESIA
NO 02002/SK/KBPOM
REGARDING CLINICAL TRIAL PROCEDURE

Flow Chart
Trial for Educational Purpose
(Separate Scientific and Ethics Committee)



ATTACHMENT IVb
DECREE OF THE HEAD OF THE NATIONAL AGENCY OF DRUG AND FOOD CONTROL
REPUBLIC OF INDONESIA
NO 02002/SK/KBPOM
REGARDING CLINICAL TRIAL PROCEDURE

Flow Chart
Trial for Educational Purposes
(Inseparate Scientific and Ethics Committee)



UK-1 FORM

ATTACHMENT I
DECRRE OF THE HEAD OF THE NATIONAL AGENCY OF DRUG AND FOOD CONTROL
REPUBLIC OF INDONESIA
NO 02002/SK/KBPOM
REGARDING CLINICAL TRIAL PROCEDURES

To:
The Head of the National Agency of Drug and Food Control Republic of Indonesia
Percetakan Negara 23
JAKARTA

☐ Pre-Marketing Clinical Trial ☐ Post-Marketing Clinical Trial

I. GENERAL INFORMATION

1. Title of Clinical Trial:
2. Protocol number and dated (final protocol) :
3. Objective of the trial :
4. Phase of the trial (I, II, III, IV) :
5. Design :
6. Use of comparator drug (s) Yes ☐ No ☐
7. Use of placebo Yes ☐ No ☐
8. Number of Subject :

9. Protocol, Investigator's Brochure, Informed Consent and amandements (if any)

Yes ☐ No ☐

10. The categories of study medications used in the clinical trial

☐ Category I
New study medication that has never been studied in human before.

☐ Category II
New study medication that phase I, II, or III trials is still being conducted.

☐ Category III
Study medication has been marketed and this trial is to be conducted for new indication, new administered, and/or new strength.

☐ Category IV
Study medication has been marketed and its trial is being conducted as Post-Marketing Trial.

II. INSTITUTIONS

Multi-center Clinical Trial

Yes ☐ No ☐

Local Center :

Overseas Center :

Name of the (Principle) Investigators, Sub/Co Investigators, and their institution respectively and coordinating investigator (if any) :

III. STUDY DRUG

Study medication : Imported ☐

Local ☐

1. Generic name :
2. Trade name :
3. Chemical name :
4. Pharmacological Class :
5. Dosage form and strength :
6. Packaging :
7. Route of Administration:
8. Expiry date :
9. Batch number :
10. Certificate of analysis :
11. GMP certificate :
12. Imported drug (s) (Name and amount):
13. Manufacturer (Name and address):
14. Imported by :
15. Marketed in other countries (if any):

IV. COMPARATOR DRUG

Study medication	: Imported	☐
	Local	☐

1. Generic name :
2. Trade name :
3. Chemical name :
4. Pharmacological Class :
5. Dosage form and strength :
6. Packaging :
7. Route of Administration:
8. Expiry date :
9. Batch number :
10. Certificate of analysis :
11. GMP certificate :
12. Imported drugs (Name and amount):
13. Manufacturer (Name and address):
14. Imported by :
15. Marketed in other countries (if any):

V. SPONSOR

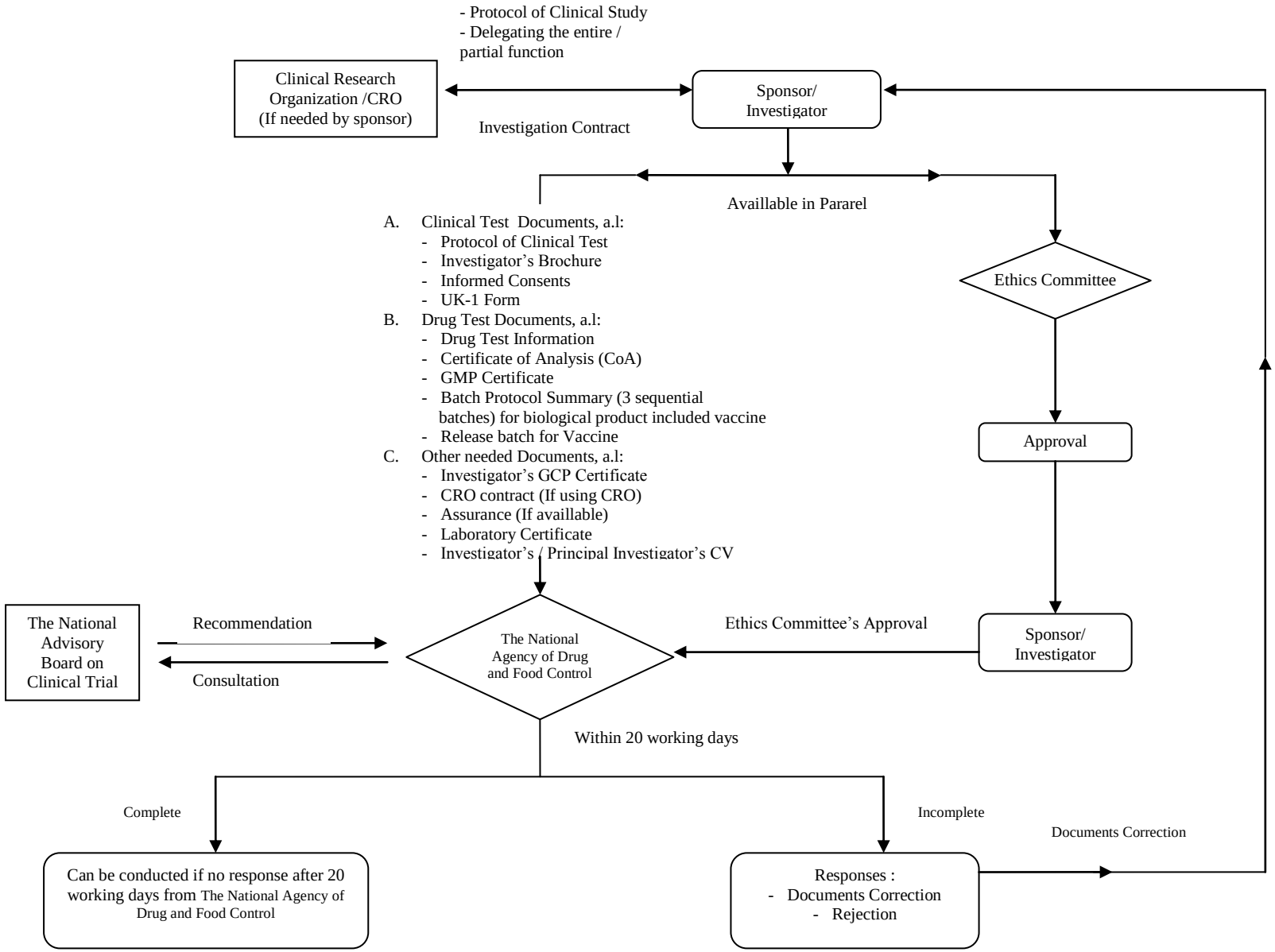
1. Name and address :
2. Sponsor's representative (name and telephone) :
3. Contract Research Organization, (if any, Name and address):

VI. SCIENTIFIC COMMITTEE AND ETHIC COMMITTEE' S APPROVAL

Conclusion of scientific review (attached)
Conclusion of ethical review (attached)
Scientific Committee's approval (attached) - Number and date : - Name and address of Institution :
Ethics Committee' s approval (attached) - Number and date : - Name and address of Institution :

Flow Chart Post-Marketing Trial

Annex 2 Indonesia



MFDS IND Approval Process

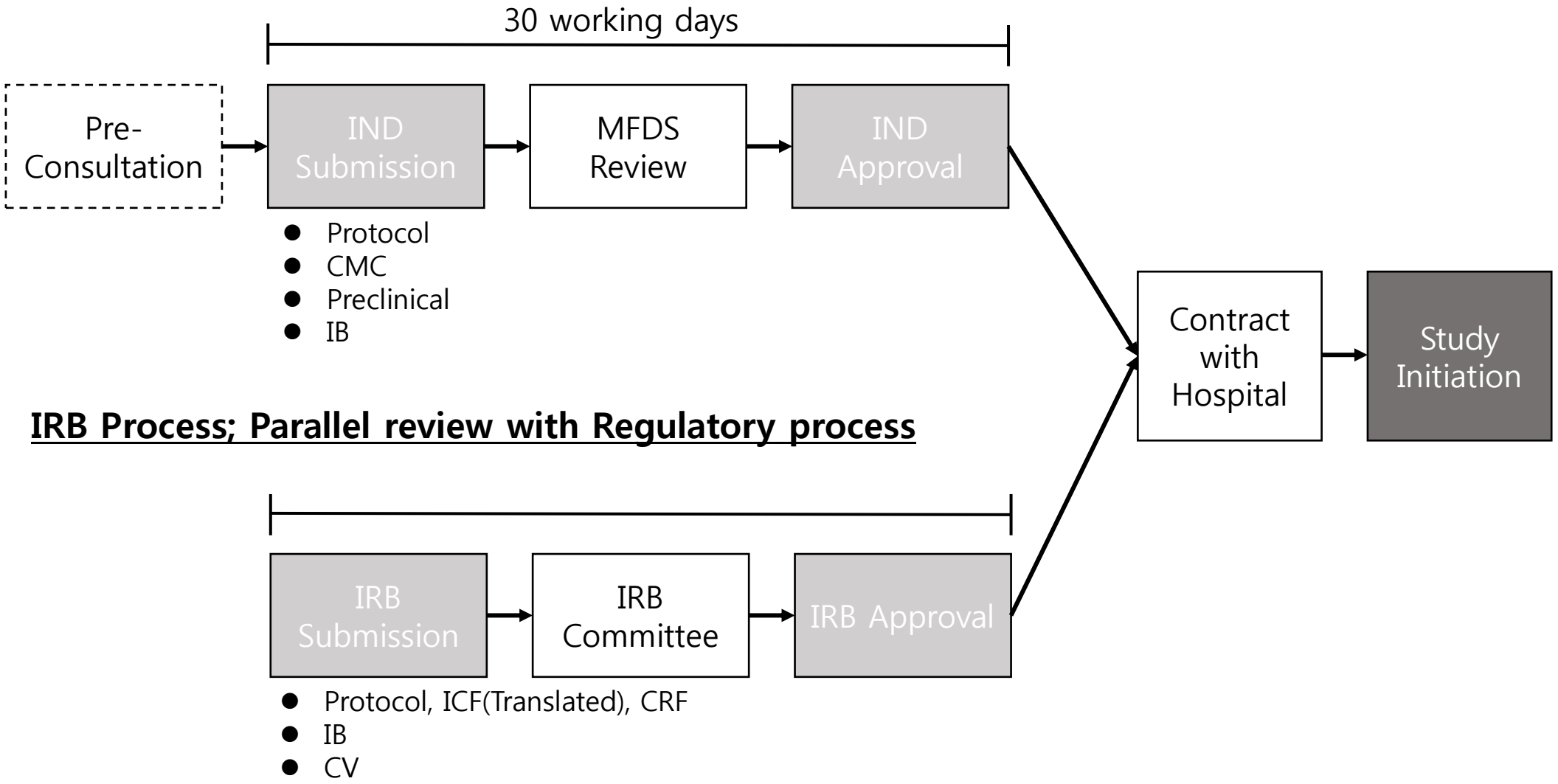
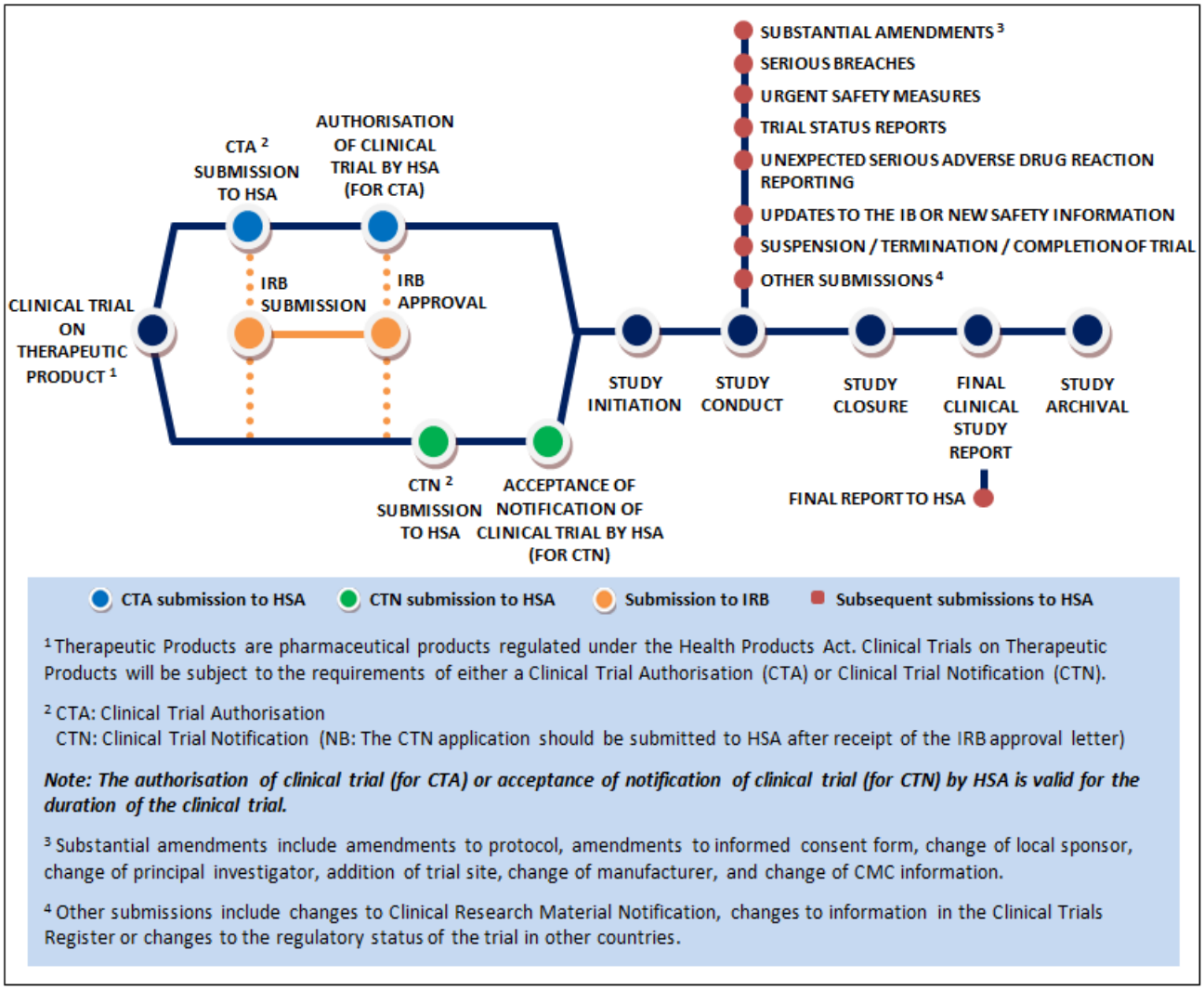


Figure 1. Regulatory roadmap for clinical trials on therapeutic products



[1] Therapeutic Products are pharmaceutical products regulated under the Health Products Act. Clinical Trials on Therapeutic Products will be subject to the requirements of either a Clinical Trial Authorisation (CTA) or Clinical Trial Notification (CTN).

[2] CTA: Clinical Trial Authorisation
CTN: Clinical Trial Notification (NB: The CTN application should be submitted to HSA after receipt of the IRB approval letter)

Note: The authorisation of clinical trial (for CTA) or acceptance of notification of clinical trial (for CTN) by HSA is valid for the duration of the clinical trial.

[3] Substantial amendments include amendments to protocol, amendments to informed consent form, change of local sponsor, change of principal investigator, addition of trial site, change of manufacturer, and change of CMC information.

[4] Other submissions include changes to Clinical Research Material Notification, changes to information in the Clinical Trials Register or changes to the regulatory status of the trial in other countries.

Source:
CLINICAL TRIALS GUIDANCE REGULATORY REQUIREMENTS FOR NEW APPLICATIONS AND SUBSEQUENT SUBMISSIONS, HSA
GN-CTB-2-003A-001

Annex 4

Guidelines on procedures and data requirements for changes to approved vaccines

Guidelines published by WHO are intended to be scientific and advisory in nature. Each of the following sections constitutes guidance for national regulatory authorities (NRAs) and for manufacturers of biological products. If an NRA so desires, these WHO Guidelines may be adopted as definitive national requirements, or modifications may be justified and made by the NRA.

1. Introduction

Changes to the vaccine manufacturing process or product labelling information often need to be implemented after a new vaccine has been approved (that is, licensed or marketing authorization (MA) received). Changes may be made for a variety of reasons, such as to maintain the routine production of vaccines (for example, replenishment of cell banks, seed lots and reference standards), to improve the quality attributes of the vaccine or the efficiency of manufacture (for example, changes in the manufacturing process, equipment or facility) or to update product labelling information (for example, to add a new indication and/or improve the management of risk by adding a warning, limiting the target population, changing the dosage regimen and adding information on co-administration with other vaccines or medicines).

National regulatory authorities (NRAs) and MA holders should recognize that:

- any change to a vaccine may impact upon the quality, safety and efficacy of that vaccine;
- any change to the information associated with the vaccine (that is, product labelling information) may impact on the safe and effective use of that vaccine.

The regulation of changes to approved vaccines is one of the most important elements in ensuring that vaccines of consistent quality, safety and efficacy are distributed after they receive authorization or licensure. WHO provides support to its Member States through the provision of written standards and guidelines (*1*–*3*). However, the NRAs of Member States requested further guidance on the data needed to support changes to approved vaccines to ensure the comparability – with respect to quality, safety and efficacy – of vaccines manufactured with the change. Although it is difficult to provide guidance that applies to all national situations, an attempt has been made to cover a range of possible changes in manufacture, quality control, safety, efficacy and product labelling information.

This document is intended to serve as a guide for establishing national requirements for the regulation of post-approval changes. The categories of such changes and reporting procedures are provided in the main body of the document and the data requirements to support the proposed changes are provided in the appendices. If an NRA so desires, the contents of these WHO Guidelines may be adopted as definitive national requirements. It is possible that modifications to this document may be justified due to risk–benefit and legal considerations specific to each NRA. In such cases, it is recommended that any modifications of the principles and technical specifications set out in this document be made only

on condition that they ensure a level of vaccine quality, safety and efficacy at least equivalent to that which would be achieved by following the guidance provided here (that is, ensure that the risks of introducing vaccines for use in public health programmes are no greater than those that are outlined in this document).

2. Scope

This document provides guidance for NRAs and MA holders on the regulation of changes to the original MA dossier or product licence for an approved vaccine in terms of: (a) procedures and criteria for the appropriate categorization and reporting of changes; and (b) the data required to enable NRAs to evaluate the impact of the change on the quality, safety and efficacy of the vaccine. Additionally, the purpose of these WHO Guidelines is to assist NRAs in establishing regulatory procedures for post-approval changes to vaccines.

The guidance given below applies to the manufacture and use of approved prophylactic vaccines for humans. However, the general principles set out in this document may also apply to other biological products.

3. General considerations

For each change to the original MA dossier or product licence the MA holder should decide if the information in the original MA or product licence needs to be supplemented (that is, requires the official submission of a supplement or a change application dossier to the NRA) based on the guidance provided in this document. Prior to implementing the change, the MA holder should assess the effects of the change and demonstrate through appropriate studies (analytical testing, functional assays, and/or clinical or nonclinical studies) the absence of any negative effect of the change on the quality, safety and efficacy of the vaccine. A supplement requiring approval prior to implementation of a change is referred to as a prior approval supplement (PAS). In general, no change should be implemented without the approval of the NRA unless otherwise indicated in this document (for example, minor quality changes).

Changes to approved vaccines are categorized on the basis of a risk analysis. When a change affects the manufacturing process, this assessment should include evaluation of the effect of the change on the quality (that is, identity, strength, purity and potency) of the final product as it may relate to the safety and/or efficacy of the vaccine. When a change affects the clinical use or product labelling information, this assessment should include evaluation of the effect of the change on the safety and efficacy of the vaccine. Changes that may potentially have a major or moderate impact require submission of a PAS to the NRA. For each change, the supplement should contain information developed

by the MA holder to allow the NRA to assess the effects of the change. When changes may potentially have a minimal impact or no impact on product quality, safety and efficacy, they should be recorded and retained by the manufacturer or MA holder.

Assessment of the extent to which the quality change (also referred to as manufacturing change) affects the quality attributes (that is identity, strength, purity and potency) of the vaccine is generally accomplished by comparing manufacturing steps and test results from in-process and release testing of pre-change and post-change processes, and determining if the test results are comparable (that is, the antigen, intermediate or final product made after the change should be shown to be comparable to and/or to meet the acceptance criteria of the final product made before the change). However, additional supporting data may be required, as noted in Appendices 2–4 below.

An MA holder making a change to an approved vaccine should also conform to other applicable laws and regulations, including good manufacturing practice (GMP), good laboratory practice (GLP) and good clinical practice (GCP). MA holders should comply with relevant GMP validation and record-keeping requirements, and should ensure that relevant records are readily available for examination by authorized NRA personnel during inspections. For example, changes of equipment used in the manufacturing process generally require installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ). This information does not need to be included in a PAS for equipment changes, but is part of GMP requirements and should be available during inspections. Inspections may occur routinely, may be required before submission of a supplement for a major manufacturing change such as a move to a new facility, or may be triggered by a major manufacturing change such as a change in production capacity or filtration or purification systems.

Certain major changes, such as changes in the vaccine antigen composition (for example, addition of virus or bacterial types), use of new cell substrates (for example, use of cells unrelated to the established master cell bank (MCB) or pre-MCB material) or changes in the composition of vaccine adjuvants are generally considered to be a new product and as such require the submission of a product licence application for a new MA. In addition, in some countries a change in the quantity of antigen per dose of vaccine also requires a product licence application for a new MA (see section 8.2 for changes to the seasonal influenza virus vaccine composition; and Appendix 2 (changes 9.a and 10.a) for information on changes to the cell banks and seed lots, respectively).

Administrative changes related to acquisitions and mergers, company names or contact information should be submitted directly to the NRA as general correspondence to the MA or product licence. When these changes affect the product labelling information, the revised labelling items should be submitted to the NRA, as described in this document (see section 6.4).

The implementation of new regulations should not affect vaccine supply and access by the public to vaccines. NRAs are therefore strongly encouraged to establish requirements that are commensurate with public health priorities and with their own regulatory capacity and resources. NRAs of vaccine-procuring countries should strongly consider establishing alternative procedures for the expedited approval of changes on the basis of previous expert review and approval of the same changes by the NRAs of countries in which the vaccines are produced and/or licensed, or on the basis of decisions made by a recognized regional regulatory authority. If a change has been approved by another competent NRA, the NRA receiving the submission may choose to recognize this approval decision or may make an independent decision based on its own assessment. Foreign approval documentation may accompany the required information to support the change, as outlined in this document. Nevertheless, responsibility for the final regulatory decision on the approval of the change will still lie with the receiving NRA (see section 7 and Appendix 1).

To ensure vaccine supply and encourage adequate reporting of changes by manufacturers, NRAs should also consider establishing procedures for the concurrent (that is, parallel) review of changes to each product. Vaccine production requires the replenishment of biological starting materials such as cell banks, seed lots and reference standards, which are considered routine changes beyond the control of manufacturers. Consequently, these changes often need to be reviewed concurrently with other manufacturing or safety and efficacy changes. Similarly, clinical safety and efficacy changes, such as the addition of a new indication for a vaccine or a new age group for use of a vaccine, require considerable supporting data and review time and should not preclude or impede the review of unrelated manufacturing changes or the immediate implementation of urgent changes to product labelling information. However, multiple related changes may be submitted in the same supplement (see section 7).

The establishment of regional NRA associations or networks that can serve as forums for sharing information and exchanging experience on technical issues and regulatory decisions is highly encouraged. The development of such networks would expand the capacity of individual NRAs through work-sharing and recognition of the decisions of other NRAs in the network, thus avoiding unnecessary repetition of evaluations of the same change by multiple members of the network. NRA associations should establish work-sharing procedures that ensure the protection of confidential proprietary information with the engagement of MA holders and experts on the proprietary laws of each country. Any regional association or network of NRAs should, at a minimum, ensure the confidential nature of the technical information in the MA or licence application, especially information on product quality.

Establishing networks would be part of capacity-building activities for countries in each region. A fully functional regional network would be a

long-term goal, but cooperation can begin in the short term with the sharing of scientific information and experience regarding regulatory decisions on the evaluation of changes to approved products. Meetings should be organized periodically to promote transparency and mutual confidence between the NRAs. Effective regional networks could serve as the foundations for achieving full mutual recognition among NRAs.

In these WHO Guidelines, descriptions of the reporting categories are provided for both quality changes (section 5) and for safety, efficacy and product labelling information changes (section 6). Proposed recommendations on the regulatory procedures for the reporting of changes to NRAs are described in section 7. Examples of suggested review timelines for changes in the various categories are given in Appendix 1. A comprehensive list of quality changes and the type of information that should be included in a supplement application are provided in Appendix 2 (for the antigen and intermediates) and Appendix 3 (for the final product). Examples of changes that affect clinical use and product labelling information (safety, efficacy, dosage, administration, vaccine components and expiry date) are provided in Appendix 4.

4. Terminology

The definitions given below apply to the terms as used in these WHO Guidelines. They may have different meanings in other contexts, including the compendial references and regulations or guidelines issued by NRAs and by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

Adjuvant: a substance or combination of substances used in conjunction with a vaccine antigen to enhance (for example, increase, accelerate, prolong and/or possibly target) or modulate a specific immune response to the vaccine antigen in order to enhance the clinical effectiveness of the vaccine.

Antigen: the following definitions apply in this document:

- The active ingredient in a vaccine against which the immune response is induced. Antigens may be: (a) live attenuated or inactivated preparations of bacteria, viruses or parasites; (b) crude cellular fractions or purified antigens, including recombinant proteins (that is, those derived from recombinant DNA expressed in a host cell); (c) polysaccharides and conjugates formed by covalent linkage of polysaccharides to components such as mutated or inactivated proteins and/or toxoids; (d) synthetic antigens; (e) polynucleotides (such as plasmid DNA vaccines); or (f) living vectored cells expressing specific heterologous antigens. Also referred to as "immunogen" in other documents.

- Also used to describe (a) a component that may undergo chemical change or processing before it becomes the antigen or active ingredient used to formulate the final product (also referred to as an "intermediate" in other documents); or (b) an active ingredient present in an unmodified form in the final product (also referred to as "drug substance" or "active substance" in other documents). For example, in this document the term "antigen" applies, in the case of a polysaccharide conjugated vaccine, to the polysaccharide intermediate as well as to the conjugated polysaccharide that will not undergo further modification prior to formulation.

Cell bank: a collection of vials of cells of uniform composition (though not necessarily clonal) derived from a single tissue or cell, and used for the production of a vaccine directly or via a cell bank system. The following terms are used in these Guidelines – **master cell bank (MCB):** a bank of a cell substrate from which all subsequent cell banks used for vaccine production will be derived. The MCB represents a well characterized collection of cells derived from a single tissue or cell; and **working cell bank (WCB):** a cell bank derived by propagation of cells from an MCB under defined conditions and used to initiate production of cell cultures on a lot-by-lot basis. Also referred to as "manufacturer's working cell bank" in other documents.

Change: refers to a change that includes, but is not limited to, the product composition, manufacturing process, quality controls, equipment, facilities or product labelling information made to an approved MA or licence by the MA holder. Also referred to as "variation" in other documents.

Comparability study: the activities, including study design, conducting of studies and data evaluation that are designed to investigate whether the pre- and post-change products are comparable. In addition to routine analysis performed during production and control of the antigen or final product, these evaluations typically include a comparison of manufacturing process steps and parameters impacted by the change, characterization studies and an evaluation of product stability following the change. In some cases, nonclinical or clinical data might contribute to the conclusion reached.

Comparability protocol: establishes the tests to be done and acceptable limits to be achieved to demonstrate the lack of a negative effect of specific manufacturing changes on the safety or effectiveness of the product. A comparability protocol is a highly specific, well defined plan for the future implementation of a quality (that is, manufacturing) change. Also referred to as "post-approval change management protocol" in other documents.

Container closure system: refers to the following components: (a) a primary container closure system is a packaging component (for example, a vial or pre-filled syringe) that is in, or may come into, direct contact with the final

product dosage form, or components that contribute to the container/closure integrity of the primary packaging material for a sterile product; and (b) a secondary container closure system is a packaging component (for example, a carton or tray) that is not, and will not be, in direct contact with the dosage form.

Dosage form: in this document "dosage form" refers to the physical form in which a pharmaceutical product is presented by the manufacturer (form of presentation) and the form in which it is administered (form of administration). Also referred to as "pharmaceutical form" in other documents.

Excipient: any component of the final product other than the active component/antigen and the packaging material. Also referred to as "inactive ingredient" in other documents. In the context of this document, adjuvants are not considered to be excipients.

Final lot: a collection of sealed final containers that is homogeneous with respect to the composition of the product and the risk of contamination during filling. A final lot must therefore have been filled from a formulated bulk in one continuous working session.

Final product: a finished dosage form (for example, suspension or lyophilized cake) that contains an active ingredient, generally but not necessarily in association with inactive ingredients (excipients) or adjuvants. Also referred to as "finished product" or "drug product" in other documents.

Formulated bulk: an intermediate in the drug product manufacturing process, consisting of the final formulation of antigens, adjuvants and excipients at the concentration to be filled into primary containers.

Intermediate: a material produced during steps in the manufacture of a vaccine that undergoes further processing before it becomes the final product. See the definition for **Antigen** above.

Manufacturer: any person or legal entity engaged in the manufacture of a product subject to MA or licensure. In other documents, "manufacturer" may also refer to any person or legal entity that is an applicant or a holder of a MA or product licence where the applicant assumes responsibility for compliance with the applicable product and establishment standards. See the definition for **Marketing authorization holder** below.

Marketing authorization (MA): a formal authorization for a medicine to be marketed. Once an NRA approves an MA application for a new medicine, the medicine may be marketed and may be available for physicians to prescribe. Also referred to as "product licence" or "licence" in this and other documents.

Marketing authorization application (MA application): a formal application to the NRA for approval to market a new medicine. The purpose of the MA application is to determine whether the medicine meets the statutory standards for safety, effectiveness, product labelling information and manufacturing. Also referred to as "licence application" in other documents.

Marketing authorization holder (MA holder): any person or legal entity that has received MA or licensure to manufacture and/or distribute a medicine. It also refers to a person or legal entity allowed to apply for a change to the MA or licence. Also referred to as the "manufacturer" or "applicant" in this and other documents.

Product labelling information: printed materials that accompany a prescription medicine and all labelling items, namely: (a) prescribing information (an instruction circular that provides product information on indication, dosage and administration, safety and efficacy, contraindications and warnings, along with a description of the product for health care providers (also referred to as "summary of product characteristics" or "package insert" in various countries); (b) patient labelling or consumer information; (c) inner label or container label; and (d) outer label or carton.

Quality attribute: a physical, chemical, biological or microbiological property or characteristic. A critical quality attribute refers to a characteristic or property that should be within an appropriate limit, range or distribution to ensure the desired product quality.

Quality change: in the context of this document, quality change refers to a change in the manufacturing process, product composition, quality control testing, equipment or facility. Also referred to as "chemistry manufacturing and control (CMC) change" in other documents.

Raw materials: a general term used to denote reagents or solvents intended for use in the production of starting materials, intermediates or final products.

Seed lot: a preparation of live cells (prokaryotic or eukaryotic) or viruses constituting the starting material for the vaccine antigen. A seed lot is of uniform composition (although not necessarily clonal), is derived from a single culture process and is aliquoted into appropriate storage containers, from which all future vaccine production will be derived either directly or via a seed lot system. The following derived terms are used in these Guidelines – **master seed lot (MSL):** a lot or bank of cells or viruses from which all future vaccine production will be derived. The MSL represents a well characterized collection of cells or viruses of uniform composition. Also referred to as "master virus seed" for virus seeds, "master seed bank" or "master seed antigen" in other documents; and **working seed lot (WSL):** a cell or viral seed lot derived by propagation from the MSL under defined conditions and used to initiate production of vaccines on a lot-by-lot basis. Also referred to as "working virus seed" for virus seeds, "working seed bank" or "working seed antigen" in other documents.

Specification: the quality standard (that is, tests, analytical procedures and acceptance criteria) provided in an approved application to confirm the quality of antigens (drug substances), final products (drug products), intermediates, raw materials, reagents, components, in-process materials, container closure systems

and other materials used in the production of the antigen (drug substance) or final product (drug product). For the purpose of this definition, acceptance criteria mean numerical limits, ranges or qualitative criteria for the applied tests.

Starting material: any material used at the beginning of the manufacturing process, as described in an MA or product licence. Generally, the term refers to a substance of defined chemical properties and structure that contributes an important and/or significant structural element (or elements) to the active substance (for example in the case of vaccines, synthetic peptides, synthetic glycans and starting materials for adjuvants). The starting material for an antigen (drug substance) obtained from a biological source is considered to consist of: (a) cells; (b) microorganisms; (c) plants, plant parts, macroscopic fungi or algae; or (d) animal tissues, organs or body fluid from which the antigen (drug substance) is derived.

Supplement: written request submitted to the NRA to approve a change in the original application for MA (or product licence) or any other notification to add to (that is, supplement) the information in the original MA or product licence file. A prior approval supplement (PAS) is a supplement requiring approval from the NRA prior to implementation of the change. Also referred to as "change application dossier" in other documents.

Vaccine: a preparation containing antigens capable of inducing an active immune response for the prevention, amelioration or treatment of infectious diseases.

Vaccine efficacy: the relative reduction in disease incidence or severity in vaccinated individuals compared to unvaccinated individuals measured in a randomized, placebo-controlled clinical trial. In the context of these Guidelines, vaccine efficacy has a broad meaning and relates to all clinical data obtained to ensure vaccine efficacy, immunogenicity or field effectiveness.

5. Reporting categories for quality changes

Based on the potential effect of the quality change (for example, manufacturing change) on the quality attributes (that is, identity, strength, purity and potency) of the vaccine, and the potential impact of this on the safety or efficacy of the vaccine, a change should be categorized and identified as:

- a major quality change
- a moderate quality change, or
- a minor quality change.

The implementation of changes in the major or moderate categories requires reporting to the NRA in order to supplement the information in the

original MA or product licence. The major and moderate quality changes should be reviewed and approved by the NRA prior to implementation of the change.

Minor quality changes that are expected to have a potential minimal effect or no effect on the quality, safety or efficacy of the vaccine do not require submission of a supplement. The changes included in this category may be implemented by the MA holder without prior review and approval by the NRA. However, a list of minor changes should be made available by the MA holder upon request by the NRA.

Further information on each category is given below. In addition, Appendices 2 and 3 provide a comprehensive list of major, moderate and minor quality changes, and the information required to support each change. Appendix 2 includes changes to the antigen or intermediates and Appendix 3 includes changes to the final product. The quality changes listed in Appendices 2 and 3 should be reported or recorded in the appropriate categories, as recommended in this section and in the appendices. If a quality change may potentially have an impact on the quality, safety or efficacy of the vaccine, but is not included in Appendix 2 or 3, the NRA may be consulted for the correct classification. When procedures and timelines for such consultations are not in place, manufacturers should determine the classification of the change based on a change-specific risk assessment using the principles and examples provided in this document. The NRA should consider establishing a mechanism that allows for the updating of its guidelines to address technological changes that require new regulatory category classifications.

5.1 Major quality changes

Major quality changes are changes to the product composition, manufacturing process, quality controls, facilities or equipment that have significant potential to have an impact on the quality, safety or efficacy of the vaccine. The MA holder should submit a PAS and receive a notification of approval from the NRA before implementing the change. For a change in this category, the supplement should specify the products concerned and should include a detailed description of the proposed change. Additional supporting information is needed, as noted in Appendix 2 for the antigen and in Appendix 3 for the final product, and should include information on: (a) the methods used and studies performed to evaluate the effect of the change on the product's quality attributes; (b) the data derived from those studies; (c) relevant validation protocols and results; (d) updated product labelling information; and (e) summaries of relevant standard operating procedures (SOPs) or a list referencing previously approved relevant SOPs. In some cases, major quality changes may also require nonclinical and/or clinical data. The recommendations given in WHO guidelines on nonclinical evaluation of vaccines (*4*), Guidelines on clinical evaluation of vaccines: regulatory

expectations (*5*), Guidelines on stability evaluation of vaccines (*6*), other related WHO guidance (*7–12*), and recommendations for specific products and adjuvants should apply.

5.2 Moderate quality changes

Moderate quality changes are changes to the product composition, manufacturing process, quality controls, facilities or equipment that have a moderate potential to have an impact on the quality, safety or efficacy of the vaccine. The MA holder should submit a supplement and receive a notification of approval from the NRA before implementing the change. The requirements for the supplement content of the moderate quality changes are the same as for the major quality changes (see section 5.1 above). However, the amount of supporting data required will generally be less than for major changes and the review time should be shorter.

5.3 Minor quality changes

Minor quality changes are changes to the product composition, manufacturing process, quality controls, facilities or equipment that have a minimal potential to have an impact on the quality, safety or efficacy of the vaccine. The changes included in this category may be implemented by the MA holder without prior review by the NRA (that is, such changes do not need to be reported to and approved by the NRA). However, these changes must be retained as part of the product's record by the manufacturer or MA holder, must comply with GMP requirements and must be available for review during GMP inspections.

When a minor quality change affects the lot release specifications (for example, narrowing of a specification, or compliance with pharmacopoeial changes) and affects the quality control testing as summarized in the vaccine lot release protocol, the MA holder should inform the institution responsible for reviewing the release of vaccine lots (see introductory sections in Appendices 2 and 3).

For each approved product, the MA holder or manufacturer should maintain a comprehensive chronological list of all quality changes, including minor quality changes that occur in all production areas. Additionally, this list should include a description of the manufacturing and quality control changes, including the manufacturing site(s) or area(s) involved, the date each change was made, and the references of relevant validations and SOPs. The data to support minor quality changes, as listed in Appendices 2 and 3, should be available to the NRA upon request or during inspections.

When minor quality changes are related to a major or moderate change, they should be described in the supplement for the major or moderate quality change (see section 7.2).

6. Reporting categories for safety, efficacy and/or product labelling information changes

After assessing the effect of a change related to clinical use or to product labelling information on the safe and effective use of a vaccine, MA holders should classify this change as belonging to one of the following categories:

- a safety and efficacy change;
- a product labelling information change;
- an urgent product labelling information change; or
- an administrative product labelling information change (in cases where prior approval before implementation is needed).

The product labelling information includes prescribing information (or package insert) for health care providers or patients, outer label (carton), and inner label (container label). After approval, the MA holder should promptly revise all promotional and advertising items relating to the vaccine to make them consistent with implementation of the product labelling information change.

Further information on each category is provided in the following sections, with examples of efficacy, safety and product labelling information changes considered to be appropriate for each category provided in Appendix 4.

6.1 Safety and efficacy changes

Safety and efficacy changes are changes that have an impact on the clinical use of the vaccine in relation to safety, efficacy, dosage and administration, and that require data from clinical studies to support the change. Safety and efficacy changes require supplement submission and approval prior to implementation.

Generally, safety and efficacy changes affect the product labelling information and have the potential to increase or decrease the exposure levels of the vaccine, either by expanding the population that is exposed or by changing dosage or dosing. These changes may relate to the clinical use of the vaccine, for example:

- addition or expansion of a safety claim or efficacy claim, including expansion of the population that is exposed;
- change in the strength or route of administration;[1]

[1] Some NRAs consider that changes in the route of administration or strength may require a new MA. Furthermore, in some cases, changes involving the subcutaneous and intramuscular administration routes may not require a new application while others, such as changes from intramuscular to intranasal administration routes, may require a new application.

- change in the recommended dose and/or dosing schedule, including the addition of a booster dose;
- co-administration with other vaccines or medicines;
- deletion or reduction of existing risk-management measures (such as contraindications, adverse events, warnings or cautionary text/ statements in the product labelling information).

The type and scope of the required supporting nonclinical and/or clinical safety and efficacy data are determined case by case on the basis of risk–benefit considerations related to the impact of the changes, the vaccine attributes and the disease that the vaccine is designed to prevent. Other considerations include:

- robustness of the immune response elicited by the vaccine and availability of a correlate of protection (that is, data establishing a threshold level of antibody needed to protect against the development of disease following exposure);
- availability of animal models;
- vaccine attributes (for example, live as opposed to inactivated vaccines).

MA holders are encouraged to consult with NRAs on the adequacy of the clinical data needed to support a safety and efficacy change if deemed necessary. Additionally, some changes such as dosage form, content of excipients or residual components, or delivery device may require clinical data as well as revision of the product labelling information. NRAs may also be consulted on the data required to support such changes.

For nonclinical and clinical studies, the recommendations given in WHO guidelines on nonclinical evaluation of vaccines (*4*), Guidelines on clinical evaluation of vaccines: regulatory expectations (*5*) and other related WHO guidance (*7–12*) should apply.

For a change under this category, the MA holder should submit a supplement to the NRA that may include the following:

- detailed description and rationale of the proposed change;
- summary of the methods used and studies performed to evaluate the effect of the change on the vaccine's safety or efficacy;
- amended product labelling information;
- clinical studies (protocol, statistical analysis plan and clinical study report);
- clinical assay methods (including SOPs) and validations;
- the pharmacovigilance plan.

6.2 Product labelling information changes

Product labelling information changes are changes to the labelling items that have the potential to improve the management of risk to the population currently approved for use of the vaccine through:

- identification or characterization of any adverse event following immunization (AEFI) resulting in the addition or strengthening of risk-management measures for an adverse event identified to be consistent with a causal association to immunization with the vaccine concerned;
- identification of subgroups for which the benefit-to-risk profile of the vaccine has the potential to be less favourable;
- addition or strengthening of risk-management measures, including instructions on dosing or any other conditions of use.

Product labelling information changes require supplement submission and approval prior to distribution of the product. Supplements for product labelling information changes related to clinical use often require data from pharmacovigilance reports ("periodic safety update reports"). Changes supported by large clinical or nonclinical studies are usually not considered as product labelling information changes but as safety and efficacy changes.

For a change under this category, the MA holder should submit a supplement to the NRA that may include the following:

- detailed description and rationale of the proposed change
- pharmacovigilance reports and statistical analysis of results
- amended product labelling information.

6.3 Urgent product labelling information changes

Urgent product labelling information changes are changes to the labelling items that need to be implemented in an expedited manner in order to mitigate a potential risk to the population currently approved for use of the vaccine. MA holders should consult with the NRA and agree on the supporting documentation required prior to supplement submission.

6.4 Administrative product labelling information changes

Administrative product labelling information changes are changes that are not expected to affect the safe and efficacious use of the vaccine. In some cases, these changes may require reporting to the NRA and receipt of approval prior to implementation, while in other cases reporting may not be required, as follows:

- Examples of product labelling information changes that require approval by the NRA prior to implementation are changes in the name of the MA holder that are due to a merger, or changes in the proper name or trade name of the vaccine. The changes in this category are considered important for reasons of liability and monitoring.
- Examples of product labelling information changes that do not require approval by the NRA prior to implementation are changes to a distributor's address or minor changes in format. These changes should be reported to the NRA as part of subsequent supplements for safety and efficacy changes or product labelling information changes when updated product labelling information is included.

7. Procedures

Establishing procedures and criteria for the adequate oversight of changes is the responsibility of the regulators. Therefore, NRAs should establish written instructions regarding the submission procedures and timelines with action dates, to be consulted by MA holders when they prepare to submit a supplement for a change. As supplements for a major quality change or an efficacy and safety change require extensive documentation and data, the review times should be longer than those for supplements for moderate quality changes or product labelling information changes. Furthermore, NRAs may establish different timelines for reviews of major quality changes that do not require clinical data, compared to safety and efficacy changes that do require clinical data. Examples of regulatory categories and review timelines are provided in Appendix 1 below.

MA holders may contact the NRA to determine the appropriate category of a supplement prior to submission of the information in support of a change, especially if the change is not included in Appendices 2–4 of this document. Similarly, MA holders may also consult NRAs for major changes (such as the introduction of new equipment, change in process step or facility expansion) that require the inclusion of a GMP certificate and may trigger a pre-submission inspection, or that may require clinical data to support a change in safety and efficacy or in product labelling information. MA holders should generally be encouraged to contact the NRA regarding plans for future changes and proposed filing dates for changes to existing products in order to aid NRAs in planning the allocation of review resources. NRAs should establish procedures for the conducting and recording of communications between themselves and MA holders.

To aid in the acceptance of submissions for review, the covering letter accompanying a supplement for a quality change should specify that the change is being reported in the selected category by labelling the submission as either a major quality change or a moderate quality change.

The covering letter accompanying a supplement for a safety, efficacy or product labelling information change should specify that the change is being reported in the selected category by labelling the submission as:

- a safety and efficacy change;
- a product labelling information change;
- an urgent product labelling information change; or
- an administrative product labelling information change (in cases where prior approval is needed before implementation).

Major quality change supplements that contain both quality data and revised product labelling information but no clinical data should be labelled "Major quality change and product labelling information change" and the covering letter should specify that the submission includes both quality changes and revised product labelling information items.

Major quality change supplements that contain quality, safety and efficacy data (from clinical studies) and revised product labelling information, should be labelled "Major quality change and safety and efficacy change" and the covering letter should specify that the submission includes quality changes, results from clinical studies and revised product labelling information items.

Each supplement should include a list of all the changes contained in the submission. The list should describe each change in sufficient detail to allow the NRA to determine quickly whether the appropriate reporting category has been used. The list should be part of the covering letter. If the submission has been inappropriately classified, the MA holder should be notified. Minor quality changes that are related to a moderate or major quality change should be included in the PAS if they were implemented after the submission of a previous supplement for a moderate or major quality change. For example, a minor change such as the narrowing of a specification should be included in a supplement for a moderate or major change which includes updated quality control release information.

Regulation of post-approval changes is part of the whole regulatory framework which incorporates elements such as MA, GMP inspection, lot release and post-marketing surveillance (PMS). These activities are often performed by different branches of the NRA. It is essential that these different branches – particularly the MA (or regulatory affairs), GMP inspection and lot release branches – interact and exchange information effectively and that the roles and responsibilities of each branch are clearly defined, especially when they operate as separate entities. When multiple branches are involved in the evaluation of a supplement, a formal decision-making process should be in place to discuss, for example, whether a change may require a GMP inspection or may be reviewed

during the next routine inspection. Procedures should also be established so that the outcomes of inspections are verified or taken into account prior to the approval of supplements. Good coordination and communication are pivotal.

Expedited review procedures

NRAs of vaccine-procuring countries that decide to recognize the decisions of other NRAs should establish alternative regulatory procedures for the expedited approval of changes based on previous expert review and approval by the NRA of the country where the vaccines are produced and/or licensed (see Appendix 1). On the basis of regulatory and regional considerations, regulatory procedures for recognizing the decision of other NRAs on the approval of changes could include:

- The NRA recognizes the decision of other regulatory authorities and does not perform a review of supporting data, but is informed of the change. The submission consists of a covering letter from the MA holder informing the procuring NRA of the change and including as an attachment a copy of the approval letter issued by the NRA of the producing and/or licensing country.
- The NRA performs an assessment of the decision of the NRA from the producing and/or licensing country to determine if recognition of that NRA's decision is appropriate. The submission consists of: (a) the covering letter from the MA holder informing the procuring NRA of the change; (b) a copy of the approval letter issued by the NRA of the producing and/or licensing country; (c) assessment reports and relevant correspondence from the NRA of the producing and/or licensing country (if made available by the NRA); and (d) a detailed description of the change with no supporting data.
- The NRA performs a partial review and evaluation of a complete package of supporting data, as originally submitted in the vaccine-producing and/or -licensing country and/or as recommended in these WHO Guidelines.

Similarly, recognition of inspection activities conducted by the authorities in the place where a vaccine is produced may also be considered part of the expedited review process, and may be included in the regulatory pathways listed above.

Additionally, for previously approved changes addressing urgent safety issues in the product labelling information, procedures should be in place to allow for the expedited implementation of such changes (see section 7.4 and Appendix 1).

In special or urgent circumstances, an MA holder may ask the NRA to expedite the review of a supplement for public health reasons (for example, a vaccine shortage, or during an epidemic or pandemic) or if a delay in making the change would impose extraordinary hardship on the MA holder or manufacturer.

Multiple changes

Multiple related changes, involving various combinations of individual changes, may be submitted in the same supplement. For example, a site change may also involve changes to the equipment and manufacturing process, or a vaccine component change may necessitate a change in a specification. For submissions that include multiple changes, the MA holder should clearly specify which data support each change.

Multiple major or moderate quality changes for the same vaccine may be filed in a single submission provided that the changes are related and/or supported by the same information. Minor quality changes that were implemented previously and that are related to a moderate or major quality change should be included in the supplement for the moderate or major quality change. If the changes are related, the MA holder should indicate the association between the proposed changes. Such changes could affect both the antigen and the final product. If too many changes are filed within the same submission, or if major issues are identified with a change and extensive time would be required to review them, the NRA may ask the MA holder to divide the changes into separate submissions and to re-submit the file. If the recommended reporting categories for the individual changes differ, the submission should be in accordance with the most restrictive of the categories recommended for the individual changes. In the case of numerous changes of the same category, the NRA may reclassify the submission to the next higher level on the basis of the potential impact of the totality of the changes on the quality, safety and efficacy of the vaccine. This reclassification should be communicated to the MA holder at the start of the assessment.

7.1 Procedures for prior approval supplements

The procedures in this section apply to all changes requiring approval prior to implementation: that is, major and moderate quality changes, safety and efficacy changes, product labelling information changes, urgent product labelling information changes and selected administrative product labelling information changes.

The following items should be included, where applicable, in the supplement submission for post-approval changes:

- A covering letter that includes: (a) the type of submission (for example, major quality change, moderate quality change, safety and efficacy change); (b) a list of the change(s) and a rationale for the change(s) with sufficient detail to allow for processing and reviewer assignments by NRAs; (c) an indication of the general type of supporting data; and (d) cross-referenced information if applicable (including product name, MA holder's name, submission type control number and date of submission/approval);
- Completed documents or forms based on NRA requirements, such as a medicines submission application form, signed and dated;
- The anticipated date for implementation of the change;
- GMP document information, as applicable;
- A rationale for the change and a justification for the selected reporting category;
- When relevant, a side-by-side comparison showing the differences between the approved manufacturing process (including quality control tests) and the proposed ones (see section 5);
- When relevant, clinical study reports, pharmacovigilance reports, and annotated and clean drafts of product labelling information (see section 6).

In addition to the above common information items, the specific information required to support the various quality changes is outlined in Appendices 2 and 3. It should be noted that the common information items listed above are not included under each of the various changes outlined in these appendices. All data recommended to support a change should be provided with the submission along with all appropriate common information items. When recommended supporting data cannot be submitted, a detailed rationale should be provided.

If the same change is applicable to multiple products, a separate submission is generally required for each product but the data may be cross-referenced. When cross-references are made to information that has been submitted previously, the details of the cross-referenced information should be indicated in the covering letter (for example, brand name of the product, name of manufacturer and/or MA holder, submission type, control number and date approved).

Submissions filed in electronic or paper format should be based upon the requirements of the NRA. The data submitted should be well organized and should be provided in the format defined by the NRA.

After the NRA completes the review of the supporting data in a supplement there are two possible outcomes:

- If the NRA determines that the information in a supplement indicates no adverse impact on the quality, safety or efficacy of the product manufactured with the change, the NRA will issue a written approval notification by which the change can be implemented and the product manufactured with the change can be distributed.
- If the NRA determines that the information submitted in a supplement fails to demonstrate the quality, safety or efficacy of the product manufactured with the change, the NRA will issue a written request notification for additional documentation, information and clarification to be submitted by the MA holder. If the identified deficiencies are minor, they may be addressed without stopping the review clock. If the deficiencies are major or are not resolved during the allotted review time frame, the NRA may decide to issue a written notification of noncompliance by means of which the review clock is stopped, the change may not be implemented and the product manufactured with the change may not be distributed.

In the case of a noncompliance notification being issued, the following outcomes are possible:

- If the information in the MA holder's response document to the noncompliance notification is adequate and all identified deficiencies are resolved in a satisfactory manner, the NRA will issue a written notification of approval by which the change can be implemented and the product manufactured with the change can be distributed.
- If the information in the MA holder's response document to the noncompliance notification is not adequate and not all identified deficiencies are resolved in a satisfactory manner, the NRA will issue a written notification of rejection by means of which the change cannot be implemented and the product manufactured with the change cannot be distributed.

The NRA should establish procedures and timelines for the review of the MA holder's responses to the notification of noncompliance in cases where the review is stopped. Documentation subsequent to the original supplement submission (in response to information requests or noncompliance notifications) should be submitted and filed as amendments to the original supplement, and communications with MA holders should be properly recorded.

Appeal procedures should be established for resolving disagreements and disputes between the NRA and the MA holder. Such procedures should allow the MA holder to request a re-evaluation of the submitted application in cases where the application is rejected by the NRA.

In some cases, following approval, the distribution of a vaccine made with a change may be delayed to allow for depletion of the previously approved vaccine or to allow for global approval. Therefore, the MA holders should provide the anticipated date for implementation of the change. If deemed necessary, any issues related to the implementation dates and distribution of product with the approved manufacturing changes should be communicated to the NRA.

NRAs may consider the following approaches when an MA holder is submitting changes.

Comparability protocol

A comparability protocol (also referred to as a "post-approval change management protocol" in other documents) establishes a framework for a well defined and highly specific plan for the future implementation of a quality change, including the tests to be done and acceptable limits to be achieved to demonstrate the lack of negative effects caused by specific manufacturing changes on the quality, safety or efficacy of a vaccine. For some changes, the routine quality tests performed to release the antigen or final product are not considered adequate for assessing the impact of the change, and additional in-process tests and characterization tests may be needed (for example, addition of bioburden and endotoxin tests to support the removal of preservatives from the manufacturing process). Comparability protocols are often used for the routine replenishment of WCBs and reference standards used in quality control tests when the remaining aliquots of reference standards expire or diminish.

The purpose of a comparability protocol is to allow for a more expedient distribution of a product by permitting the MA holder to submit a protocol for a change which, if approved, may justify a reduced reporting category for the change when the comparability data are obtained and the change is implemented. This concept is not discussed in further detail in these Guidelines as the use of a comparability protocol is not currently harmonized among NRAs. It is the decision of the NRA whether or not to include the review and approval of comparability protocols in its approach to regulating changes to approved vaccines. For NRAs currently taking this approach, a new comparability protocol, or a change to an existing one, requires submission of a supplement and approval prior to implementation because it may result in a lower reporting category for the changes covered in the comparability protocol once the actual comparability data are submitted. The change in reporting category for the comparability protocol in relation to the comparability data should be established by the NRA at the time the comparability protocol is approved.

Production documents

Production documents (that is, executed lot records) are not required to support changes to the MA dossier or product licence. However, such documents may be requested during review and should be available to the NRA upon request or during inspections.

7.2 Procedures for minor quality changes

Minor quality changes do not require notification to, or prior approval from, the NRA for their implementation. However, any minor changes that have been implemented should be noted in the affected documents (for example, SOPs and batch records). As recommended in Appendices 2 and 3 of this document, minor quality changes should be recorded or compiled with related supporting data in a document or file dedicated to minor changes. The documents or files for all minor quality changes should be available to the NRA upon request or during inspections.

Minor quality changes that have previously been implemented and are related to a major or moderate quality change should be described in the relevant parts of the documentation when submitting a PAS for the major or moderate change. As for all minor quality changes, the supporting data for these changes do not need to be included in the supplement but should be retained by the manufacturer. In general, changes to SOPs which are not mentioned in Appendices 2 and 3 do not need to be submitted to the NRA for approval.

NRAs may audit minor quality changes by requesting and reviewing the supporting data, as deemed appropriate during an inspection or review of related changes. If the classification of the change or the supporting data are not considered to be acceptable, the MA holder may be requested to file a major or moderate quality change supplement.

For changes that are not reported, if the NRA determines (during an inspection or review of related changes) that the information relating to the change fails to demonstrate the continued safety or efficacy of the product manufactured using the changes, the NRA will try to resolve the problem with the MA holder. If the NRA finds that the product in distribution poses a danger to public health, or if it determines that there are unresolved issues, it may require the MA holder to cease distribution of the product manufactured using the changes or to remove the product from distribution pending resolution of the issues related to the changes.

7.3 Procedures for urgent product labelling information changes

For urgent changes to product labelling information which address safety updates and have the potential to have an impact on public health (for example, the addition of a contraindication or warning) NRAs should establish a specific

mechanism to allow for the immediate or speedy approval and implementation of such changes on a case-by-case basis after previous agreement between NRAs and MA holders.

Since product labelling safety updates invariably need to be implemented and are generally approved, NRAs should establish a mechanism by which urgent product labelling changes that have been approved in the country where the vaccines are produced and/or licensed may be implemented immediately upon receipt of the supplement by the NRAs of countries procuring the vaccines. Such accelerated procedures would contribute to the dissemination of the most current information to health care providers, and would also help to mitigate the effects of discrepancies between labelling information in different countries and between the information posted on different web sites.

7.4 Procedures for administrative product labelling information changes

Administrative product labelling information changes may require approval prior to implementation depending on the scope of the change. For example, changes in the name of the MA holder require approval before implementation while minor formatting changes do not (see Section 6.4).

For an administrative product labelling information change that requires approval prior to implementation, the MA holder should submit a supplement containing background information on the change, and annotated and clean drafts of the product labelling information.

Administrative product labelling information changes that do not need prior approval and that have been implemented since the last approved product labelling information should be included when submitting subsequent supplements for safety and efficacy changes or for product labelling information changes. In these cases, the product labelling information should be annotated when filing the next PAS to indicate the new changes and those administrative changes that have been implemented since the last approval.

8. Special considerations

8.1 Adjuvants

Because adjuvants are considered to be components of vaccines, each new adjuvanted vaccine is considered to be a new entity that will require appropriate physicochemical characterization and nonclinical and clinical evaluation. It is the specific antigen-adjuvant formulation (as a whole) that is tested in nonclinical and clinical trials and which receives MA or licensure on the basis of demonstration of safety and efficacy.

There is substantial diversity among vaccine adjuvants, antigens and the diseases they are designed to prevent. Therefore, the supporting information needed for adjuvant-related changes will depend upon product-specific features, the clinical indications and the impact of the change. The recommendations in WHO Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines (*12*) should be followed.

8.2 Influenza vaccines

To ensure that influenza vaccines are effective against circulating influenza viruses, WHO reviews global virological and epidemiological data twice a year, and if necessary recommends new vaccine strain(s) in accordance with the available evidence for the northern and southern hemispheres (*13*, *14*). WHO and NRAs recommend the use of certain vaccine virus strains on the basis of their antigenic characteristics. Influenza vaccine viruses are usually derived from isolates obtained from laboratories in the WHO Global Influenza Surveillance and Response System.

For seasonal influenza vaccines, annual changes in the vaccine strain composition are considered to be moderate quality changes because of extensive experience with such changes and in order to maximize the flexibility and brevity of the review process. MA holders of approved seasonal vaccines are expected to submit a supplement for a moderate quality change to support annual changes in the influenza strain composition. To allow for the timely distribution of vaccines, NRAs should review the supplement as part of a streamlined and prompt process. The supporting quality information generally consists of: (a) information on the source of the seed viruses; (b) passage history until establishment of working seeds; (c) results of quality release tests performed on working virus seeds (including identity confirmation); and (d) specific validation data (including inactivation kinetics). Generally, stability data for antigen bulks or final drug product produced in the previous influenza season are expected to be submitted to continuously support the approved shelf-life. In addition, updated product labelling information items (package insert and inner and outer labels with relevant strain composition and formula year) should be provided (*13*).

Changes to the manufacturing processes, posology and product labelling information of influenza vaccines that are not related to the annual update should follow the normal categorization process, as described in Appendices 2–4, and should not be included in the strain change supplements to avoid delays in the approval process. Due to time constraints related to the seasonality of influenza vaccines, changes that are not related to vaccine strain composition should be timed such that approval will allow for vaccines manufactured with the change to be distributed prior to the start of the influenza season.

8.3 Bridging studies

Clinical bridging studies are trials in which a parameter of interest (such as manufacturing process, formulation or dosing schedule) is directly compared with a changed version of that parameter with respect to the effect of the change on the product's clinical performance. The comparison of immune responses and safety outcomes (for example, rates of common and serious AEFIs) is often the primary objective. If the immune response and safety profiles are similar, the safety and efficacy of the vaccine can be inferred.

In some cases, safety and efficacy data comparing the approved vaccine to the vaccine produced with the change may be required by NRAs. The following are examples of manufacturing changes that may require clinical bridging studies:

- use of a new or re-derived antigen (that is, re-derived virus seed or bacterial cell bank) or host cell line (that is, re-derived MCB);
- new agents used for inactivation or splitting of the antigen;
- a new dosage form;
- a new formulation (for example, amount of ingredients, adjuvants, preservatives or reactogenic residual components from the manufacturing process).

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The first draft of the document was prepared by Dr S. Gagneten, United States Food and Drug Administration Center for Biologics Evaluation and Research, USA; Ms S. Boucher, Health Canada, Canada; Mr M. Welin, Medical Products Agency, Sweden; Dr D. Lei, World Health Organization, Switzerland; Dr H. Meyer, Paul-Ehrlich-Institut, Germany; with contributions from the following drafting group members: Mrs S. Srivastava, Central Drugs Standard

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vaccine manufacturers during a round of public consultation on the WHO Biologicals website in 2014. Further changes were then made by the WHO Expert Committee on Biological Standardization.

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Appendix 1

Reporting categories and suggested review timelines

It is recommended that NRAs establish review timelines to allow MA holders or applicants to plan the implementation of changes. The review times established will depend upon the capability of the NRA, the impact of the change and the amount of data required to support the change. As a result, the review time frames for major changes should be longer than those for moderate changes. The review times suggested in Table 1 below are shown as examples, based upon the experience of several NRAs, and apply to situations where the NRA performs a full review or assessment of the supplement. The review time would start when the supplement has been accepted for review and found to be complete and would end at the time when the initial assessment is shared with the MA holder, either by the issuance of an approval notification or a noncompliance notification with a list of comments and deficiencies. In the case of the latter, the MA holder may seek approval for the change by submitting an amendment to the supplement with responses to all the comments in the notification of noncompliance. The NRA should also establish timelines for the secondary review cycle following the receipt of responses from the MA holder. If minor deficiencies are identified during the initial review cycle, the NRA may communicate these to the MA holder without stopping the clock to try to finalize the assessment within the established timeline (see section 7.1).

For product labelling information changes which address urgent safety issues, procedures should be in place to allow for the expedited implementation of such changes (see section 7.4).

For annual updates of influenza virus strain composition, the review timeline of moderate quality change supplements should be as short as possible (around 30 days). This may be achieved by reducing the amount of supporting information required and by clearly describing to MA holders the required content and format of the information to be submitted (see section 8.2).

Table 1

Examples of review timelines for a prior approval supplement (PAS)

Category	Supplement	Maximum review period
	Quality changes	
Major quality changes	PAS	6 months
Moderate quality changes	PAS	3 months

Table 1 *continued*

Category	Supplement	Maximum review period
	Quality changes	
Minor quality changes	Do not require notification to the NRA[a]	N/A
	Safety, efficacy and product labelling information changes	
Safety and efficacy changes	PAS	10 months
Product labelling information changes	PAS	5 months
Urgent product labelling information changes[b]	PAS for urgent safety restrictions	Immediate implementation on receipt of supplement by the NRA
Administrative product labelling information changes	PAS	30 days
	Do not require approval prior to implementation[c]	N/A

N/A: not applicable.

[a] Minor quality changes that are related to a moderate or major quality change should be included in the PAS if they have been implemented after the submission of a previous supplement for a moderate or major quality change (for example, a minor change such as the narrowing of a specification should be included in a supplement for a moderate or major change which includes updated quality control release information).

[b] Urgent product labelling information changes are applicable only to label changes which address urgent safety updates or have the potential to have an impact on public health, with immediate implementation allowed after prior agreement between NRAs and MA holders.

[c] Administrative product labelling information changes that do not require approval prior to implementation and that have been implemented since the last approved product labelling information change should be reported by including all changes in subsequent supplements for safety and efficacy changes or product labelling information changes.

NRAs of countries that procure vaccines from countries where the vaccines are produced and/or licensed are encouraged to establish alternative regulatory procedures for the expedited approval of changes that have previously been approved by the licensing NRAs. As described in section 7 above, expedited regulatory approval procedures that could be established include:

- The NRA recognizes the decision of other regulatory authorities and does not perform a review of supporting data, but is informed of the change. Using this approach, NRAs could allow changes to be implemented immediately after receipt of the change notification.

- The NRA performs an assessment of the decision of the NRA of the producing and/or licensing country to determine if recognition of the latter's decision is appropriate. In this case, NRAs could establish abbreviated review timelines, such as 2 months for major quality changes, 4 months for safety and efficacy changes, and immediate implementation upon receipt of the change notification for moderate quality changes and product labelling information changes.
- The NRA performs a partial review and evaluation of a complete package of supporting data, as originally submitted in the vaccine producing and/or licensing country and/or as recommended in these WHO Guidelines. In this case, timelines could range from those shown in Table 1 or could be abbreviated as described in the preceding bullet point.

Appendix 2

Changes to the antigen

The examples presented in this appendix are intended to assist with the classification of changes made to the quality information for a vaccine antigen. The information summarized in the antigen table below provides recommendations on:

- the ***conditions to be fulfilled*** for a given change to be classified as major, moderate or minor (if any of the conditions outlined for a given change are not fulfilled, the change is automatically considered to be the next higher level of change – for example, if any conditions recommended for a moderate quality change are not fulfilled, the change is considered to be a major quality change);
- the ***supporting data*** for a given change, either to be submitted to the NRA or maintained by the MA holder (if any of the supporting data outlined for a given change are not provided, are different or are not considered applicable then adequate scientific justification should be provided);
- the ***reporting category*** (that is, major, moderate or minor quality change).

It is important to note that the NRA reserves the right to request additional information or material, as deemed appropriate, or to define conditions not specifically described in this document in order to allow for adequate assessment of the quality, safety and efficacy of a vaccine. In addition, MA holders should contact the NRA if a change not included in the antigen table below has the potential to impact upon vaccine quality.

Supporting data should be provided according to the submission format accepted by the NRA. For example, for NRAs that accept the ICH common technical document (CTD) and/or ICH eCTD formatted submissions, the supporting data should be provided in the appropriate sections of the CTD modules and not in separate documents. For the placement of data in the appropriate section of the CTD please see the ICH guidelines (*1*, *2*).

For additional information on data requirements to support quality changes, WHO guidelines on GMP requirements and stability evaluation of vaccines (*3*, *4*) should be consulted, together with relevant ICH guidelines.

Quality changes to comply with updated compendia and/or pharmacopoeia

NRAs should make a list of the recognized compendia and/or pharmacopoeia available to MA holders. Manufacturers are expected to comply with the current versions of compendia and/or pharmacopoeia as referenced in the approved MA. Changes in the compendial and/or pharmacopoeial methods or specifications referenced by a particular NRA do not need to be submitted for review, but information on such changes should be available for inspection.

In some cases, changes to comply with recognized compendia and/or pharmacopoeia may require approval by the NRA prior to implementation regardless of the timing of the change with respect to the date the pharmacopoeia was updated. For example, supplement submission and approval by the NRA may be required for some changes to quality control tests performed for product release (for example, tests for potency), for changes which have an impact on any items of the product labelling information, and for changes which may potentially affect the quality, safety or efficacy of the product.

Quality changes affecting lot release

Where post-approval changes to the antigen affect the lot release protocol (for example, changes to test procedures, reference standards or laboratory sites) or sample testing requirements for lot release, the MA holder should inform the institution responsible for reviewing the release of vaccine lots. These procedures apply to changes that have been authorized by the NRA in the case of major and moderate quality changes and to changes that have been implemented in the case of minor quality changes. For example, the qualification of a new lot of reference standard against the approved reference standard may be considered a minor quality change if the qualification of a new standard is done in accordance with an approved protocol and specification. Nevertheless, these changes must be reported to the NRA or NCL as appropriate.

General information

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
1. Change in the name of the antigen *Note: This change generally applies only to influenza vaccines (see section 8.2).*	None	1, 2	Moderate
Conditions None			

Table *continued*

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Supporting data 1. Revised product labelling information (all labelling items). 2. Information on the proposed nomenclature of the antigen and evidence that the proposed name for the antigen is recognized (for example, proof of acceptance by WHO).			

Manufacture

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
2. Change to an antigen manufacturing facility:			
a. replacement or addition of a manufacturing facility for the antigen bulk, or any intermediate of the antigen	None	1–4, 6–8	Major
	1–4	2, 4–8	Moderate
b. deletion of a manufacturing facility or manufacturer of an antigen intermediate, or antigen bulk	5, 6	None	Minor
Conditions 1. The new manufacturing facility/suite is an approved antigen manufacturing site. 2. Any changes to the manufacturing process and/or controls are considered either moderate or minor. 3. The new facility/suite is under the same quality assurance/quality control (QA/QC) oversight. 4. The proposed change does not involve additional containment requirements. 5. There should remain at least one site/manufacturer, as previously authorized, performing the same function as the one(s) to be deleted. 6. The deletion should not be due to critical deficiencies in manufacturing (such as recurrent deviations, recurrent out-of-specification events, environmental monitoring failures and so on).			
Supporting data 1. Evidence that the facility is GMP compliant. 2. Name, address and responsibility of the proposed facility. 3. Process validation study reports.			

Table *continued*

Supporting data

4. Comparability of the pre- and post-change antigen with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may occasionally be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis, taking into consideration the quality-comparability findings, the nature and level of knowledge of the vaccine, existing relevant nonclinical and clinical data, and aspects of vaccine use.
5. Justification for the classification of any manufacturing process and/or control changes as moderate or minor.
6. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change antigen. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller-scale batches, and/or the use of fewer than 3 batches may be acceptable where justified and agreed by the NRA.
7. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale antigen batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months of testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the antigen under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
8. Updated post-approval stability protocol.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
3. Change to the antigen fermentation, viral propagation or cellular propagation process:			
a. a critical change (a change with high potential to have an impact on the quality of the antigen or final product) (for example, incorporation of disposable bioreactor technology)	None	1–7, 9, 11	Major

Table *continued*

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
b. a change with moderate potential to have an impact on the quality of the antigen or final product (for example, extension of the in vitro cell age beyond validated parameters)	2, 4	1–6, 8, 10	Moderate
c. a noncritical change with minimal potential to have an impact on the quality of the antigen or final product (for example, a change in harvesting and/or pooling procedures which does not affect the method of manufacture, recovery, intermediate storage conditions, sensitivity of detection of adventitious agents or production scale; or duplication of a fermentation train)	1–6, 9–11	1–4	Minor
4. Change to the antigen purification process involving:			
a. a critical change (a change with high potential to have an impact on the quality of the antigen or final product) (for example, a change that could potentially have an impact on the viral clearance capacity of the process or the impurity profile of the antigen)	None	1, 2, 5–7, 9, 11, 12	Major
b. a change with moderate potential to have an impact on the quality of the antigen or final product (for example, a change in the chemical separation method, such as from ion-exchange HPLC to reverse-phase HPLC)	2, 4	1, 2, 5–7, 10, 11	Moderate

Table *continued*

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
c. a noncritical change with minimal potential to have an impact on the quality of the antigen or final product (for example, addition of an in-line filtration step equivalent to the approved filtration step)	1–5	1, 2	Minor
5. Change in scale of the manufacturing process:			
a. at the fermentation, viral propagation or cellular propagation stage	3–6, 11–13	2, 3, 5–7, 9, 11	Moderate
b. at the purification stage	1, 3, 5, 7	2, 5–7, 9, 11	Moderate
6. Change in supplier of raw materials of biological origin (for example, fetal calf serum, human serum albumin, trypsin)	None	4, 8, 12, 13	Moderate
	8	4, 8	Minor
7. Change in source of raw materials of biological origin	None	4, 7, 12, 13	Moderate
	8	4, 7	Minor
8. Introduction of reprocessing steps	14	8, 10, 11, 14	Moderate

Conditions

1. No change in the principle of the sterilization procedures of the antigen.
2. The change does not have an impact on the viral clearance data or the chemical nature of an inactivating agent.
3. No change in the antigen specification outside the approved limits.
4. No change in the impurity profile of the antigen outside the approved limits.
5. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
6. The change does not affect the purification process.
7. The change in scale is linear with respect to the proportionality of production parameters and materials.
8. The change is for compendial raw materials of biological origin (excluding human plasma-derived materials).
9. The new fermentation train is identical to the approved fermentation train(s).
10. No change in the approved in vitro cell age.
11. The change is not expected to have an impact on the quality, safety or efficacy of the final product.

Table *continued*

Conditions

12. No change in the proportionality of the raw materials (that is, the change in scale is linear).
13. The change in scale involves the use of the same bioreactor (that is, it does not involve the use of a larger bioreactor).
14. The need for reprocessing is not due to recurrent deviations from the validated process and the root cause triggering reprocessing is identified.

Supporting data

1. Justification for the classification of the change(s) as critical, moderate or noncritical as this relates to the impact on the quality of the antigen.
2. Flow diagram (including process and in-process controls) of the proposed manufacturing process(es) and a brief narrative description of the proposed manufacturing process(es).
3. If the change results in an increase in the number of population doublings or subcultivations, information on the characterization and testing of the post-production cell bank for recombinant product, or of the antigen for non-recombinant product.
4. For antigens obtained from, or manufactured with, reagents obtained from sources that are at risk of transmitting bovine spongiform encephalopathy/transmissible spongiform encephalopathy (BSE/TSE) agents (for example, ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (for example, name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, and use and previous acceptance of the material) (*5*).
5. Process validation study reports.
6. Comparability of the pre- and post-change antigen with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may occasionally be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis, taking into consideration the quality-comparability findings, the nature and level of knowledge of the vaccine, existing relevant nonclinical and clinical data, and aspects of vaccine use.
7. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change antigen. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller-scale batches, and/or the use of fewer than 3 batches may be acceptable where justified and agreed by the NRA.

Table *continued*

Supporting data

8. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for one (1) commercial-scale batch of the pre- and post-change antigen. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Batch data on the next two full-production batches should be made available on request and should be reported by the MA holder if outside the specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified and agreed by the NRA.
9. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale antigen batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months of testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the antigen under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
10. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least one (1) commercial-scale antigen batch produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months of testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the antigen under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
11. Updated post-approval stability protocol and stability commitment to place the first commercial-scale batch of the final product manufactured using the post-change antigen into the stability programme.
12. Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on viral clearance studies and BSE/TSE risk) (*5*).
13. Information demonstrating comparability of the raw materials/reagents of both sources.
14. Data describing the root cause triggering the reprocessing, as well as validation data (for example, extended hold-times and resistance to additional mechanical stress) to help prevent the reprocessing from having an impact on the antigen.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
9. Change to the cell banks:			
Note: New cell substrates that are unrelated to the licensed master cell bank (MCB) or pre-MCB material generally require a new application for MA or licence application.			
a. generation of a new MCB	1	1, 2, 5, 7–9	Moderate
b. generation of a new working cell bank (WCB)	None	1, 2	Moderate
	2–4	1, 2	Minor
c. change in cell bank storage site	7	10	Minor
10. Change to the seed lots:			
Note: New viral or bacterial seeds that are unrelated to the master seed lot (MSL) or pre-MSL material generally require a new application for MA or licence application.			
a. generation of a new MSL	1	1, 5–9, 11	Major
b. generation of a new working seed lot (WSL)	2, 3	5–9, 11	Moderate
	2–4	5–6	Minor
c. generation of a new WSL by extending the passage level of an existing WSL beyond an approved level	None	5–7, 11	Moderate
d. change in seed lot storage site	7	10	Minor
11. Change in cell bank/seed lot testing/storage site	5, 7	10	Minor
12. Change in cell bank/seed lot qualification protocol	None	3, 4	Moderate
	6	4	Minor

Conditions

1. The new MCB is generated from a pre-approved MCB or WCB or the new MSL is generated from a pre-approved MSL or WSL.
2. The new cell bank/seed lot is generated from a pre-approved MCB/MSL.
3. The new cell bank/seed lot is at the pre-approved passage level.
4. The new cell bank/seed lot is released according to a pre-approved protocol/process or as described in the original licence.
5. No changes have been made to the tests/acceptance criteria used for the release of the cell bank/seed lot.
6. The protocol is considered more stringent (that is, addition of new tests or narrowing of acceptance criteria).
7. No changes have been made to the storage conditions used for the cell bank/seed lot and the transport conditions of the cell bank/seed lot has been validated.

Table *continued*

Supporting data

1. Qualification of the cell bank or seed lot according to guidelines considered acceptable by the NRA.
2. Information on the characterization and testing of the MCB/WCB, and cells from the end-of-production passage or post-production passage.
3. Justification of the change to the cell bank/seed lot qualification protocol.
4. Updated cell bank/seed lot qualification protocol.
5. Comparability of the pre- and post-change antigen with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may occasionally be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis, taking into consideration the quality-comparability findings, the nature and level of knowledge of the vaccine, existing relevant nonclinical and clinical data, and aspects of vaccine use.
6. Quality control test results as quantitative data in tabular format for the new seed lot.
7. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the antigen derived from the new cell bank/seed lot. Matrixing, bracketing, the use of smaller-scale batches, and/or the use of fewer than 3 batches may be acceptable where justified and agreed by the NRA.
8. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale antigen batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the antigen under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
9. Updated post-approval stability protocol.
10. Evidence that the new company/facility is GMP compliant.
11. Revised information on the quality and controls of critical starting materials (for example, specific pathogen-free eggs and chickens) used in the generation of the new WSL, where applicable.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
13. Change in equipment used in the antigen manufacturing process, such as:			
a. introduction of new equipment with different operating principles and different product contact material	None	1–6	Moderate
b. introduction of new equipment with the same operating principles but different product contact material	None	1, 3–6	Moderate
c. introduction of new equipment with different operating principles but the same product contact material	None	1–3, 5, 6	Moderate
d. replacement of equipment with equivalent equipment (including filter)	None	1, 5–7	Minor

Conditions

None

Supporting data

1. Information on the in-process control testing.
2. Process validation study reports.
3. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for one (1) commercial-scale batch of the antigen produced with the approved and proposed product contact equipment/material. Batch data on the next two full-production batches should be made available on request and reported by the MA holder if outside specification (with proposed action).
4. Information on leachables and extractables.
5. Information on the new equipment and comparison of similarities and differences regarding operating principles and specifications between the new and the replaced equipment.
6. Information demonstrating requalification of the equipment or requalification of the change.
7. Rationale for regarding the equipment as similar/comparable, as applicable.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
14. Change in specification for the materials, involving:			
a. raw materials/intermediates: widening of the approved specification limits for starting materials/intermediates, which may have a significant effect on the overall quality of the antigen and/or final product and are not changes to the cell banks or seed lots	None	1, 3–6, 8, 11	Moderate
b. raw materials/intermediates: narrowing of the approved specification limits for starting materials/intermediates	1–4	1, 3–7	Minor
15. Change to in-process tests and/or acceptance criteria applied during manufacture of the antigen, involving:			
a. narrowing of in-process limits	3, 5, 8, 9	2, 6	Minor
b. addition of new in-process test and limits	4, 5, 10, 11	2–6, 8, 10	Minor
c. deletion of a non-significant in-process test	4–6	2, 6, 9	Minor
d. widening of the approved in-process limits	None	2–6, 8, 10, 11	Moderate
	3–5	2, 6, 8, 10, 11	Minor
e. deletion of an in-process test which may have a significant effect on the overall quality of the antigen	None	2, 6, 8, 10	Moderate
f. addition or replacement of an in-process test as a result of a safety or quality issue	None	2–6, 8, 10	Moderate
16. Change in in-process controls testing site	3–5, 7, 8	12	Minor

Conditions

1. The change in specification for the materials is within the approved limits.
2. The grade of the materials is the same or is of higher quality, where appropriate.
3. No change in the antigen specification outside the approved limits.
4. No change in the impurity profile of the antigen outside the approved limits.

Table *continued*

Conditions
5. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
6. The test does not concern a critical attribute (for example, content, impurity, any critical physical characteristics or microbial purity).
7. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity, if applicable.
8. No change in the in-process controls outside the approved limits.
9. The test procedure remains the same, or changes in the test procedure are minor.
10. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
11. The new test method is not a biological/immunological/immunochemical or physicochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods).
Supporting data
1. Revised information on the quality and controls of the materials (for example, raw materials, starting materials, solvents, reagents and catalysts) used in the manufacture of the post-change antigen.
2. Revised information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed antigen.
3. Updated antigen specification, if changed.
4. Copies or summaries of analytical procedures, if new analytical procedures are used.
5. Validation study reports, if new analytical procedures are used.
6. Comparative table or description, where applicable, of pre- and post-change in-process tests/limits.
7. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for one (1) commercial-scale batch of the pre- and post-change antigen. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Batch data on the next two full-production batches should be made available on request and reported by the MA holder if outside specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified and agreed by the NRA.
8. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change antigen. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than 3 batches may be acceptable where justified and agreed by the NRA.
9. Justification/risk assessment showing that the attribute is non-significant.

Table *continued*

Supporting data

10. Justification for the new in-process test and limits.
11. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
12. Evidence that the new company/facility is GMP compliant.

Control of the antigen

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
17. Change affecting the quality control (QC) (release and stability) testing of the antigen, involving:			
a. transfer of the QC testing activities for a non-pharmacopoeial assay to a new company not approved in the current MA or licence	1–3	1, 2	Minor
b. transfer of the QC testing activities for a pharmacopoeial assay to a new company not approved in the current MA or licence	1	1, 2	Minor

Conditions

1. The transferred QC test is not a potency assay (for example, the test may be a bioassay such as an endotoxin assay or sterility assay).
2. No changes to the test method.
3. Transfer within a site approved in the current MA for the performance of other tests.

Supporting data

1. Information demonstrating technology transfer qualification.
2. Evidence that the new company/facility is GMP compliant.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
18. Change in the specification used to release the antigen, involving:			
a. deletion of a test	None	1, 5, 8	Moderate
b. addition of a test	1–3	1–3, 5	Minor
c. replacement of an analytical procedure	None	1–5	Moderate
d. change in animal species/strains for a test (for example, new species/strains, animals of different age, new supplier where genotype of the animal cannot be confirmed)	None	6, 7	Moderate
e. minor changes to an approved analytical procedure	4–7	1, 4, 5	Minor
f. change from an in-house analytical procedure to a recognized compendial/pharmacopoeial analytical procedure	4, 7	1–3	Minor
g. widening of an acceptance criterion	None	1, 5, 8	Moderate
h. narrowing of an acceptance criterion	1, 8, 9	1	Minor

Conditions

1. The change does not result from unexpected events arising during manufacture (for example, new unqualified impurity or change in total impurity limits).
2. No change in the limits/acceptance criteria outside the approved limits for the approved assays.
3. The addition of the test is not intended to monitor new impurity species.
4. No change in the acceptance criteria outside the approved limits.
5. The method of analysis is the same and is based on the same analytical technique or principle (for example, a change in column length or temperature, but not a different type of column or method) and no new impurities are detected.
6. The modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
7. The change does not concern potency testing.
8. Acceptance criteria for residuals are within recognized or approved acceptance limits (for example, within ICH limits for a Class 3 residual solvent, or pharmacopoeial requirements).
9. The analytical procedure remains the same, or changes to the analytical procedure are minor.

Table *continued*

Supporting data

1. Updated antigen specification.
2. Copies or summaries of analytical procedures, if new analytical procedures are used.
3. Validation reports, if new analytical procedures are used.
4. Comparative results demonstrating that the approved and proposed analytical procedures are equivalent.
5. Justification for deletion of the test or for the proposed antigen specification (for example, tests, acceptance criteria or analytical procedures).
6. Data demonstrating that the change in animals/strains give results comparable to those obtained using the approved animals/strains.
7. Copies of relevant certificate of fitness for use (for example, veterinary certificate).
8. Declaration/evidence that consistency of quality and of the production process is maintained.

Reference standards or materials

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
19. Qualification of a new reference standard against a new primary international standard	None	1, 2	Moderate
20. Change in the reference standard from in-house (no relationship with international standard) to pharmacopoeial or international standard	None	1, 2	Moderate
21. Qualification of a new lot of reference standard against the approved reference standard (including qualification of a new lot of a secondary reference standard against the approved primary standard)	1	1, 2	Minor
22. Change to reference standard qualification protocol	None	3, 4	Moderate
23. Extension of reference standard shelf-life	2	5	Minor

Table *continued*

Conditions

1. Qualification of the new reference standard is according to an approved protocol.
2. The extension of the shelf-life is according to an approved protocol.

Supporting data

1. Justification for the change in reference standard.
2. Information demonstrating qualification of the proposed reference standards or materials (for example, source, characterization, certificate of analysis and comparability data).
3. Justification of the change to the reference standard qualification protocol.
4. Updated reference standard qualification protocol.
5. Summary of stability testing and results to support the extension of reference standard shelf-life.

Container closure system

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
24. Change in the primary container closure system(s) for the storage and shipment of the antigen	None	1, 2, 4, 5	Moderate
	1	1, 3, 5	Minor

Conditions

1. The proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties.

Supporting data

1. Information on the proposed container closure system (for example, description, composition, materials of construction of primary packaging components and specification).
2. Data demonstrating the suitability of the container closure system (for example, extractable/leachable testing).
3. Results demonstrating that the proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties (for example, results of transportation or interaction studies, and extractable/leachable studies).

Table *continued*

Supporting data

4. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale antigen batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the antigen under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
5. Comparative table of pre- and post-change specifications.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
25. Change in the specification of the primary container closure system for the antigen, involving:			
a. deletion of a test	1, 2	1, 2	Minor
b. addition of a test	3	1–3	Minor
c. replacement of an analytical procedure	6, 7	1–3	Minor
d. minor changes to an analytical procedure	4–7	1–3	Minor
e. widening of an acceptance criterion	None	1, 2	Moderate
f. narrowing of an acceptance criterion	8	1	Minor

Conditions

1. The deleted test has been demonstrated to be redundant compared to the remaining tests or is no longer a pharmacopoeial requirement.
2. The change to the specification does not affect the functional properties of the container closure component nor result in a potential impact on the performance of the antigen.
3. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.

Table *continued*

Conditions

4. There is no change in the acceptance criteria outside the approved limits.
5. The new analytical procedure is of the same type.
6. Results of method validation demonstrate that the new or modified analytical procedure is at least equivalent to the approved analytical procedure.
7. The new or modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
8. The change is within the range of approved acceptance criteria or has been made to reflect a new pharmacopoeial monograph specification for the container closure component.

Supporting data

1. Updated copy of the proposed specification for the primary container closure system.
2. Rationale for the change in specification for a primary container closure system.
3. Description of the analytical procedure and, if applicable, validation data.

Stability

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
26. Change in the shelf-life/hold-time for the antigen or for a stored intermediate of the antigen, involving:			
a. extension	None	1–5	Moderate
	1–5	1, 2, 5	Minor
b. reduction	None	1–5	Moderate
	6	2–4	Minor

Conditions

1. No changes to the container closure system in direct contact with the antigen with the potential of impact on the antigen, or to the recommended storage conditions of the antigen.
2. The approved shelf-life is at least 24 months.
3. Full long-term stability data are available covering the proposed shelf-life and are based on stability data generated on at least three (3) commercial-scale batches.
4. Stability data were generated in accordance with the approved stability protocol.
5. Significant changes were not observed in the stability data.
6. The reduction in the shelf-life is not necessitated by recurring events arising during manufacture or because of stability concerns. *Note: Problems arising during manufacturing or stability concerns should be reported for evaluation*.

Table *continued*

Supporting data

1. Summary of stability testing and results (for example, studies conducted, protocols used and results obtained).
2. Proposed storage conditions and shelf-life, as appropriate.
3. Updated post-approval stability protocol and stability commitment.
4. Justification of the change to the post-approval stability protocol or stability commitment.
5. Results of stability testing (that is, full real-time/real-temperature stability data covering the proposed shelf-life generated on at least three (3) commercial-scale batches). For intermediates, data to show that the extension of shelf-life has no negative impact on the quality of the antigen. Under special circumstances and with prior agreement of the NRA, interim stability testing results and a commitment to notify the NRA of any failures in the ongoing long-term stability studies may be provided.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
27. Change in the post-approval stability protocol of the antigen, involving:			
a. significant change to the post-approval stability protocol or stability commitment, such as deletion of a test, replacement of an analytical procedure or change in storage temperature	None	1–6	Moderate
	1	1, 2, 4–6	Minor
b. addition of time point(s) into the post-approval stability protocol	None	4, 6	Minor
c. addition of test(s) into the post-approval stability protocol	2	1, 2, 4, 6	Minor
d. deletion of time point(s) from the post-approval stability protocol beyond the approved shelf-life	None	4, 6	Minor
e. deletion of time point(s) from the post-approval stability protocol within the approved shelf-life	3	4, 6	Minor

Conditions

1. For the replacement of an analytical procedure, the new analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.

Table *continued*

Conditions

2. The addition of test(s) is not due to stability concerns or to the identification of new impurities.
3. The approved antigen shelf-life is at least 24 months.

Supporting data

1. Copies or summaries of analytical procedures, if new analytical procedures are used.
2. Validation study reports, if new analytical procedures are used.
3. Proposed storage conditions and/or shelf-life, as appropriate.
4. Updated post-approval stability protocol and stability commitment.
5. If applicable, stability testing results to support the change to the post-approval stability protocol or stability commitment (for example, data showing greater reliability of the alternative test).
6. Justification for the change to the post-approval stability protocol.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
28. Change in the storage conditions for the antigen, involving:			
a. addition or change of storage condition for the antigen (for example, widening or narrowing of a temperature criterion)	None	1–4	Moderate
	1, 2	1–3	Minor

Conditions

1. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
2. The change consists in the narrowing of a temperature criterion within the approved ranges.

Supporting data

1. Proposed storage conditions and shelf-life.
2. Updated post-approval stability protocol and stability commitment.
3. Justification of the change in the labelled storage conditions/cautionary statement.
4. Results of stability testing (that is, full real-time/real-temperature stability data covering the proposed shelf-life generated on at least three (3) commercial-scale batches).

References

1. The common technical document for the registration of pharmaceuticals for human use: quality – M4Q(R1) (Step 4 version, 12 September 2002). Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2002 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R1_Quality/M4Q__R1_.pdf, accessed 14 December 2014).
2. M4Q Implementation Working Group. Questions & Answers (R1) (Current version, 17 July 2003). Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2003 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R1_Quality/M4_Quality_Questions_Answers_R1.pdf, accessed 14 December 2014).
3. Good manufacturing practices for biological products. In: WHO Expert Committee on Biological Standardization: forty-second report. Geneva: World Health Organization; 1992: Annex 1 (WHO Technical Report Series, No. 822; http://whqlibdoc.who.int/trs/WHO_TRS_822.pdf?ua=1, accessed 2 December 2014).
4. Guidelines on stability evaluation of vaccines. In: WHO Expert Committee on Biological Standardization: fifty-seventh report. Geneva: World Health Organization; 2011: Annex 3 (WHO Technical Report Series, No. 962; http://whqlibdoc.who.int/trs/WHO_TRS_962_eng.pdf?ua=1, accessed 2 December 2014).
5. WHO Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products. Geneva: World Health Organization; 2003 (WHO/BCT/QSD/2003.01; http://www.who.int/biologicals/publications/en/whotse2003.pdf, accessed 30 November 2014).

Appendix 3

Changes to the final product

The examples presented in this appendix are intended to assist with the classification of changes made to the quality information of the final product. The information summarized in the final product table below provides recommendations on:

- the ***conditions to be fulfilled*** for a given change to be classified as major, moderate or minor (if any of the conditions outlined for a given change are not fulfilled, the change is automatically considered to be the next higher level of change – for example, if any conditions recommended for a moderate quality change are not fulfilled, the change is considered to be a major quality change);
- the ***supporting data*** for a given change, either to be submitted to the NRA or maintained by the MA holder (if any of the supporting data outlined for a given change are not provided, are different or are not considered applicable then adequate scientific justification should be provided);
- the ***reporting category*** (that is, major, moderate or minor quality change).

It is important to note that the NRA reserves the right to request additional information or material, as deemed appropriate, or to define conditions not specifically described in this document in order to allow for adequate assessment of the quality, safety and efficacy of a vaccine. In addition, MA holders should contact the NRA if a change not included in the final product table below has the potential to impact upon vaccine quality.

Supporting data should be provided according to the submission format accepted by the NRA. For example, for NRAs that accept the ICH common technical document (CTD) and/or ICH eCTD formatted submissions, the supporting data should be provided in the appropriate sections of the CTD modules and not in separate documents. For the placement of data in the appropriate section of the CTD please see the ICH guidelines (*1*, *2*).

For additional information on data requirements to support quality changes, WHO guidelines on GMP requirements and stability evaluation of vaccines (*3*, *4*) should be consulted, together with relevant ICH guidelines.

Quality changes to comply with updated compendia and/or pharmacopoeia

NRAs should make a list of the recognized compendia and/or pharmacopoeia available to MA holders. Manufacturers are expected to comply with the current versions of compendia and/or pharmacopoeia as referenced in the approved MA. Changes in the compendial and/or pharmacopoeial methods or specifications referenced by a particular NRA do not need to be submitted for review, but information on such changes should be available for inspection.

In some cases, changes to comply with recognized compendia and/or pharmacopoeia may require approval by the NRA prior to implementation regardless of the timing of the change with respect to the date the pharmacopoeia was updated. For example, supplement submission and approval by the NRA may be required for some changes to quality control tests performed for product release (for example, tests for potency), for changes which have an impact on any items of the product labelling information, and for changes which may potentially affect the quality, safety or efficacy of the product.

Quality changes affecting lot release

Where post-approval changes to the final product affect the lot release protocol (for example, changes to test procedures, reference standards or laboratory sites) or sample testing requirements for lot release, the MA holder should inform the institution responsible for reviewing the release of vaccine lots. These procedures apply to changes that have been authorized by the NRA in the case of major and moderate quality changes and to changes that have been implemented in the case of minor quality changes. For example, the qualification of a new lot of reference standard against the approved reference standard may be considered a minor quality change if the qualification of a new standard is done in accordance with an approved protocol and specification. Nevertheless, these changes must be reported to the NRA or NCL as appropriate.

Description and composition of the final product

Note: Changes in dosage form and/or presentation may, in some cases, necessitate the filing of a new application for MA or licensure. MA holders are encouraged to contact the NRA for further guidance.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
29. Change in the description or composition of the final product, involving:			
a. addition of a dosage form or change in the formulation (for example, lyophilized powder to liquid, change in the amount of excipient or new diluent for lyophilized product) *Note: Change in formulation does not include changes in antigen(s) or adjuvants. A change in antigen(s) or adjuvant(s) requires the filing of a new application for MA or licensure. MA holders are encouraged to contact the NRA for further guidance.*	None	1–10	Major
b. change in fill volume (that is, same concentration, different volume)	None	1, 5, 7, 10	Major
	1, 2	1, 5, 7	Moderate
	1–3	5, 7	Minor
c. addition of a new presentation (for example, addition of a new pre-filled syringe where the approved presentation is a vial for a vaccine in a liquid dosage form)	None	1, 5, 7–10	Major

Conditions

1. No changes classified as major in the manufacturing process to accommodate the new fill volume.
2. No change in the dose recommended.
3. Narrowing of fill volume while maintaining the lower limit of extractable volume.

Supporting data

1. Revised final product labelling information (as applicable).
2. Characterization data demonstrating that the conformation and immunogenicity of the antigen is comparable in the new dosage form and/or formulation.
3. Description and composition of the dosage form if there are changes to the composition or dose.
4. Discussion of the components of the final product, as appropriate (for example, choice of excipients, compatibility of antigen and excipients, leachates or compatibility with new container closure system, as appropriate).

Table *continued*

Supporting data

5. Information on the batch formula, manufacturing process and process controls, control of critical steps and intermediates, and process validation study reports.
6. Control of excipients, if new excipients are proposed (for example, specification).
7. Information on specification, analytical procedures (if new analytical methods are used), validation of analytical procedures (if new analytical methods are used), batch analyses (certificate of analysis for three (3) consecutive commercial-scale batches should be provided). Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.
8. Information on the container closure system and leachables and extractables, if any of the components have changed (for example, description, materials of construction and summary of specification).
9. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
10. Supporting clinical data or a justification for why such studies are not needed.

Description and composition of the final product: change to an adjuvant

Note:

- *Change in type/structure of a chemical adjuvant, in the type of a biological adjuvant or in a component of a biological adjuvant may necessitate the filing of a new application for MA or licensure. MA holders are encouraged to contact the NRA for further guidance.*
- *For additional guidance on the required supporting data for quality changes for chemical and biological adjuvants, see recommendations for other changes to the final product, such as changes to facilities, equipment, manufacturing process, quality control, shelf-life, and so on, as applicable.*

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
30. Change involving an approved chemical/synthetic adjuvant:			
a. change in supplier of a chemical/synthetic adjuvant	None	4, 5, 10, 11	Moderate
	1–3	5	Minor
b. change in manufacture of a chemical/synthetic adjuvant	None	3–5, 10, 11	Moderate
c. change in specification of a chemical/synthetic adjuvant (including tests and/or the analytical procedures)	None	7–11	Moderate
	1, 3	7–9	Minor
31. Change involving a biological adjuvant:			
a. change in supplier of a biological adjuvant	None	1–7, 10–13	Major
b. change in manufacture of a biological adjuvant	None	1–7, 10–12	Major
	4	1–7, 10–12	Moderate
c. change in specification of a biological adjuvant (including tests and/or the analytical procedures)	None	6–10	Moderate
	1, 3	7–8	Minor

Conditions

1. The specification of the adjuvant is equal to or narrower than the approved limits (that is, narrowing of acceptance criterion).
2. The adjuvant is an aluminium salt.
3. The change in specification consists of the addition of a new test or of a minor change to an analytical procedure.
4. There is no change in the manufacturer and/or supplier of the adjuvant.

Supporting data

1. Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on the viral clearance studies, BSE/TSE risk) (*5*).
2. Information on the quality and controls of the materials (for example, raw materials, starting materials) used in the manufacture of the proposed adjuvant.
3. Flow diagram of the proposed manufacturing process(es), a brief narrative description of the proposed manufacturing process(es), and information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed adjuvant.

Table *continued*

Supporting data

4. Process validation study reports (for example, for manufacture of the adjuvant) unless otherwise justified.
5. Description of the general properties, including stability, characteristic features and characterization data of the adjuvant, as appropriate.
6. Comparability of the pre- and post-change adjuvant with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may occasionally be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and clinical studies should be determined on a case-by-case basis, taking into consideration the quality-comparability findings, the nature and level of knowledge of the adjuvant, existing relevant nonclinical and clinical data, and aspects of vaccine use.
7. Updated copy of the proposed specification for the adjuvant (and updated analytical procedures if applicable).
8. Copies or summaries of analytical procedures, if new analytical procedures are used.
9. Validation study reports, if new analytical procedures are used.
10. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the final product with the pre-change (approved) and post-change (proposed) adjuvant, as applicable. Comparative test results for the approved adjuvant do not need to be generated concurrently; relevant historical testing results are acceptable.
11. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
12. Supporting nonclinical and clinical data, if applicable.
13. Evidence that the facility is GMP compliant.

Description and composition of the final product: change to a diluent

Note: Changes to diluents containing adjuvants and/or antigens are considered final products and as such the corresponding changes to final product (not diluent) should be applied.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
32. Change to the diluent, involving:			
a. change in manufacturing process	None	1–5	Moderate
	1, 3	1–4	Minor
b. replacement of or addition to the source of a diluent	None	1–5	Moderate
	1–3	1–3	Minor
c. change in facility used to manufacture a diluent (same company)	1, 2	1, 3, 5	Minor
d. addition of a diluent filling line	1, 2, 4	1, 3, 5	Minor
e. addition of a diluent into an approved filling line	1, 2	1, 3, 5	Minor
f. deletion of a diluent	None	None	Minor

Conditions

1. The diluent is water for injection or a salt solution (including buffered salt solutions) – that is, it does not include an ingredient with a functional activity (such as a preservative) and there is no change to its composition.
2. After reconstitution, there is no change in the final product specification outside the approved limits.
3. The proposed diluent is commercially available in the NRA country/jurisdiction.
4. The addition of the diluent filling line is in an approved filling facility.

Supporting data

1. Flow diagram (including process and in-process controls) of the proposed manufacturing process(es) and a brief narrative description of the proposed manufacturing process(es).
2. Updated copy of the proposed specification for the diluent.
3. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the approved and proposed diluent. Comparative test results for the approved diluent do not need to be generated concurrently; relevant historical testing results are acceptable.

Table *continued*

Supporting data

4. Updated stability data on the product reconstituted with the new diluent.
5. Evidence that the facility is GMP compliant.

Manufacture

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
33. Change involving a final product manufacturer/ manufacturing facility, such as:			
a. replacement or addition of a manufacturing facility for the final product (including formulation/ filling and primary packaging)	None	1–7	Major
	1–5	1–3, 5–8	Moderate
b. replacement or addition of a secondary packaging facility, a labelling/storage facility or a distribution facility	2, 3	1–3	Minor
c. deletion of a final product manufacturing facility	None	None	Minor

Conditions

1. The proposed facility is an approved formulation/filling facility (for the same company/MA holder).
2. There is no change in the composition, manufacturing process and final product specification.
3. There is no change in the container/closure system and storage conditions.
4. The same validated manufacturing process is used.
5. The newly introduced product is in the same family of product(s) or therapeutic classification as the products already approved at the site, and also uses the same filling process/equipment.

Supporting data

1. Name, address and responsibility of the proposed production facility involved in manufacturing and testing.
2. Evidence that the facility is GMP compliant.
3. Confirmation that the manufacturing process description of the final product has not changed as a result of the submission (other than the change in facility), or revised description of the manufacturing process.
4. Comparative description of the manufacturing process if different from the approved process, and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed final product.

Table *continued*

Supporting data

5. Process validation study reports. The data should include transport between sites, if relevant.
6. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change final product. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.
7. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
8. Rationale for considering the proposed formulation/filling facility as equivalent.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
34. Change in the final product manufacturing process, such as:			
a. scale-up of the manufacturing process at the formulation/filling stage	1–4	1–6	Moderate
b. addition or replacement of equipment (for example, formulation tank, filter housing, filling line and head, and lyophilizer); see change 13 above.	None	1–8	Moderate
	5	2, 7–9	Minor
c. addition of a new scale bracketed by the approved scales or scale-down of the manufacturing process	1–4	1, 4	Minor

Table *continued*

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
d. addition of a new step (for example, filtration)	3	1–6	Moderate

Conditions

1. The proposed scale uses similar/comparable equipment to the approved equipment. Note: Change in equipment size is not considered as using similar/comparable equipment.
2. Any changes to the manufacturing process and/or to the in-process controls are only those necessitated by the change in batch size (for example, the same formulation, controls and SOPs are utilized).
3. The change should not be a result of recurring events having arisen during manufacture or because of stability concerns.
4. No change in the principle of the sterilization procedures of the final product.
5. Replacement of equipment with equivalent equipment; the change is considered "like for like" (that is, in terms of product contact material, equipment size and operating principles).

Supporting data

1. Description of the manufacturing process, if different from the approved process, and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed final product.
2. Information on the in-process control testing, as applicable.
3. Process validation study reports (for example, media fills), as appropriate.
4. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change final product. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.
5. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.

Table *continued*

Supporting data

6. Information on leachables and extractables, as applicable.
7. Information on the new equipment and comparison of similarities and differences regarding operating principles and specifications between the new and the replaced equipment.
8. Information demonstrating requalification of the equipment or requalification of the change.
9. Rationale for regarding the equipment as similar/comparable, as applicable.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
35. Change in the controls (in-process tests and/or acceptance criteria) applied during the manufacturing process or on intermediates, such as:			
a. narrowing of in-process limits	2, 3, 7	1, 5	Minor
b. addition of new in-process test and limits	2, 3, 8, 9	1–6, 8	Minor
c. deletion of a non-significant in-process test	2–4	1, 5, 7	Minor
d. widening of the approved in-process limits	None	1–6, 8, 9	Major
	1–3	1, 5, 6, 8, 9	Moderate
e. deletion of an in-process test which may have a significant effect on the overall quality of the final product	None	1, 5, 6, 8	Major
f. addition or replacement of an in-process test as a result of a safety or quality issue	None	1–6, 8	Moderate
36. Change in in-process controls testing site	1–3, 5, 6	10	Minor

Conditions

1. No change in final product specification outside the approved limits.
2. No change in the impurity profile of the final product outside the approved limits.
3. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
4. The test does not concern a critical attribute (for example, content, impurities, any critical physical characteristics or microbial purity).

Table *continued*

Conditions

5. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity, if applicable.
6. No change in the in-process control limits outside the approved limits.
7. The test procedure remains the same, or changes in the test procedure are minor.
8. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
9. The new test method is not a biological/immunological/immunochemical or physicochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods)

Supporting data

1. Revised information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed antigen.
2. Updated final product specification if changed.
3. Copies or summaries of analytical procedures, if new analytical procedures are used.
4. Validation study reports, if new analytical procedures are used.
5. Comparative table or description, where applicable, of current and proposed in-process tests.
6. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change final product (certificates of analysis should be provided). Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable.
7. Justification/risk assessment showing that the attribute is non-significant.
8. Justification for the new in-process test and limits.
9. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
10. Evidence that the new company/facility is GMP compliant.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
37. Change in the specification used to release the excipient, involving: *Note: This change excludes adjuvants. See adjuvant-specific changes above for details (**changes 30** and **31**).*			
a. deletion of a test	5, 8	1, 3	Minor
b. addition of a test	4	1–3	Minor
c. replacement of an analytical procedure	1–3	1, 2	Minor
d. minor changes to an approved analytical procedure	None	1, 2	Minor
e. change from an in-house analytical procedure to a recognized compendial analytical procedure	None	1, 2	Minor
f. widening of an acceptance criterion	None	1, 3	Moderate
g. narrowing of an acceptance criterion	3, 4, 6, 7	1	Minor

Conditions

1. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
2. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
3. The change is within the range of approved acceptance criteria or has been made to reflect the new pharmacopoeial monograph specification for the excipient.
4. Acceptance criteria for residual solvents are within recognized or approved acceptance limits (for example, within ICH limits for a Class 3 residual solvent or pharmacopoeial requirements).
5. The deleted test has been demonstrated to be redundant compared to the remaining tests or is no longer a pharmacopoeial requirement.
6. The analytical procedure remains the same, or changes in the test procedure are minor.
7. The change does not result from unexpected events arising during manufacture (for example, new unqualified impurity or change in total impurity limits).
8. An alternative test analytical procedure is already authorized for the specification attribute/test and this procedure has not been added through a minor change submission.

Table *continued*

Supporting data

1. Updated excipient specification.
2. Where an in-house analytical procedure is used and a recognized compendial standard is claimed, results of an equivalency study between the in-house and compendial methods.
3. Justification of the proposed excipient specification (for example, demonstration of the suitability of the monograph to control the excipient and potential impact on the performance of the final product).

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
38. Change in the source of an excipient from a vegetable or synthetic source to a human or animal source that may pose a TSE or viral risk	None	2–7	Major
39. Change in the source of an excipient from a TSE risk (for example, animal) source to a vegetable or synthetic source	None	1, 3, 5, 6	Moderate
40. Replacement in the source of an excipient from a TSE risk source to a different TSE risk source	5, 6	2–7	Minor
41. Change in manufacture of a biological excipient *Note: This change excludes biological adjuvants; see adjuvant-specific changes above for details (**changes 30** and **31**).*	None	2–7	Major
	2	2–7	Moderate
	1, 2	2–7	Minor
42. Change in supplier for a plasma-derived excipient (for example, human serum albumin)	None	3–8	Major
	3, 4	5, 6, 9	Moderate
43. Change in supplier for an excipient of non-biological origin or of biological origin (excluding plasma-derived excipient) *Note: This change excludes adjuvants; see adjuvant-specific changes above for details (**changes 30** and **31**).*	None	2, 3, 5–7	Moderate
	1, 5, 6	3	Minor

Table *continued*

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
44. Change in excipient testing site	1	10	Minor

Conditions

1. No change in the specification of the excipient or final product outside the approved limits.
2. The change does not concern a human plasma-derived excipient.
3. The human plasma-derived excipient from the new supplier is an approved medicinal product and no manufacturing changes were made by the supplier of the new excipient since its last approval in the country/jurisdiction of the NRA.
4. The excipient does not influence the structure/conformation of the active ingredient.
5. The TSE risk source is covered by a TSE certificate of suitability and is of the same or lower TSE risk as the previously approved material (*5*).
6. Any new excipient does not require the assessment of viral safety data.

Supporting data

1. Declaration from the manufacturer of the excipient that the excipient is entirely of vegetable or synthetic origin.
2. Details of the source of the excipient (for example, animal species, country of origin) and the steps undertaken during processing to minimize the risk of TSE exposure (*5*).
3. Information demonstrating comparability in terms of physicochemical properties, and the impurity profile of the proposed excipient compared to the approved excipient.
4. Information on the manufacturing process and on the controls performed at critical steps of the manufacturing process, and on the intermediate of the proposed excipient.
5. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) commercial-scale batches of the proposed excipient.
6. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.

Table *continued*

Supporting data

7. Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on the viral clearance studies, or BSE/TSE risk (*5*)) including viral safety documentation where necessary.
8. Complete manufacturing and clinical safety data to support the use of the proposed human plasma-derived excipient.
9. Letter from the supplier certifying that no changes were made to the plasma-derived excipient compared to the currently approved corresponding medicinal product.
10. Evidence that the new company/facility is GMP compliant.

Control of the final product

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
45. Change affecting the QC testing of the final product (release and stability), involving:			
Note: Transfer of testing to a different facility within a GMP-approved site is not considered to be a reportable change but is treated as a minor GMP change and reviewed during inspections.			
a. transfer of the QC testing activities for a non-pharmacopoeial assay (in-house) to a new company or to a different site within the same company	None	1, 2	Moderate
b. transfer of the QC testing activities for a pharmacopoeial assay to a new company	1	1, 2	Minor

Conditions

1. The transferred QC test is not a potency assay or a bioassay.

Supporting data

1. Information demonstrating technology transfer qualification.
2. Evidence that the new company/facility is GMP compliant.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
46. Change in the specification used to release the final product, involving:			
a. for products or components subject to terminal sterilization by heat (for example, diluent for reconstitution of lyophilized vaccines), replacing the sterility test with process parametric release	None	1, 2, 6, 8, 10	Major
b. deletion of a test	None	2, 9, 10	Moderate
c. addition of a test	1, 2, 9	2–4, 8	Minor
d. change in animal species/strains for a test (for example, new species/strains, animals of different ages, and/or new supplier where genotype of the animal cannot be confirmed)	None	5, 11	Moderate
e. replacement of an analytical procedure	None	2–4, 7, 8	Moderate
f. minor changes to an approved analytical procedure	3–6	3, 8	Minor
g. change from an in-house analytical procedure to a recognized compendial analytical procedure	3, 6	2–4	Minor
h. widening of an acceptance criterion	None	2, 8, 10	Moderate
i. narrowing of an acceptance criterion	7–10	2	Minor

Conditions

1. No change in the limits/acceptance criteria outside the approved limits for the approved assays.
2. The additional test is not intended to monitor new impurity species.
3. No change in the acceptance criteria outside the approved limits.
4. The method of analysis is the same (for example, a change in column length or temperature, but not a different type of column or method) and no new impurities are detected.

Table *continued*

Conditions

5. The modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
6. The change does not concern potency testing.
7. The change is within the range of approved acceptance criteria.
8. Acceptance criteria for residual solvents are within recognized or approved acceptance limits (for example, within ICH limits for a Class 3 residual solvent, or pharmacopoeial requirements).
9. The change does not result from unexpected events arising during manufacture (for example, new unqualified impurity, or impurity content outside of the approved limits).
10. The analytical procedure remains the same, or changes to the analytical procedure are minor.

Supporting data

1. Process validation study reports on the proposed final product.
2. Updated copy of the proposed final product specification.
3. Copies or summaries of analytical procedures, if new analytical procedures are used.
4. Validation study reports, if new analytical procedures are used.
5. Data demonstrating that the change in animals gives results comparable to those obtained using the approved animals.
6. Description of the batches and summary of results as quantitative data for a sufficient number of batches to support the process parametric release.
7. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) commercial-scale batches of the final product.
8. Justification for the change to the analytical procedure (for example, demonstration of the suitability of the analytical procedure in monitoring the final product, including the degradation products) or for the change to the specification (for example, demonstration of the suitability of the revised acceptance criterion in controlling the final product).
9. Justification for the deletion of the test (for example, demonstration of the suitability of the revised specification in controlling the final product).
10. Declaration/evidence that consistency of quality and of the production process is maintained.
11. Copies of relevant certificates of fitness for use (for example, veterinary certificate).

Reference standards or materials

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
47. Qualification of a reference standard against a new primary international standard	None	1, 2	Moderate
48. Change of the reference standard from in-house (no relationship with international standard) to pharmacopoeial or international standard	None	1, 2	Moderate
49. Qualification of a new lot of reference standard against the approved reference standard (including qualification of a new lot of a secondary reference standard against the approved primary standard)	1	2	Minor
50. Change to the reference standard qualification protocol	None	3, 4	Moderate
51. Extension of the shelf-life of the reference standard	2	5	Minor

Conditions

1. The qualification of a new standard is carried out in accordance with an approved protocol.
2. The extension of the shelf-life of the reference standard is carried out in accordance with an approved protocol.

Supporting data

1. Revised product labelling to reflect the change in reference standard (as applicable).
2. Qualification data of the proposed reference standards or materials (for example, source, characterization and certificate of analysis).
3. Justification of the change to the reference standard qualification protocol.
4. Updated reference standard qualification protocol.
5. Summary of stability testing and results or retest data to support the extension of the reference standard shelf-life.

Container closure system

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
52. Modification of a primary container closure system (for example, new coating, adhesive, stopper or type of glass) *Note: The addition of a new container closure system (for example, addition of a pre-filled syringe where the currently approved presentation is only a vial) is considered a change in presentation; see **change 29.c** above.*	None	1–7	Moderate
	1–3	3	Minor
53. Change from a reusable container to a disposable container with no changes in product contact material (for example, change from reusable pen to disposable pen)	None	1, 3, 6	Moderate
54. Deletion of a container closure system *Note: The NRA should be notified of the deletion of a container closure system, and product labelling information should be updated, as appropriate.*	None	1	Minor

Conditions

1. No change in the type of container closure or materials of construction.
2. No change in the shape or dimensions of the container closure.
3. The change is made only to improve the quality of the container and does not modify the product contact material (for example, increased thickness of the glass vial without changing interior dimensions).

Supporting data

1. Revised product labelling information, as appropriate.
2. For sterile products, process validation study reports, or providing equivalency rationale. For a secondary functional container closure system, validation testing report.
3. Information on the proposed container closure system, as appropriate (for example, description, materials of construction of primary/secondary packaging components, performance specification).

Table *continued*

Supporting data

4. Results demonstrating protection against leakage, no leaching of undesirable substance and compatibility with the product, and results from the toxicity and biological reactivity tests.
5. Summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change final product. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.
6. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
7. Information demonstrating the suitability of the proposed container/closure system with respect to its relevant properties (for example, results from last media fills; results of transportation and/or interaction studies demonstrating the preservation of protein integrity and maintenance of sterility for sterile products; results of maintenance of sterility in multidose containers and results of user testing).

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
55. Change in the supplier for a primary container closure component, involving:			
a. replacement or addition of a supplier	1, 2	4, 5	Minor
*Note: A change in container closure system involving new materials of construction, shape or dimensions would require supporting data such as is shown for **change 52** above.*			
b. deletion of a supplier	None	None	Minor

Table *continued*

Conditions

1. No change in the type of container closure, materials of construction, shape and dimensions, or in the sterilization process for a sterile container closure component.
2. No change in the specification of the container closure component outside the approved limits.

Supporting data

1. Information on the supplier and make of the proposed container closure system (for example, certificate of analysis, description, materials of construction of primary packaging components, specification).
2. Data demonstrating the suitability of the container closure system (for example, extractable/leachable testing).
3. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
5. Letter from the MA holder certifying that there are no changes to the container closure system.
6. Certificate of analysis for the container provided by the new supplier and comparison with the certificate of analysis for the approved container.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
56. Change in the specification used to release a primary container closure component or functional secondary container closure component, involving:			
a. deletion of a test	1, 2	1, 2	Minor
b. addition of a test	3	1, 2	Minor
c. replacement of an analytical procedure	6, 7	1–3	Minor
d. minor changes to an analytical procedure	4–7	1–3	Minor

Table *continued*

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
e. widening of an acceptance criterion	None	1, 2	Moderate
f. narrowing of an acceptance criterion	8	1	Minor

Conditions

1. The deleted test has been demonstrated to be redundant compared to the remaining tests or is no longer a pharmacopoeial requirement.
2. The change to the specification does not affect the functional properties of the container closure component nor result in a potential impact on the performance of the final product.
3. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
4. There is no change in the acceptance criteria outside the approved limits.
5. The new analytical procedure is of the same type.
6. Results of method validation demonstrate that the new or modified analytical procedure is at least equivalent to the approved analytical procedure.
7. The new or modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
8. The change is within the range of approved acceptance criteria or has been made to reflect new pharmacopoeial monograph specifications for the container closure component.

Supporting data

1. Updated copy of the proposed specification for the primary or functional secondary container closure component.
2. Rationale for the change in specification for a primary container closure component.
3. Description of the analytical procedure and, if applicable, validation data.

Stability

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
57. Change in the shelf-life of the final product, involving:			
a. extension (includes extension of shelf-life of the final product as packaged for sale, and hold-time after opening and after dilution or reconstitution)	None	1–5	Moderate

Table *continued*

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
b. reduction (includes reduction as packaged for sale, after opening, and after dilution or reconstitution)	None	1–5	Moderate
Conditions None			
Supporting data 1. Updated product labelling information, as appropriate. 2. Proposed storage conditions and shelf-life, as appropriate. 3. Updated post-approval stability protocol. 4. Justification of the change to the post-approval stability protocol or stability commitment. 5. Results of stability testing under real-time/real-temperature conditions covering the proposed shelf-life generated on at least three (3) commercial-scale batches.			

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
58. Change in the post-approval stability protocol of the final product, involving:			
a. major change to the post-approval stability protocol or stability commitment, such as deletion of a test, replacement of an analytical procedure or change in storage temperature	None	1–6	Moderate
b. addition of time point(s) into the post-approval stability protocol	None	4, 6	Minor
c. addition of test(s) into the post-approval stability protocol	1	4, 6	Minor
d. deletion of time point(s) from the post-approval stability protocol beyond the approved shelf-life	None	4, 6	Minor
e. deletion of time point(s) from the post-approval stability protocol within the approved shelf-life	2	4, 6	Minor

Table *continued*

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
f. replacement of the sterility testing by the container/closure system integrity testing	None	1, 2, 4, 6	Moderate
	3	4, 6	Minor

Conditions

1. The addition of the test(s) is not due to stability concerns or to the identification of new impurities.
2. The approved shelf-life of the final product is at least 24 months.
3. The method used to demonstrate the integrity of the container/closure system has already been approved as part of a previous application.

Supporting data

1. Copies or summaries of analytical procedures, if new analytical procedures are used.
2. Validation study reports, if new analytical procedures are used.
3. Proposed storage conditions and or shelf-life, as appropriate.
4. Updated post-approval stability protocol and stability commitment.
5. If applicable, stability testing results to support the change to the post-approval stability protocol or stability commitment (for example, data showing greater reliability of the alternative test).
6. Justification of the change to the post-approval stability protocol or stability commitment.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
59. Change in the labelled storage conditions for the final product or the diluted or reconstituted vaccine, involving:			
a. addition or change of storage condition(s) for the final product, or for diluted or reconstituted vaccine (for example, widening or narrowing of a temperature criterion, or addition of or change to controlled temperature chain conditions)	None	1–4, 6	Moderate
b. addition of a cautionary statement (for example, "Do not freeze")	None	1, 2, 4, 5	Moderate

Table *continued*

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
c. deletion of a cautionary statement (for example, "Do not freeze")	None	1, 2, 4, 6	Moderate

Conditions

None

Supporting data

1. Revised product labelling information, as applicable.
2. Proposed storage conditions and shelf-life.
3. Updated post-approval stability protocol and stability commitment.
4. Justification of the change in the labelled storage conditions/cautionary statement.
5. Results of stability testing under appropriate stability conditions covering the proposed shelf-life, generated on one (1) commercial-scale batch unless otherwise justified.
6. Results of stability testing under appropriate conditions covering the proposed shelf-life, generated on at least three (3) commercial-scale batches unless otherwise justified.

References

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2. M4Q Implementation Working Group. Questions & Answers (R1) (Current version, 17 July 2003). Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2003 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R1_Quality/M4_Quality_Questions_Answers_R1.pdf, accessed 14 December 2014).
3. Good manufacturing practices for biological products. In: WHO Expert Committee on Biological Standardization: forty-second report. Geneva: World Health Organization; 1992: Annex 1 (WHO Technical Report Series, No. 822; http://whqlibdoc.who.int/trs/WHO_TRS_822.pdf?ua=1, accessed 2 December 2014).
4. Guidelines on stability evaluation of vaccines. In: WHO Expert Committee on Biological Standardization: fifty-seventh report. Geneva: World Health Organization; 2011: Annex 3 (WHO Technical Report Series, No. 962; http://whqlibdoc.who.int/trs/WHO_TRS_962_eng.pdf?ua=1, accessed 2 December 2014).
5. WHO Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products. Geneva: World Health Organization; 2003 (WHO/BCT/QSD/2003.01; http://www.who.int/biologicals/publications/en/whotse2003.pdf, accessed 30 November 2014).

Appendix 4

Safety, efficacy and product labelling information changes

The examples of safety and efficacy changes, product labelling information changes and administrative product labelling information changes given in this appendix are provided for clarification. However, such changes are not limited to those included in this appendix. They may also result in changes to the product labelling information for health care providers and patients, and inner and outer vaccine labels.

The amount of safety and efficacy data needed to support a change may vary according to the impact of the change, risk–benefit considerations and product-specific characteristics (that is, there is no "one size fits all" approach). This appendix therefore provides a list of examples of changes in the various categories rather than a detailed table linking each change with the data required to support that change (as provided in Appendices 2 and 3 for quality changes). MA holders or applicants are encouraged to contact the NRA for guidance on the data needed to support major changes if deemed necessary.

Safety and efficacy changes

Safety and efficacy change supplements require approval prior to implementation of the change and are generally submitted for changes related to clinical practice, safety and indication claims.

In some cases, safety and efficacy data comparing the approved clinical use (for example, indications or dosing regimens) of a vaccine with a new one may be required. Such studies, often referred to as clinical bridging studies, are trials in which a parameter of interest (such as formulation, dosing schedule or population group) is directly compared with a changed version of that parameter to assess the effect of the change on the product's clinical performance. Comparisons of immune responses and safety outcomes (for example, rates of common and serious AEFIs) are often the primary objectives. If the immune response and safety profiles are non-inferior, then the efficacy and safety of the vaccine can be inferred.

Examples of safety and efficacy changes that require data from clinical studies, post-marketing observational studies or extensive post-marketing safety data include:

- change to the indication:
  (a) addition of a new indication (such as prevention of a previously unspecified disease);

(b) modification of an approved indication (such as expansion of the age of use or restriction of an indication based on clinical studies demonstrating lack of efficacy).

- Change in the recommended dose and/or dosing schedule:
  (a) addition of a new vaccination regimen (such as addition of accelerated vaccination regimens);
  (b) addition or modification of the existing vaccination regimen (such as addition of a booster dose or modification of the recommended time interval for booster vaccinations).
- Change to add information on shedding and transmission.
- Change to the use in specific at-risk groups (such as addition of information on use in pregnant women or immunocompromised patients).
- Change to add information on co-administration with other vaccines or medicines.
- Change to add a new route of administration.[1]
- Change to add a new dosage form[1] (such as replacement of a suspension for injection with a lyophilized cake).
- Change to add a new strength.[1]
- Change to add a new delivery device.[1] (such as adding a needle-free jet injector).
- Change in existing risk-management measures:
  (a) deletion of an existing route of administration, dosage form and/or strength due to safety reasons;
  (b) deletion of a contraindication (such as use in pregnant women).

Product labelling information changes

Supplements on product labelling information change should be submitted for changes which do not require clinical efficacy data, safety data or extensive pharmacovigilance (safety surveillance) data. Product labelling information changes require approval prior to implementation of the change.

Examples of product labelling information changes associated with changes that have an impact on clinical use include:

- Addition of an adverse event identified as consistent with a causal association with immunization with the vaccine concerned.

[1] Some NRAs consider that these changes may require a new application for MA or licence.

- Change in the frequency of occurrence of a given adverse reaction.
- Addition of a contraindication or warning (such as identification of a specific subpopulation as being at greater risk, such as individuals with a concomitant condition or taking concomitant medicines, or a specific age group). These changes may include the provision of recommended risk-management actions (for example, required testing prior to vaccination, specific monitoring following vaccination and ensuring patient awareness of certain risks).
- Strengthening or clarification of product labelling information text relating to contraindications, warnings, precautions and adverse reactions.
- Revisions to the instructions for use, including dosage, administration and preparation for administration to optimize the safe use of the vaccine.

In some cases, the safety-related changes listed above may be urgent and may require rapid implementation (for example, the addition of a contraindication or warning). To allow for the rapid processing of such requests, the supplements for these changes should be labelled as "Urgent product labelling information changes" and should be submitted after prior agreement between the NRA and the MA holder (see section 7.3 and Appendix 1).

Administrative product labelling information changes

Administrative product labelling information changes are changes to any of the labelling items which are not expected to have an impact on the safe and efficacious use of the vaccine. In some cases, these changes may need to be reported to the NRA and approval received prior to implementation, while in other cases reporting may not be required.

Examples of changes which ***do*** require reporting to the NRA and approval prior to implementation by the MA holder include:

- Change in the name of the MA holder and/or manufacturer (such as change of name due to a merger).
- Change in the trade name of the vaccine.

Examples of changes which ***do not*** require approval by the NRA prior to implementation include:

- Minor changes to the layout of the product labelling information items, or revision of typographical errors without changing the content of the label.

- Update of the MA holder's contact information (for example, customer service number or web site addresses) or the distributor's name.
- Update of the existing information for referenced literature without adding or removing references.
- Changes made to comply with an official compendium (such as change of common name).
- Minor changes to the text to add clarity in relation to maintaining consistency with common label phrase standards (for example, a change from "not recommended for children" to "not for use in children").

These administrative product labelling information changes (that is, changes that have been implemented since the time of the last approved product labelling information not subject to prior approval) should be included when submitting subsequent supplements for safety and efficacy changes, or for product labelling information changes (see section 7.4).

CLASSIFY 4 : MAJOR VARIATION REGISTRATION (VaMa)

No	Variation Type	Conditions to be fullfilled	Documentation to be supplied	Pages
A	**Change product information which influence efficacy safety which needed clinical data**			
1	**Change indication and/or posology; additional new indication and/or new posology**		**A. Administrative Document, Product Information and labelling** 1. Product Information **B. Non Clinical Document (if needed)** 1. Overview Non Clinical Study 2. Summary and Matrix of Non Clinical Study **C. Clinical Document** 1.Overview Clinical Study 2.Summary Clinical Study 3.Matriks Clinical Study for change or additional indication and/or posology 4.Report of Clinical Study (reffering to the matrix at clinical study) 5.Periodic Safety Update Report until latest PSUR 6.Other references.	**216**
2	**Change product information which influence safety**		**A. Administrative Document, Product Information and labelling** 1. Product Information **B. Non Clinical Document (if needed)** 1. Overview Non Clinical Study or Justification Document data for change/additional information non-clinical. 2. Summary and Matrix of Non Clinical Study as proposed change. **C. Clinical Document** 1. Overview Clinical Study or Justification document for change/or additional clinical data 2. List Document for change product information 3.Matriks Clinical Study for change product information 4.Report of Clinical Study (reffering to the matrix at clinical study) 5. Periodic Safety Update Report until latest PSUR (if needed) 6.Other references.	**216**
B	**Change related with active substance that affect of drug safety which not need clinical study**			
1	**Change product information which influence safety**	**Special for New Drug and Biological Product**	**A. Administrative Documents, Product Information and Labelling** 1. Product Information **B. Clinical Document** 1. Justification and/or other supporting documents as proposed change. 2. PSUR (if needed) 3. Other references	**216-217**
C	**Change related drug substance and/or formula that affect of drug safety and efficacy, which need clinical data**			
1	**Change related with active substance and/or formula which needed clinical study**		**A. Administrative Document, Product information and labelling** 1. Product Information **B. Quality Document** 1. Full Quality Documents of Active Substance. 2. Full Quality Document of Drug Product. 3. Characterization data are describing that the conformation and immunogenicity of the antigen is proportional to the new dosage form and / or formula (especially vaccine)	**217**

			4. Commitment to continue long-term stability studies **C. Clinical Document** 1. Overview Clinical Study or Justification document for change /additional clinical information 2. List Document for change information product 3.Matriks Clinical Study for change of product information 4. Report of Clinical Study (reffering to the matrix at clinical study) 5. Latest Periodic Safety Update Report (if needed) 6. Other references. (if needed)	
2	**Change Master Cell Bank (MCB)/Master Seed Lot**	**1. Special for Biological Product** **2. For manufacturer new Master Cell/Seed Lot which source from original or preapproved master cell/seed lot or working cell/seed lot with sub-cloning** **3. Not related with any change at host cell line.**	**A. Quality Document** 1. Source, history and number of new master cell/seed passage with all documents of all raw materials, animal or human origin used in all histories of cell cultures. 2. Result of all identity tests, include cytogenic characteristic that might be used to cell identification. 3. Information on the characterization and testing of the MCB/ Working Cell Bank (WCB) and cells from the end-of-production passage or post production. 4. Result of all tests, available adventitious agent to the donor and new master cell. 5. Growth and expression characteristic when cell substrate used to produced protein recombinant, include copy number evaluation and stability introduced nucleic acid and quality and quantity of protein expression to passage level later than anticipated production cycle. 6. Qualification cell bank or seed lot according to guidelines. 7. Cells stability which are validated in cold storage and storage condition with cell viability and recovery data . 8. For viral master seed, all relevant documents and all manipulations to the viral phenotypes, for example attenuation, virulency or genetic re-assortment or recombinant include the determination nucleic acid sequence and the biological source of starting material. 9. Sterility test data, mycoplasma, adventitious virus (if necessary). 10. Comparable approved and proposed drug substance related in physicochemical characteristics, biological activities and impurities. 11. Comparative Batch analysis (in tabulated), at least 3 batches drug substance which it from new cell/seed lot and old cell/seed lot. 12. Appropriates of stability study report, at least 3 batches which are produced with new cell/seed lot refer to relevant stability guideline; and Commitment to undertake long-term stability studies until approved shelf-life, if needed to report to the NAFDC any failures in these which was not fulfillment requirement (with action plan) or if was requested by NAFDC 13.Commitment to undertake long-term stability study of drug product refer to proposed	**217-218**

			changed. **B. Clinical Document** 1. Overview Clinical Study or Justification document for change /additional clinical information 2. List Document for change information product 3. Matriks Clinical Study for change of product information 4. Report of Clinical Study (reffering to the matrix at clinical study) 5. Latest Periodic Safety Update Report (if needed) 6. Other references. (if needed)	
3	**Critical changed at fermentation process (changed with potential give influences at quality drug substance or drug product)**	**1.Special for recombinant product**	**A. Quality Document** 1. Flow Diagram {including process and in -process control (IPC) and narrative description proposed manufacturing process. 2. Characterization information and test after Production cell bank for recombinant product or antigen for recombinant product, if changed influences to increase fermentation result or sub-cultivated. 3. If animal source including information animal source and statement letter free Bovine Spongiform Encephalopathies (BSE) / Transmissible Spongiform Encephalopathies (TSE). 4. Process Validation study report. 5. Comparable approved and proposed drug substance related in physicochemical characteristics, biological activities and impurities. 6. Non-Clinical and/or Clinical Study, when Quality Data are insufficient to establish comparability. 7. Comparative test result release and IPC for at least 3 consecutive commercial batches drug substances before and after changed 8. Comparative long-term stability testing results drug substance, at least three (3) batches commercial scale which produced with proposed change (minimum 3 months testing unless otherwise justified). 9. Commitment to undertake long-term stability studies of drug substance	**218-219**
4	**A critical changed in purity process drug substances which it potentially have an impact on viral clearance capacity of the process or impurity profile of drug substance**	**1, Special for recombinant product**	**A. Quality Document** 1. Flow Diagram {including process and in-process control (IPC) and a brief narrative description of the proposed manufacturing process(es) 2. Process Validation Study report. 3. Comparability of the pre- and post-change active substance with respect to pyshico-chemical properties, biological activities and impurities. 4. Non-Clinical and/or Clinical Study, when Quality Data are insufficient to establish Comparability 5. Comparative test result of the pre- and post-change on release and IPC for at least three (3) consecutive commercial-scale batches 6. Comparative long-term stability testing results drug substance,at least three (3) commercial scale which produced with proposed changes (minimum 3 months testing unless otherwise	**219**

			justified). 7. Commitment to undertake long-term stability studies of drug substance 8. Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on viral clearance studies, BSE/TSE risk)	
D	**Change related quality of drug substance.**			
1	**Change New WCB or Working Seed Lot.**	**1. New Cell Bank or new seed lot from approved MCB/MSL**	**A. Administrative Documents, Product Information and Labelling** 1. Information revision related with Quality and control of critical raw material (such as specific pathogen-free egg and chickens) which it used at new generation proposed WCB. **B. Update Quality Document** 1. Qualification of cell bank or seed lot. 2. Information on the characterization and testing of the WCB and cells from after manufacturing process. 3. Comparability of the pre- and post-change with respect to physicochemical properties, biological activity, purity, impurities and contaminants. 4. Non-Clinical and/or Clinical Study, when quality Data are insufficient to establish comparability. 5. Quality control test result as quantitative data in tabular format for the new cell bank. 6. Comparative pre- and post-change test result release and IPC for at least three (3) consecutive commercial batches drug substances. 7. Comparative long-term stability testing results drug substance, at least three (3) commercial scale which produced with the proposed changes (minimum 3 months testing unless otherwise justified). 8. Commitment to undertake long-term stability studies of drug substance	**219**
2	**Change and/or additional manufacturer of active substance or manufacturer facility for bulk of drug substance or intermediate active substance**	1. Special for New Drug Product and Drug Product which need Bioequivalency test.. 2. Specification of active substance remain unchange. 3. Specification (Batch release & shelf life) of drug product remain unchange. 4. Stability study has been done following protocol stability with minimum 2 batches pilot / production scale with minimum 6 months result fullfilment all spesification.	**A. Quality Document** 1. Drug Master File (DMF) from manufacturer active substance for active substance which never approved for manufacture drug product in Indonesia. 2. Comparative batch analyses active substance from current and new manufacturer.(Special for Biological Product batch analysis from minimal 3 consecutives pilot/commercial batches of drug substance). 3. Stability report of active substance 4. Comparative batch analyses drug product from current (2 batches) and new manufacturer.(2 batches) (Special for Biological Product batch analysis from minimal 3 consecutives pilot/commercial batches of drug substance). 5. Stability Studies Report of Drug Product and Commitment to undertake long-term stability studies Drug Product if stability studies report uncomplete/on going. 6. Bioequivalency data (in vivo/ in vitro) if needed.	**220**

3	**Replacement or addition of a manufacturer facility of active substance or intermediate active substance**	1. Special for Biological Product.	**A. Quality Document** 1. Validation process report of manufacturer's active substance. 2. Comparability of the pre- and post-change with respect to physicochemical properties, biological activity, purity, impurities and contaminants. 3. Non-Clinical and/or Clinical Study, when quality Data are insufficient to establish comparability. 4. Comparative test result active substance pre- and post- change on release and IPC for at least three (3) consecutive commercial batches. 5. Comparative long-term stability testing results drug substance, at least three (3) commercial scale which produced with the proposed changes (minimum 3 months testing unless otherwise justified). 6. Commitment to undertake long-term stability studies of drug substance	**220**
4	**Change of the manufacturer process of a starting material/intermediate used in the manufacturer of the active substance**	1. Not include active substance of biological product. 2 Not include active substance which requirement BE test (for example : pellet sustained release) 3. Not used raw material which are human /animal source which need viral safety data. 4. Stability study of active substance has done following protocol stability with minimum 2 batches pilot/production scale with minimum 6 months result fulfillment all specification.	**A. Quality Document** 1. Description of syntethic route active substance. 2. Comparative batch analysis active substance (2 batches pilot/production scale) from current and new manufacturing process. 3. Stability of active substance with new manufacturing process. 4. Comparative batch analysis of 2 batches drug product (pilot/production scale) between active substance with current and new manufacturing process.	**221**
5	**Introduction reprocessing step of active substance**	1. Reprocessing is needed not because of repeat deviation from validated process and root cause problem of reprocessing identified	**A. Quality Document** 1. Comparative test result release and IPC for at least 3 consecutive commercial batches drug substances pre- and post-change. 2. Comparative long-term stability testing results drug substance, at least three (3) commercial scale which produced with the proposed changes (minimum 3 months testing unless otherwise justified). 3. Commitment to undertake long-term stability studies of drug substance 4. Having data which showing route cause reprocessing, include validation data for help to prevent reprocessing which affect to active substance,	**221**
6	**Change and/additional manufacturer /source of biological active substance**	1. Special for Biological Product	**A. Quality Documemts** 1. BSE/TSE Certificate (if used material having risk of BSE/TSE) or information and evidence that the material does not pose a potential BSE/TSE risk. 2. Comparative pre- and post-change test results on release and IPC for at least three (3) consecutive commercial batches scale active substances.	**221**

			3. Information assessing the risk with respect to potential contamination with adventitious agent. 4. Information demonstrating comparability of the raw materials/ reagents from both source.	
7	**Change production scale in fermentation step , propagasi or celluler virus.**	1. Special for Biological Product 2. Specification of drug substance remain unchanged from determined assay . 3. Impurity of drug substance remain unchanged 4. These change not occur because of repeat case during manufacturing or because of stability problem. 5. Change not influence with purity process. 6. Change not influence with Quality. Safety or efficacy drug product. 7. Not having change with raw material propostional (where the scale change in linier). 8. Scale change used similar bioreactor	**A. Quality Documents** 1. Flow Diagram {including process and in -process control (IPC) and narrative description proposed manufacturing process 2. Information characteristic and test after manufacturer of cell bank for re-combinant product or antigen for non re-combinant product, if change influence with increase population doublings or subcultivated. 3. Process Validation study report 4. Comparability of the pre- and post-change with respect to physicochemical properties, biological activity, purity, impurities and contaminants 5. Non-Clinical and/or Clinical Study, when quality Data are insufficient to establish comparability. 6. Comparative the pre- and post- change active substance test result release and IPC for at least three (3) consecutive commercial batches	**221-222**
8	**Change production scale in manufacturing process in purity step**	1. Special for Biological Product 2.No change in the principle of the sterilization procedure. 3. No change in the antigen specification outside the approved limits. 4. These change not occur because of repeat case during manufacturing or because of stability problem. 5. Not having change with raw material propostional (where the scale change in linier and production)	**A. Quality Documents** 1. Flow Diagram {including process and in -process control (IPC) and narrative description proposed manufacturing process 2. Process Validation study report 3. Comparability of the pre- and post-change with respect to physicochemical properties, biological activity, purity, impurities and contaminants. 4. Non-Clinical and/or Clinical Study, when quality Data are insufficient to establish comparability. 5. Comparative test result release and IPC for at least three (3) consecutive commercial batches drug substances pre- and post-changed. 6. Comparative long-term stability testing results drug substance, at least three (3) commercial scale which produced with the proposed changes (minimum 3 months testing unless otherwise justified). 7. Commitment to undertake long-term stability studies of drug substance	**222**
9	**Widening limit in process manufacturer of approved drug substance**	1.Special for Biological Product	**A. Quality Documemts** 1. Scientific data and/or history for support reason / justification proposed changed. 2. IPC information in critical step and intermediate product drug substance. 3. Copy or summaries analytical procedure, if use new procedure analysis, 4. Validation process report, if used new procedure analysis. 5. Comparative IPC or specification pre- and post-changed. 6. Comparative test result release and IPC for at least 3 consecutive commercial batches drug	**222-223**

			substances pre- and post-changed. 7. Justification of new limit and in process. 8. Comparative long-term stability testing results drug substance, at least three (3) commercial scale which produced with the proposed changes (minimum 3 months testing unless otherwise justified). 9. Commitment to undertake long-term stability studies of drug substance 10. Comparative change of specification of drug substance (if necessary)	
10	**Delete in process test which can cause significant effect at quality of all drug substance.**	1. Special for Biological Product	**A. Quality Documemts** 1. Scientific data and/or history for support reason / justification proposed changed. 2. IPC information in critical step and intermediate product drug substance. 3. Comparative IPC or specification pre- and post-changed. 4. Comparative test result release and IPC for at least three (3) consecutive commercial batches drug substances pre- and post-changed.	**223**
11	**Additional or replacement test in process because of quality or safety issue.**	1. Special for Biological Product	**A. Quality Documemts** 1. Scientific data and/or history for support reason / justification proposed changed. 2. IPC information in critical step and intermediate product drug substance. 3. Copy or summaries analytical procedure, if use new procedure analysis, 4. Process Validation Report, if used new procedure analysis. 5. Comparative IPC or specification pre- and post-changed. 6. Comparative test result release and IPC for at least three (3) consecutive commercial batches drug substances pre- and post-changed. 7. Comparative change specification drug substance (if necessary)	**223**
12	**Change animal species/strain for batch release active substance (for example new species/strain, animal from different ages, new manufacturer as animal gentotype can not confirmation.**	1. Special for Biological Product	**A. Quality Documents** 1. Data with showing that proposed change at proposed animal/strain showing comparable result with approved data. 2. Certificate suitability of animal used in trial.	**223**
13	**Modification of non Compendial active substance specification**	1. Not including Biological Product 2. Stability study has been done following protocol stability with minimum 2 batches pilot/production scale with minimum 6 months results fullfilment all specification	**A. Quality Document** 1. New Specification of active substance. 2. Analytical Method of active substance. 3. Validation of Analytical Method of active Substance. 4. Batch analysis active substance for all test parameter in new specification (2 pilot /production batches scale) 5. Stability Studies Report of Drug Substances and Commitment Stability to undertake long-term stability studies Drug Substances if stability studies report uncomplete/on going.	**223**
14	**Widening limit specification starting material/intermediate which significant influence at all quality of active substance and/or drug product.**	1, Change not as consequency from current commitment for evaluate limit specification 2. Changed not as result	**A. Quality Document** 1. Comparative specification between approved and proposed changed. 2. Complete new test method and validation of test method, if necessary.	**223-224**

		from un-expected cases during process of manufacturing process active substance (for example new impurity, change limit total impurity. 3. Similar or minor analytical procedure 4. Test method not as biological method/ immune-logical chemical or method used biological reagent for biological active substance (not include standard method microbiology Pharmacopea) 5. every ingredient, not a change in genotoxic impurity. If on the final active ingredient, residual solvent must conform to the limit of the International Council for Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), a new impurity control must be in accordance with Pharmacopoeia	3. Batch analysis of two batches production of active substance (for Biological Product: three (3) Batches production, unless otherwise justified) for all specification parameter. 4. Comparative dissolution profile drug product, minimum one batch pilot scales which contain approved and proposed active substance. 5.. Justification for new limit specification and parameter.	
15	**Delete parameter test release active substance**	1. Special for Biological Product	**A. Quality Document** 1. Proposed specification of active substance. 2. Scientific data and/or history for support reason / justification proposed changed. 3. Evidence consistency of quality and sustainable of manufacturing process	**224**
16	**Widening criteria of specification released active substance**	1. Special for Biological Product	**A. Quality Document** 1. Proposed specification of active substance. 2. Scientific data and/or history for support reason / justification proposed changed. 3. Evidence consistency of quality and sustainable of manufacturing process	**224**
17	**Modification of specification shelf life of active substance**	1. Special for Biological Product 2. For any changed to specification shelf-life active substance 3. Specification of drug substance remain unchanged	**A. Quality Document** 1. Scientific data and/or history for support reason/justification proposed changed**.** 2. Comparative specification between approved and proposed changed. 3. Stability Study Report of active substance minimum three batches production scale with proposed specification and Commitment Stability to undertake long-term stability studies Drug Product if stability studies report uncomplete/on going.	**224**
18	**Modification of excipient of Biological Product**	1. For each mofidication of qualitative and quantitative excipient. 2. Modification of excipient does not affect the specification of released and shelf-life drug product 3. Batch formula and drug product specification remain unchanged.	**A. Quality Documents** 1. Justification of modification presents as appropriate pharmaceutical development (include aspect of stability and preservation with antimicrobial agent if appropriate). 2. Description and flow chart of active substance manufacturing process. 3. Specification of approved and proposed excipient. 4. CoA of proposed excipients.	**225**

			5. Comparative approved and proposed specification of drug substance. 6. Comparative study of Excipients with approved excipient and proposed excipient related with physicochemical biological activity, purity and contaminant. 7. Stability data of drug substance with new / proposed excipient. 8. For excipient having risk of TSE, if necessary : - Certificate of suitability for excipients - Documentation proven which showing that risk of BSE in the excipient has been evaluated. 9. Specification of released and shelf-life of drug product. 10. Comparative batch analysis (in tabulated) minimal three (3) batches drug product of Drug substance with approved excipient and proposed excipient. 11. Appropriates of stability study report, minimal (three) 3 batches which are produced with new cell/seed lot refer to relevant stability guideline; and Commitment to undertake long-term stability studies drug product if stability studies report uncomplete/on going and to report to the NAFDC any failures in (with action plan) or if was requested by NAFDC	
19	**Modification of analytical procedure in process control , release and active substance stability**	1. Special for Biological Product 2. For any modifications of in-process specification in manufacturing process of drug substance . 3. Drug specification remain unchanged.	**A. Quality Documents** 1. Description of modification of analytical procedure. 2. Validation analytical procedure report of modification analytical procedure. 3. Comparative analytical procedure between approved analytical procedure and modification analytical procedure.	**225**
20	**Modification of active substance Closure system**	1. Biological Product only 2. For each modification, includes type of closure system, composition of qualitative and quantitative, dosage form and dimension of closure system of drug substance 3. for any changes that do not belong to the minor variation category.	**A. Quality Document** 1. Information of construction material and feature design of closure system that has been submitted. 2. Comparability of the study report of leaching materials, leak test, etc. to appointed the linearity of the submit usage of closure system. 3. Validation process with modification of active substance closure system (if necessary) 4. Specification of the released and shelf-life of active substance. 5. Comparative of stability studies report, at least 3 batches which are produced with new cell/seed lot refer to relevant stability guideline; and Commitment to undertake long-term stability studies drug product until approved shelf-life, if stability studies report uncomplete/on going and to report to the NAFDC any failures in (with action plan) or if was requested by NAFDC.	**225**
21	**Update the modification in Plasma Master File**	1. Variation of registered blood product. 2. Modification affect the potential of product quality and safety	**A. Administrative Document** 1. GMP Certificate facilities the collecting and process of the plasma and/or commitment letter to fulfill the aspect of GMP from facilitating of plasma-collecting and processing in case of updating the modification of plasma sources. **B. Quality Documents** 1. Specification of released and shelf-life of	**226**

			active substance. 2. Specification of released and shelf-life of drug product. 3. Comparative batch analysis (in table) minimal 3 batches using approved and new plasma sources. 4. Appropriate result of stability study of minimal 3 batches which is manufactured using new sources of PMF and/or new plasma source conformed to the relevant stability guideline. 5. Report of adventitious agent safety evaluation (if necessary). 6. Expert statement that mentioned the outline of modification has been conducted on new PMF or documents contained the evaluation result on the potential effect to PMF modification on drug product include the assessment of specific risk. 7. For new PMF/ the modification should be followed with: a. New PMF/new version. b. Plasma specification and plasma pool batch analysis data. c. Letter of EMA recertification yearly, and the report of recertification assessment result of available. d. Letter of access,, issued by PMP holder to product owner and e. Information on section S.2.3 include: - Source and plasma collecting - Donation characteristic - Epidemiological data on blood transmissible infections - Criteria of selection/exclusion - Plasma quality and safety - Transport and storage conditions - Specification of plasma and batch analysis data in plasma pool	
E	**Change related with Quality of drug product**			
1	**Increase in finished product batch size more than 10-fold.**	1. Not include Biological Product 2. Formula and specification (batch release and shelf life) drug product remain unchange. 3. Stability study has been done following protocol stability with minimum 2 batches pilot / production scale with minimum 6 months result fullfilment all specification. 4. changes do not affect the reproducibility and / or consistency of the drug 5. the stability test has been performed according to the protocol with a minimum of two batches of production scale with a minimum of six months of data providing results that meet the specifications	**A. Quality Document** 1**.** Manufacturing process and in-process control . 2. Batch Formula 3. Flowchart production process from begininng until secondary packaging 4. Validation Report of manufacturing Procees. 5. Specification of Drug Product 6. Batch analysis of Drug Product 7. Comparation batch analysis between current batch production (3 production batch scale) and proposed batch production (minimum 2 production batch scale). 8. Commitment to undertake batch analysis new production scale (if only provide batch analysis pilot scale). 9. Stability Studies Report of Drug Product and Commitment to undertake long-term stability studies drug product if stability studies report uncomplete/on going.	**226-227**

2	**Increase in finished product batch size more than 10-fold for sterile product.**	1. Not include Biological Product 2. Formula and specification (batch release and shelf life) drug product remain unchange. 3. Validation Report of Manufacturing Process appropiate with approved batch size. 4. The changes does not affect reproducibility and/or consistency of the product. 5. Stability study has been done following protocol stability with minimum 2 batches pilot / production scale with minimum 6 months result fulfill all specification	**A. Quality Document** 1. Manufacturing process and in-process control . 2. Batch Formula 3. Flowchart production process from begininng until secondary packaging 4. Validation Report of manufacturing Procees. 5. Specification of Drug Product 6. Batch analysis of Drug Product 7. Comparative batch analysis between current batch production (2 production batch scale) and proposed batch production (minimum 2 production batch scale). 8. Stability Studies Report of Drug Product and Commitment to undertake long-term stability studies drug product if stability studies report uncomplete/on going	**227**
3	**Decreaee of finished product batch size to 10-fold of sterile product**	1. Not include Biological Product 2. Formula and specification (batch release and shelf life) drug product remain unchange. 3. Validation Report of Manufacturing Process appropiate with approved batch size. 4. The changes does not affect reproducibility and/or consistency of the product. 5. The change should not be the result of unexpected events arising during manufac-ture or because of stability concerns. 6. Stability study has been done following protocol stability with minimum 2 batches pilot / production scale with minimum 6 months result fullfilment all specification	**A. Quality Document** 1. Manufacturing process and in-process control . 2. Batch Formula 3. Flowchart production process from begininng until secondary packaging 4. Validation Report of manufacturing Procees. 5. Specifiation of Drug Product 6. Batch analysis of Drug Product 7. Comparative batch analysis between current batch production (2 production batch scale) and proposed batch production (minimum 2 production batch scale). 8. Stability Studies Report of Drug Product and Commitment to undertake long-term stability studies drug product if stability studies report uncomplete/on going.	**227**
4	**Scale up production process in formulation/filling step**	1. Special for Biological Product 2, Proposed scale used similar equipment or comparable with approved. Note : change scale equipment consider as not similar type/comparable. 3. Other change related with production process and/or at IPC only because by change batch size (for example formulation, test and Standard of Operating Procedure). 4. Change not because of repeat case problem	**A. Quality Documents** 1. Description of production process, if different with approved process, and information IPC critical step and intermediate proposed Drug Product. 2. Information IPC test, refer to the proposed. 3. Process Validation study report (for example media fill, refer to proposed), 4. Comparative batch release for minimal 3 consecutive commercial batches between before and after changed. 5. Comparative long-term stability testing results drug product at least three (3) commercial scale which produced with proposed change (minimum 3 months testing unless otherwise justified). 6. Commitment to undertake long-term stability	**227-228**

		during production or stability. 5. Not having change in principle procedure sterilization of Drug Product.	studies to support shelf-life/hold-time of final product under its normal storage condition and report to NAFDC any failures in these ongoing long-term stability studies 7. Information on leachables and extracables, refer to proposed change.	
5	**Change of tablet coating weight or capsule weight, gastro-resistant preparation or slow released tablet and the change.**	1. Drug formula (qualitative) remain unchange . 2. Composition of coating and capsule shell weight remain unchange 3. The dissolution profile drug product remain unchange for oral dosage form (if needed) . 4. Specification (batch release and shelf -life) remain unchange except weight of coating 5 Stability study has been done following protocol stability with minimum 2 batches pilot / production scale with minimum 6 months result fullfilment all specification. .	**A. Quality Document** 1. Batch Formula 2. Batch analysis of Drug Product 3. Comparation batch analysis between current batch production (2 production batch scale) and proposed batch production (minimum 2 production batch scale) from curent coating weight and proposed coating weight or from current capsule shell and proposed capsule shell. 4. Comparative dissolution data on at least two pilot batches of drug product with new formula and 2 production batches of drug product with current formula. 5. Stability Study Report of 2 batches Drug Product and Commitment Stability Drug Product if Stability Study report uncomplete/on going. 6. Bioequivalency Data (in vivo/in vitro) if needed. 7. Justification letter not necessary to provide new BE.	**228**
6.	**Change in the qualitative or quantitative of excipient**	1. Not include Biological Product 2. Not for the change with needed clinical study (efficacy and safety) 3. Stability study has been done following protocol stability with minimum 2 batches pilot / production scale with minimum 6 months result fullfilment all specification	**A. Quality Documents** 1. Pharmaceutical Development 2. Batch Formula 3. Flowchart manufacturing process from the Beginning until secondary packaging 4. Validation Report of Manufacturing Process 5. Specification and Analytical method of excipient 6. Specification od Drug Product 7. Analytical Procedure of Drug Product 8. Validation Report of Analytical Method 9. Batch analysis of Drug Product 10.Comparative batch analysis between current batch production (2 production batch scale) and proposed batch production (minimum 2 production batch scale) from current and proposed formula. 11. Uniformity assay result test (for scoring / breakline) 12. Stability Study Report of 2 batches Drug Product and Commitment to undertake long--term stability studies drug product if stability studies report uncomplete/on going 13. Bioequivalency data (in vivo/in vitro) if needed. 14. Justification not need BE test	**228 - 229**
7	**Change of excipient biological product**	1. For each modification of qualitative and quantitative of excipient formulation in drug product 2. Modification of excipient does not affect the specification of analytical procedure, released and shelf-life of drug product.	**A. Quality Documents** 1. Both approved and submitted batch formula and per unit dose of drug. 2. Justification of modification should be represent an appropriate pharmaceutical development (include stability aspect and microbial reservation if appropriate). 3. Information that appointed the compatibility of approval and submitted of excipient in physico-chemical characteristics and impurities profile.	**229**

			4. For excipient with TSE risk, if necessary: - Certificate of suitability of excipients - Documentation proven which showing the risk of BSE in the excipient has been evaluated. 5. Both approved and proposed specification of drug released and shelf-life. 6. Comparative batch analysis (in tabulated) of minimal two batches manufactured drug conformed to the approved and submitted formula. 7. Result of stability studies report, at least three (3) batches of manufacturing drug with proposed formula conformed to relevant stability guideline; and commitment to undertake long-term stability studies until approved shelf-life, and report to the NAFDC any failures not fulfill the criteria in these ongoing long-term stability studies.	
8	**Change on process production of Drug product which influences Stability**	1. Not include Biological Product . 2. Not influence eficacy safety of the product. 3. Validation process/ consistency process production has been done. 4. Specification (batch release and shelf -life) remain unchange . 5. Stability study has been done following protocol stability with minimum 2 batches pilot / production scale with minimum 6 months result fullfillment all specification .	**A. Quality Documents** 1. Pharmaceutical Development 2. Manufacturing Process and in-process control . 3. Flowchart manufacturing process from the beginning until secondary packaging 4. Validation Report of Manufacturing Process 5. Batch analysis of Drug Product 6. Comparative batch analysis between current batch production (3 production batch scale) and proposed batch production (at least 2 production batch scale or 1 production batch scale and 2 pilot batch scale) . 7. Stability Studies Report of 2 batches Drug Product and Commitment to undertake long-term stability studies drug product if stability studies report uncomplete/on going.	**229**
9	**Change of drug manufacturing process in the same industry of finished drug manufacturer**	1. Special for Biological Product 2. For any modification in manufacturing procedure and/or modifications of production scale in each step of manufacturing process of drug product. 3. For any modification that is not available in drug minor variation.	**A. Quality Documents** 1. Summary and validation process report of submitted manufacturing procedure. 2. Specification of drug released and shelf-life. 3. Comparative batch analysis (in tabulated) of at least 3 batches of drug that manufactured using approved and submitted procedure. 4. Result of stability studies report, at least 3 batches of manufacturing drug with proposed formula conformed to the relevant stability guideline; and Commitment to undertake long-term stability studies drug product until approved shelf-life, and report to the NAFDC any failures not fulfill the criteria (with action plan) or if required by the NAFDC. 5. Statement letter contains that: a. There is no change in the case of qualitative and quantitative impurity profile or physicochemical properties; b. Changes do not give a negative change to the reproducibility of the process; c. Changes made are not a result of unexpected events during production or due to stability issues; d. The drug specifications have not changed.	**229-230**
10	**Change of partial or all steps of drug manufacturing**	1. Evaluation /Inspection of Site Master File	**A. Administrative Document , Product Information and Labelling.**	**230 – 231**

	location.	fullfilment the requirement. 2. Satisfactory GMP inspection report in two year latest. 3. Formula, source of active substance and excipient , manufacturing process, drug specification, packaging specification remain unchange. 4. Validation report of manufacturing process following protocol with 3 batches production scale, or minimum 1 batches pilot scale and Commitment Validation Process first 3 batchs production with estimate timeline for submission. 5. Transfer method analysis from current to new site has been fullfilment the requirement. 6. Stability study has been done following protocol stability with minimum 2 batches pilot / production scale with minimum 6 months result fullfillment all specification.	1. Product Information (if needed) 2. Labelling on packaging (if needed) **B. Quality Documents .** 1. Manufacturing Process and in-process control . 2. Flowchart manufacturing process from the Beginning until secondary packaging 3. Validation Report of Manufacturing Process 4. Validation Report of Method Analysis or Verification transfer method from current site to the new site. 5. Batch analysis of Drug Product. 6. Comparative batch analysis between current batch production (3 production batch scale) and proposed batch production (at least two (2) production batch scale or one (1) production batch). 7. Comparative Dissolution Profile between drug Product from current and new site. 8. Accelerated Stability Study 6M & Long Tern Stability Study Report of 3 batches Drug Product and Commitment to undertake long-term stability studies drug product if stability studies report uncomplete/on going . 9. Bioequivalency data (if necessary).	
11	**Change of finished drug primary packaging location**	1.Not for sterile product 2.Satisfactory GMP inspection report in two year latest. 3. Formula, source of active substance and excipient , manufacturing process, drug specification, packaging specification remain unchange. 4. Validation report of manufacturing process following protocol with 3 batches production scale, or minimum 1 batches pilot scale and Commitment Validation Process first 3 batchs production with estimate timeline for submission. 5. Stability study has been done following protocol stability with minimum 2 batches pilot / production scale with minimum 6 months result fullfillment all specification.	**A. Administrative Document , Product Information and Labelling.** 1. Product Information (if needed) 2. Labelling on packaging (if needed) **B. Quality Documents .** 1. Flowchart manufacturing process from the beginning until secondary packaging and information site of each production process. 2. Validation Report of primary packaging in new Site. 3. Batch analysis of Drug Product 4. Comparative batch analysis between current batch production (3 production batch scale) and proposed batch production (minimum 2 production batch scale or 1 production batch scale and 2 pilot batch scale) . 5. Study of bulk holding time (if necessary) 6. Stability Study Report of 2 batches Drug Product scale and 2 pilot batch scale. Commitment to undertake long-term stability studies drug product if stability studies report uncomplete/on going .	**231**
12	**Change of the specification of non compendial drug product**	1. Analytical Method drug product remain unchange. 2 Stability study has been done following protocol stability with minimum 2 batches	**A. Quality Document** 1. New specification of drug product. 2. Batch analysis of drug product for all parameter in new specification (2 batches pilot/production scale). 3. Stability Report drug product and	**231**

		pilot / production scale with minimum 6 months result fullfillment all specification.	Commitment to undertake long- term stability studies drug product if stability studies report uncomplete/on going .	
13	**Change of the dosage form and/or the dimension of primary packaging (for sterile product)**	1. Specification of raw Material primary packaging remain unchange. 2. Not as important part of packaging which influence distribution, administrative, safety or stability of drug product. 3. Special for drug product with terminal sterilisation; Validation report of manufacturing process following protocol with 3 batches production scale, or minimum 1 batches pilot scale and Commitment Validation Process first 3 batchs production with estimate timeline for submission. 4. For Changing " head space" or change " surface /volume ratio" : Stability study has been done following protocol stability with minimum 2 batches pilot / production scale with minimum 6 months result fullfillment all specification.	**A. Administrative Document , Product Information and Labelling.** 1. Sample primary packaging in photo form's or design as original (mock up/dummy) **B. Quality Documents .** 1. Specification and Method Analysis of packaging. 2. Validation Report of Manufacturing Process with final sterilization . 3. Stability Studies Report drug product and Commitment to undertake long- term stability studies drug product if stability studies report uncomplete/on going .	**231-232**
14	**Change of the specification of drug release and shelf-life**	1. Special for Biological Product 2. For any modification on the drug released and shelf-life.	**A. Quality Documents** 1. Scientific data and/or history for support reason/justification proposed changed**.** 2. Comparative specification of drug released and/or shelf-life between approved and proposed changed with mark. 3. Batch analysis of drug product for all test in proposed specification (minimal three batches). 4. For any change of stability-indicating parameter in specification: - Result of stability studies that appropriate to at least three (3) batches. - Commitment to undertake long-term stability studies until approved shelf-life, and report to the NAFDC any failures which was not fulfill criteria (with action plan) or if required by the NAFDC.	**232**
15	**Change of the specification of process control in drug manufacturing procedure**	1. For any modification of the specification of process control in biological product manufacturing procedure	**A. Quality Documents** 1. Scientific data and/or history for support reason/justification proposed changed**.** 2. Comparative specification of in process control between approved and proposed changed with mark. 3. Batch analysis of drug product for all test in process control (minimal three batches).	**232**
16	**Widening limit in-process which approved manufacturing process**	1, Special for Biological Product	**A. Quality Documents** 1. Information in production process control at	**232-233**

	drug product		critical step and in proposed antigent intermediate product. 2. Reform specification of drug product, if changed. 3. Copies or summary analytical procedure, if use new analytical procedure. 4.Validation study report, if used new analytical/ procedure. 5. Comparative batch release for minimal 3 consecutive commercial batches pre- and post-changed. 6. Comparative batch release for minimal 3 consecutive commercial batches pre- and post-changed. 7. Justification for new test and limit in -process control. 8. Comparative long-term stability testing result drug. at least 3 batches commercial scale which produced with proposed change (minimum 3 months testing unless otherwise justified).	
17	**Change of analytical procedure o excipient of drug product**	1. Special for Biological Product 2. For any change of analytical procedure of excipient in active substance	**A. Quality Document** 1. Description of the submitted analytical procedure. 2. Report of validation procedure of submitted analytical procedure. 3. Comparative data of analytical procedure approved and proposed analytical procedure. 4. Specification of excipient.	**233**
18	**Change on produce of biological excipient (not include biology adjuvant)**	1. Special for Biological Product	**A. Quality Document** 1. Detail information source of excipients (for Example animal species, country of origin) and step which were done during process for minimize risk of TSE contaminant. 2. Comparative physicochemical properties and impurities profile of approved and proposed excipients. 3. Information production process and controlling of critical step at production process and at drug product between approved and proposed excipient, 4. Comparative batch release for at least of 3 consecutive excipient commercial batches pre- and post-change. 5. Comparative long-term stability testing result drug substance at least 3 batches commercial scale which produced with proposed change (minimum 3 months testing unless otherwise justified). 6. Commitment to undertake long-term stability studies. 7. Information of risk evaluation regarding potentially contamination with adventitious agent (such as the aspect at viral clearance study or BSE/TSE risk) include documentation viral safety which it needed.	**233**
19	**Change excipient manufacturer with plasma source**	1. Special for Biological Product	**A. Quality Document** 1. Comparative physicochemical properties and impurities profile of approved and proposed excipients. 2. Information production process and controlling of critical step at production process and at drug product between approved and proposed excipient 3. Comparative batch release for at least of 3 consecutive excipient commercial batches pre-	**233**

			and post- changed. 4. Comparative long-term stability testing drug substance at least 3 batches commercial scale which produced with proposed change (minimum 3 months testing unless otherwise justified). 5. Commitment to undertake long-term stability studies. 6. Information of risk evaluation regarding potentially contamination with adventitious agent. 7. Full production data and clinical safety for support using proposed derivate excipient human plasma.	
20	**Change of analytical procedure of process control in manufacturing process of drug product.**	1. Special for Biological Product 2. For any changes of analytical procedure of drug released or drug stability study. 3. Specification of active substance and drug product remain unchanged.	**A. Quality Document** 1. Description of the submitted analytical procedure. 2. Report of validation procedure of submitted analytical procedure. 3. Comparative data of analytical procedure between approved and submitted analytical procedure.	**234**
21	**Change of analytical procedure of drug product for drug released/stability study.**	1. Special for Biological Product 2. For any change of analytical procedure of drug released or drug stability study. 3. Specification of active substance and drug product remain unchanged.	**A. Quality Document** 1. Specification of drug released and shelf-life. 2. Description of the submitted analytical procedure. 3. Validation study report of proposed test procedure 4. Comparative data of analytical procedure between approved and submitted analytical procedure.	**234**
22	**Change of drug packaging system**	1. Special for Biological Product and sterile product. 2. For any change includes type of closure system, composition of qualitative and quantitative, dosage form and dimension of closure system that direct related to drug product. 3. For any modification that not include to the category of minor variation.	**A. Quality Document** 1. Information of construction material and feature design of closure system that has been submitted. 2. Comparability of the study report of leaching materials, leak test, etc. to appoint the linearity of the submit usage of closure system. 3. Validation process with modification of active substance closure system (if necessary) 4. Specification of drug released and shelf-life. 5. Result of stability studies report, at least 3 batches of manufacturing drug with proposed packaging system in line with relevant stability guideline. 6. Commitment letter to undertake long-term stability studies.	**234**
23	**Change of packaging system/solvent**	1. Special for Biological Product 2. For any change, includes type of closure system, composition of qualitative and quantitative, dosage form and dimension of closure system that direct related to solvent to reconstitution. 3. For any modification that not include to the category of minor variation.	**A. Quality Document** 1. Information of construction material and feature design of closure system that has been submitted. 2. Comparability of the study report of leaching materials, leak test, etc. to appoint the linearity of the submit usage of closure system. 3. Validation process with modification of active substance closure system (if necessary) 4. Specification of the released and shelf-life of solvent. 5. Appropriates of stability study report, minimal 3 batches solvent which are manufactured using submitted packaging system in line with relevant stability study.	**234**
24	**Change packaging size/volume**	1. Drug product with new	**A. Product Information and Labelling**	**234-**

	size and/or change shape or dimension of sterile solid and solution dosage form	packaging, consistent with posology and treatment duration. 2. Drug specification remain unchanged. 3. Specification of packaging material remain unchanged. 4. Stability study has been done refer to protocol with minimally six months of two batches pilot scales or production scale which having result with fullfil the requirements.	1. Product Information 2. Label on primary and secondary packaging. **B. Quality Document** 1. Justification which mention that proposed volume size dosage form consistent with approved dosage regiment. 2. Validation process report, sterilization and packaging system (if necessary). 3. Batch analysis certificate (minimal two batches). 4. Stability study report if stability study not complete.	**235**

CLASSIFY 4 : MINOR VARIATION REGISTRATION (VaMi)

No	Variation Type	Conditions to be fullfilled	Documentation to be supplied	Pages
A	**Change related with product information and/or labelling.'**			
1	**Change of product information**	1. Special for generic product. 2. Product information (submitted claim) should be in line with the product information has been approved in Indonesia	**A. Product information and labelling** 1. Product Information 2. Labelling packaging (if necessary) 3. Supporting document in the change of submitted product information.	**236**
2	**Change in the name of applicant/pharmaceutical industry as drug importer**	1.Marketing authorization holder is unmodified 2.Location of the applicant/ pharmaceutical industry/ drug license are unmodified	**A. Product information and labelling** 1. The name in the letter of information is modified 2. Product Information 3. Labelling packaging	**236**
3	**Change of drug trade name**	1.Drug name is in lined with the valid provision 2.Product information, labelling and packaging design are unmodified	**A. Product information and labelling** 1. product information 2. labelling of primary and secondary package	**236**
4	**Size increasing of drug packaging**	1.Claim of product information is unchanged. 2.Specification of the package is unchanged	**A. Product information and labelling** 1. Product information 2. Labelling of primary and secondary package	**236**
5.	**English/ Indonesian added in product information**	1. Product information in lined with the last approval	**A. Product information and labelling** 1. Product information 2. Labelling of primary and secondary package (if necessary)	**236**
6	**Claim limited relevant to drug safety**		**A. Product information and labelling** 1. Product information 2. Labelling of primary and secondary package **B. Clinical document** 1. Justification and/or other supporting documents conformed to submitted changed, 2. Report of Post Marketing Drug safety/PSUR 3. Other references	**236 -**
B	**Change related with quality of active substance (Biological Product)**			
1	**Replacement or addition of a manufacturing facility for the bulk active substance or any intermediate active substance**	1. The new manufacturing facility is an approved antigen manufacturing site. 2. Any changes to the manufacturing process and/or control can be categorized Minor Variation or Notification Vatiation. 3.Facility in new place are considered under the same quality assurance / /quality control oversight. 4 The proposed change does not involved additional contaminant requirements.	**A. Quality Document** 1. Justification for the classification of the proposed change as minor variation. 2. Comparability of the pre- and post-change with respect to: - Physicochemical properties - Biological activity - Purity - Impurity - Contaminant As appropriate to the proposed change. 3. Comparative result of IPC test and release for at least three (3) consecutive batches drug substance commercial product pre- and post change. 4. Comparative test result long-term stability of drug substance, minimal three commercial batches scale with proposed change (minimum three months test results except	**236 - 237**

			other statement). 5. Commitment Letter to continue long-term stability study for support complete shelf-life/hold time in normal condition storage and report to NAFDC if there were failure occur during long-term stability study.	
2	**Minor change on the manufacturing procedure of active substance.**	1. The active substance is not biological substance. 2. No adverse change in qualitative and quantitative impurities profile or in physico- chemical process. 3. The Synthetic route remain the same (for ex. Intermediate compound remain unchanged. 4. The specification and stability of active substance and intermediate product are unchanged. 5. Manufacturing process of the active substance not used materials of human or animal origin for which assessment is required of viral safety.	**A. Quality Documents** 1. Characteristic active substance 2. Description Synthetic of active substance 3. Batch analysis of active substance. 4. Comparative batch analyses active substance minimal 2 batches (pilot /production scale) which produces from current and new active substance manufacturing process 5. For sterile active substance, validation report of manufacturing process of active substance (if needed).	**237**
3	**Minor change in manufacturing procedure of active substance.**	1. Special for Biological Product 2. Valid for each minor change of procedure and/or production scale in any step of manufacturing process of active substance 3. Relevant to the modification of uncritical procedure such as modification of harvesting, storage condition or production scale, duplication, of fermentation strain, adding of identic bioreactor or similar/comparable one. 4. No principal change of sterilization procedure. 5. There are no change of specification besides specification which has been approved. 6.There are no change in impurity profile of active substance , out of approved impurity. 7. Change not as resut of unexpected events during manufacturing process or stability cases. 8.The change that not effect toViral Clearance Data or Chemical Inactivating Agent	**A. Quality Documents** 1. Justification of modification 2. Justification of modification related to antigen quality effect 3. Summary of procedure modification relevant to the approved tabulated procedure. 4. Flow chart (including process and IPC) and process naratif description that proposed 5.BSE/TSE certificate (if use material that risk BSE/TSE) for example : ruminant origin, or information and evidence the material not cause BSE/TSE 6.Validation of modification procedure (if necessary). 7. For the modification of manufacturing procedure of active substance, comparability of active substance in characterizing and physico-chemistry, biological activity and impurities profile. 8. Comparative of batch analysis data (in tabulated) of minimally 3 batches that were manufactured using approved and proposed procedure. 9. Stability study that was using minimally of 3 batches active substance (pilot or production scales) in lined with relevant stability guideline and Commitment to undertake long-term stability study and report to the NAFDC any failure which is not fulfilled the criteria or if required by NAFDC 10. Commitment to submit report of stability study appropriate with proposal	**237**

4	**Widening of the approved in-process limits active substance**	1. The specification of active substance are unchanged 2. There are no modification in impurity profile of active substance, out of approved impurity. 3. Change not as result of unexpected event during manufacturing process or stability case.	**A. Quality Document** 1. Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed active substance. 2.Comparative test/acceptance criteria between current and proposed in‑process control (IPC). 3. Comparative IPC testing results and release testing results, for at least three (3) commercial-scale batches of the pre- and post-change final product 4. Justification for the new in-process test and limits. 5. Comparative long-term stability testing results active substance, at least three (3) commercial scale which produced with the proposed changes (minimum of 3 months testing unless otherwise justified). 6.Commitment to undertake long-term stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NAFDC any failures in these ongoing long-term stability studies. .	**238**
5	**Addition or replacement equipment (for example formulation tank, filter housing, filling line and head, and lyophilizer) .in drug manufacturing process**	1. Special for Biological Product	**A. Quality Document** 1. Description of the manufacturing process, if different from the approved process, and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed final product. 2. Information on the in-process control testing, as proposed change 3. Process validation study reports as proposed change. 4.Batch analysis data (on tabel) minimum 3 batches product before and after the changes 5. Comparative long-term stability testing results drug at least three (3) commercial scale which produced with the proposed changes (minimum of 3 months testing unless otherwise justified). 6. Commitment to undertake long-term stability studies. 7.Leachables and extracables information as proposed change. 8. Information of new equipment and comparative principle operational similarity and differences and specification between approved and proposed changed.	**238**
6-	**Change of analytical procedure of active ingredient (non-compendial)**	1. Not included biological product. **2.** The specification of active substance are unchanged. 3. Release and shelf-life specification of the product have not been changed	**A. Quality Documents** 1. Analytical Method of active ingredients. 2. Current and Proposed Validation Method Analysis Report. 3.Suitability Method Report of Current and proposed Method Analysis	**238**
7	**Change of specification IPC in manufacturing process active substance**	1. Change not as consequency of former commitment for review limit specification 2. Change not as result of unexpected event during manufacturing process of active substance, for example new contaminant, change total limit impurities. 3. Change still in range of	**A. Quality Documents** 1. Comparative table approved and proposed in – process test 2. Detail Analytical Method non Pharmacopea and new validation data , if needed. 3. Batch analysis of two batches production active substance (special Biological product three batches, unless otherwise justified) for all parameter specification	**239**

		approved limit. 4. Test procedure are similar or minor change 5. New Test Method not involve new nonstandard technical or standard technical which is new used,		
8	**Extend re-test period/storage active substance**	1. Change not as result of unexpected event during manufacturing process or stability case. 2. Change not related with widening acceptance criteria of test parameter, delete stability parameter or reduce frequency test	**A. Quality Documents** 1. Stability test result of active substance. 2. Specification of active substance	**239**
9	**Increase batch size active substance/intermediate more than 10 fold**	1. Active substance not include Biological Product/ immunology or sterile product 2. The change does not affect reproducibility process 3. The change should not be the result of unexpect-ed events arising during manufacture process or because of stability concerns. 4. The specification of active substance/ /intermediate are unchanged 5. Batch analysis minimum 2 bets appropriate with specification 6. Change in method of manufacturing process should do scale up, for example usage equipment/ machinery different size.	**A. Quality Documents** 1. Specification of active substance/intermediate. 2. Comparative batch analysis (in tabulated) active substance/intermediate.former production and proposed production (minimum from one production batch scale) . The next production of two batches should be available and should be reported if out of specification,	**239**
10	**Increasing or notification of the location of active substance studies include stability study and process control study**	1. Special for Biological Product 2. The analytical proce-dure are unchanged. 3. The specification of the active substances are unchanged. 4. Validation result fulfilled the criteria 5. Transfer of analytical procedure has been fulfilled the criteria	**A. Quality Documents** 1. Summary of validation study conducted in new study location. 2. Comparative study result data of minimal 3 batches that studied in minimal 3 batches in approved and proposed study location. 3. Information and specification of reference standard. 4. Specially for change of stability study location, Stability test report in new stability study location.	**239**
		.	.	**240**
11	**Additional or change storage condition of active substance (such as widening or thigtening temperature criteria)**	1. Special for Biological Product	**A. Quality Documents** 1. Proposed storage condition and shelf-life. 2. Stability test result (as full long-term stability study result refer to proposed shelf-life at least from three batches commercial scale).	**240**
12	**Reduce or delete overage**	1. Change not impact former approved overage.	**A. Quality Documents** 1. Justification of proposed change.	**240**

		2. Release and shelf-life specification of the product have not been changed	2. Table comparative of approved and proposed formula. 3. Certificate of Analysis from two batches of drug product. 4. Stability Studies Report and Commitment to undertake long-term stability studies.if stability study uncompleted/on going.	
C	**Change related with drug product**			
1	**Replacement of a manufacturer responsible for batch release (not includes drug analysis)**	1. Special for Imported Product. 2. Only for one mother company.	**A. Product Information and Labelling** 1. Product Information 2. Labelling on packaging	**240**
2	**Replacement of a manufacturer responsible for batch release (includes drug analysis)**	1. Not include Biological Product. 2. Special for Imported Product. 3. Only for one mother Company. 4. Method transfer from old to the new test laboratory has been sucessfully completed. .	**A. Product Information and Labelling** 1. Product Information 2. Labelling on packaging **B. Quality Documents** 1. Validation/ Verification of Methods Analysis which are transfer method from current and proposed manufacturer. 2. Batch analysis data (minimal 2 batch pilot scale) at current and proposed laboratory site.	**240**
3	**Replacement or addition of a site where testing of drug product take place.**	1. Owner of the prodyct and release site are similar 2. Registered test site. 3. Method transfer from old to the new test laboratory has been successfully completed. 4. The specification of the drug are unchanged.	**A. Quality documents** 1. Result of batch analysis of new drug 2. Specification of drug 3. References standard 4. Result of batch analysis drug 5. Transfer Analytical Method Result of drug	**240**
4	**Increased and/or decrease of the batch size of drugs to 10 folds, for tablets and oral liquid dosage form**	1. Not include Biological Product 2. Change not influence drug specification : should report any changes of manufactur-ing process and/or in-process control which has been done related to batch size, for example using different capacity machine . 3. Validation Report of manufacturing process suitable with approved validation report batch size. 4. The change does not affect reproducibility and/or consistency of the product. 5. The changes not as impact in manufacturing process or stability case	**A. Quality documents** 1. Manufacturing process and in process control. 2. Batch formula 3. Drug Product Specification. 4. Batch analysis of drug product. 5. Comparative Batch analysis data (at least 2 batch pilot/production scale) from current batch and proposed batch size. 6. Stability Study Report of Drug Product and Commitment to undertake Stability Drug Product if Stability studies report uncomplete/on going	**240**
5	**Change of one compound excipient with other excipient with similar characteristic functional.**	1. Not include modify release product and sterile product. 2. Not include product which need clinical test include bioequivalency test. 3. Validation of manufacturing process	**A. Quality Documents** 1. If animal source include source animal information and declaration letter free BSE/TSE. 2. Process Validation Report of drug manufacturing process. 3. Comparative dissolution test of old and new formula. 4. Stability studies Report and Commitment to undertake long-term stability if Stability Study	**241**

		has been done refer protocol of three (3) batches production scale or ar least one batch pilot scale and Commitment of Process Validation of three(3) batches first production with estimate time for submission. 4. Release and shelf-life of specification product have not been changed. 5. Stability study has been done following protocol stability with minimum 2 batches pilot / production scale with minimum 3 months result fullfilment all specification.	Report uncompleted. 5. Justification not necessary to do BE test.	
6	**Change excipient for drug included in narrow therapeutic index or Biopharmaceutics Classification System (BCS) class 4 which not require BE test**	1. Dissolution profiles new formula equivalent with old formula. 2.Validation of manufacturing process has been done refer protocol of three (3) batches production scale or ar least one batch pilot scale and Commitment of Process Validation of three (3) batches first production with estimate time for submission. 3. Release and shelf-life of specification product have not been changed. 4. Stability study has been done following protocol stability with minimum 2 batches pilot / production scale with minimum 3 months result fullfilment all specification.	**A. Quality Documents** **1.** Comparative dissolution test of old and new formula. 2. Process Validation Report of drug manufacturing process 3. Comparative batch analysis of former production (two batches production scale) and proposed production (at least two batches production scale or one batch production scale and two batches pilot scales). 4. Commitment to provide batch analysis new production scale (if submit batch analysis pilot scale). 5. Stability studies Report and Commitment to undertake long-term stability if Stability Study Report uncompleted. 6.Justification not necessary to do BE test.	**241**
7	**Change manufacturer's capsule shell**	1. The specification of the drug are unchanged. 2. Formula and process Production are unchange. 3. Stability study has been done following protocol stability with minimum 2 batches pilot / production scale with minimum 6 months result fullfilment all specification. 4. Not valid for change from hard capsule to soft capsule.	**A. Quality Document** 1. Capsule Shell Specification. 2. Certificate of Analysis of Capsule shell . 3. Information source of gelatin as raw material of capsule shell . 4. Certificate free of BSE/TSE . 5. Comparative Dissolution Test minimum 1 batch pilot scale drug product between proposed capsule shell and approved capsule shell . 6. Batch analysis of drug product.	**241**
8	**Change size of capsule shell**	1. Release and shelf-life Formula and specification of the product have not been	**A. Quality Document** 1. Appearance and Formula 2. Batch analysis Drug Product 3. Comparative Batch analysis drug product from	**242**

		changed (except for appearance). 2. Raw material of capsule shell similar with current capsule shell . 3. Only for immediate release capsule.	minimal 2 batches production scale from current and new capsule shell . 4. Capsule specification. 5. Composition Capsule Shell. 6. Information source of gelatin as raw material of capsule shell . 7. Certificate of Analysis of capsule shell . 8. Certificate free of BSE/TSE . 9. Comparative Dissolution Test minimum 1 batch pilot scale drug product between proposed capsule shell and approved capsule shell .	
9	**Change in the shape or dimensions gastro-resistant tablets, sustained release tablet and scored tablet**	1. Release and shelf-life specification of the product have not been changed (except for dimensions). 2. The dissolution profile of new dimension equivalent with current dimension (if it requirement in monograph). 3. The qualitative and Quantitative composition and mean mass remain unchanged.	**A. Quality Document** 1. Drug product Specification (include drawing and Description approved and proposed dimension). 2. Comparative current and proposed dissolution Profile. 3. Product Information (if needed) . 4. Batch analysis of drug product. 5. Comparative Batch analysis drug product from minimal 2 batches pilot / production scale from current and new dimension. 6. Uniformity assay (for scoring /break-line tablet). 7. Justification for not submitting BE study.	**242**
10	**Change in the shape or dimensions immediate release tablet , capsule , suppositoria or pessaries**	1. Not valid for scored tablet. 2. Release and shelf-life specification of the product have not been changed (except for dimensions). 3. The dissolution profile of new dimension equivalent with current dimension (if it requirement in monograph). 4. The qualitative and Quantitative composition and mean mass remain unchanged	**A. Product Information and Labelling** 1. Product Information 2. Labelling on packaging **B. Quality Documents** 1. Drug product Specification (include drawing and Description approved and proposed dimension). 2. Comparative dissolution profile of the current and proposed dimensions. 3. Batch analysis drug product. 4. Comparative Batch analysis drug product from minimal 2 batches production scale from current and new dimension	**269**
11	**Minor change in drug manufacturing process**	1. Special for Biological Product 2 Valid for any minor change of procedure and/or production scale in any step of drug manufacturing process. 3 Related with change of uncritical process such as change without change of method production, storage condition or production scale, 4. Increase production scale for drug without equipment changed such as changed filling quantity of vials. 5.No principle change on sterilization process. 6. No specification change out of approved	**A. Quality Document** 1. Summary process change related with approved process in tabulated form. 2. Justification of change. 3. Validation of change process (if needed) 4. Comparative batch analysis data (in tabulated form) at least three (3) batch which produced used approved and proposed change process. 5. Stability studies of three (3) batches active substance (pilot/production scale) refer to relevant stability guideline or commitment to undertake long-term stability study and report to NAFDC if there was testing result not fulfill requirement or if require by NAFDC.	**242-243**

		specification. 7. The change should not be the result of unexpected events arising during manufacture process or because of stability concerns.		
12	**Additional new step in drug manufacturing process**	1. Special for Biological Product 2. The change should not be the result of unexpected events arising during manufacture process or because of stability concerns.	**A. Quality Documents** 1. Detail production process, if proposed process different from approved process and information of controlling production process in critical step and intermediate product 2. Information of IPC test, refer to proposed changed. 3. Process Validation Studies Report (such as media fill) refer to proposed changed. 4. Comparative release test result for at least three (3) consecutive batches commercial scale of pre- and post-change. 5. Comparative long-term stability testing results active substance, at least three (3) commercial scale which produced with the proposed changes (minimum of 3 months testing unless otherwise justified). 6. Leachables and extractables information, refer to proposed changed.	**243**
13	**Additional or replacement in-process test because quality or safety cases.**	1. Special for biological product 2. The specification of the drug are unchanged.	**A. Quality Document** 1. Justification of change include scientific data and/or history for support proposed changed. 2. Information Controlling production process in critical step and at intermediate product proposed antigen. 3. Analytical procedure, if use new analytical procedure 4. Validation of analytical procedure, if use new analytical procedure. 5. Comparative table/ description approved and proposed refer to changed 6. Comparative batch released test report at least three (3) batches commercial scale of pre- and post changed.	**243**
14	**Deletion of the solvent/diluent from the drug product**	1. Proposed changed not impact to change of dosage form, dosage, indication and administrative of drug product	**A. Quality Document** 1. Revised Product Information and label (if needed) 2. Justification for the deletion, including a statement regarding alternative means to obtain the solvent/ diluent as required.	**243**
15	**Change in method analysis of Drug Product**	1. Not include Biological Product . 2. Release and shelf-life specification of the product have not been changed	**A. Quality Document** 1. Method analysis of Drug Product . 2. Validation Method Analysis Report curent and proposed 3. Suitability Report of current and proposed Method Analysis.	**244**
16	**Change in drug packaging system**	1. Not included Biological Product and Sterile Product. 2. For any change of packaging type which direct contact with drug. 3. Stability test has been done refer to protocol with at leasr two batches pilot/production scales with minimum three (3) months result fulfill specification.	**A. Quality Document** 1. Specification and Test Method of packaging material 2. Compatibilitas study report, proposed leak test for showing suitability usage packaging system. 3. The specification of released and shelf-life of drug. 4. Stability studies Report and Commitment to undertake long-term stability if stability studies uncompleted.	**244**
17	**Change in shape or dimension**		**A. Product Information and Labelling**	**244**

	primary packaging (for non sterile dosage form).	1. The specification of primary packaging material are unchanged. 2. Not as important part of packaging which influence distribution, administrative , or Stability drug product. 3. For change in "head space or surface volume ratio : Stability study has been done following protocol stability with minimum 2 batches pilot / production scale with minimum 6 months result fullfilment all specification.	1. Primary packaging labelling include mock up. **B. Quality Document** 1. Specification and Test Method of packaging material. 2. Stability Studies Report of Drug Product and Commitment to undertake Stability Drug Product if Stability Studies report uncomplete/on going	
18	**Change in the fill volume of nonparenteral multidosage form**	1. Drug with new packaging consisten with posology and duration of treatment. 2. The specification of the Drug are unchanged. 3. The packaging material are unchange. 4. Product Information are unchange	**A. Product Information and Labelling** 1. Product Information. 1. Primary and secondary packaging labelling . **B. Quality Document** 1. Justification which mention that proposed volume consistent with approved dosage . 2. Stability Studies Report of Drug Product and Commitment to undertake Stability Drug Product if Stability Studies report uncomplete/on going	**244**
19	**Additional of site where stability test takes place**	. 1. Release and shelf-life specification of the product have not been changed	**A. Quality Document** 1. Specification and Method analysis of drug Product. 2. Transfer Method Analysis Report / 3. Drug Product Specification 4. Reference Standard 5. Stability Test Report in new site	**244**
20	**Change storage condition include reconstitution drug product**	1. Release and shelf-life specification of the product have not been changed 2. Stability study has been done following protocol stability with result fullfilment all specification. 3. The change should not be the result of unexpected events arising during manufacturing process or stability concerns.	**A.Product Information and Labelling** 1. Product Information 2. Labelling on packaging **B. Quality Document** 1. Drug Product Specifiation. 2. Stability Study Report refer proposed Storage condition.	**245**
21	**Extension shelf life drug product: as packaged**	1. Release and shelf-life specification of the product have not been changed. 2. Stability study has been done following protocol stability with result fullfilment all specification. 3. The change should not	**A. Product Information and Labelling** 1. Product Information. **B. Quality Document** 1. Drug Product Specification. 2. Stability Report refer proposed shelf life.	**245**

		be the result of unexpected events arising during manufacture or because of stability concerns. 4. Expiry date not more than 5 years.		
22	**Extension shelf life drug product: after first opening or after reconstitution**	1. Release and shelf-life specification of the product have not been changed. 2. Stability study has been done following protocol stability with result fullfilment all specification.	**A. Product Information and Labelling** 1. Product Information. **B. Quality Document** 1. Drug Product Specifiation. 2. Stability drug product after first opening or after reconstitution refer proposed shel life.	**245**

3. CATEGORY 6 : REGISTRATION VARIATION MINOR NOTIFICATION

No	Variation Type	Conditions to be fullfilled	Documentation to be supplied	Pages
A	**Change related product information and/or labelling**			
1	**Change or additional logo (include Company's logo)**	1. Product Information remain unchange. 2. Packaging Specification remain unchange.	**A. Product Information and labelling** . 1. Photos of primary and secondary packaging from all angles and sample of commercial packaging (include Product Information)	**246**
2	**Additional claim adverse event and/or contra-indication at product information .**		**A. Product Information and labelling** 1. Photos of primary and secondary packaging from all angles and sample of commercial packaging (include Product Information) **B. Clinical Document** 1. Justification or Supporting documents refer to the proposed changed. 2. PSUR report (if needeed) . 3. Other references. .	**246**
3	**Reduce manufaturing site (include active substance , intermediate product drug product , packaging site , site of Batch release.**	1. Manufacturing site still available with the same usage/function (including : active substance, intermediate product, drug product , packaging site, site of batch release) has been approved. 2. Reduce manufacturing site is not because of critical factor relevant to manufacturing process .	**A. Product Information and labelling** 1. Registration Number Certificate (original) or Other approval letter refer to related changed. .	**246 -**
4	**Change name of active substance**	1. Active substance remain unchange. 2. New names of active substance should following INN / Pharmacopea.	**A. Administrative Document, Product Information and labelling** 1. Evidence change name of active substance. 2. Photos of primary and secondary packaging from all angle and sample of commercial packaging (include Product Information) .	**246**
5	**Change of the primary packaging that is not contacted with drug product (such as the color of flipp-off caps, the color of the ring on the ampoules, change on the shield of the needle, used different plastic).**	1. Not as important part of Packaging that affect to : distribution, usage, safety or drug stability. 2. Specification of primary Packaging material that contact with the drug remain unchanged.	**A. Quality Documents** 1. Specification and Analytical method of Packaging Material.	**246**
6	**Eradiction foreign language on drug labelling**	1. Product information remain unchange.	**A. Product Information and labelling** 1. Photos of primary and secondary packaging from all angle and sample of commercial packaging (include Product Information) .	**246**
7	**Change shape and/or dimension of packaging, secondary packaging**	1. Not for sterile production 2. Packaging material specification remain unchange . 3. Not for additional size of "Head space or surface / Volume ratio . 4. Product Information remain unchange .	**A. Product Information and labelling** 1. Photos of primary and secondary packaging from all angle and sample of commercial packaging (include Product Information) **B. Quality Documents** 1. Packaging material specification	**246**
8	**Change of Design Packaging**	1. Product Information and labelling remain unchanged. 2. Only for change position teks and Picture, colour	**A. Product Information and labelling** 1. Photos of primary and secondary packaging from all angle and sample of commercial packaging (include Product Information).	**246-247**

		and line. 3. Not include change of Picture. 4. Not contain any Promotional Information / statement .		
9	**Change address of applicant/ pharmaceutical industry/ licensor**	1. Location of applicant /pharmaceutial industry / licensor remain unchanged.	**A. Administrative Document, Product Information and labelling** 1. Statement Letter changes address. 2. Photos of primary and secondary packaging from all angle and sample of commercial packaging (include Product Information).	**247**
10	**Change Batch Numbering System**		**A. Product information and labelling** 1. Explanation of new batch number system	**247**
11	**Change Product Information and/or labelling refer to Government decree**	1. Product Information and/or labelling refer to Government decree	**A. Product Information and labelling** **1.** Photos of primary and secondary packaging from all angle and sample of commercial packaging (include Product Information).	**247**
12	**Add distributor's name**	1. Claim Product Information and labelling remain unchanged, exclude distributor's name	**A. Administrative Document, Product Information and labelling** 1. License of Wholesaler Disributor (PBF). 2. Authorization Letter 3. Photos of primary and secondary packaging from all angle and sample of commercial packaging (include Product Information).	**247**
B.	**Change related Quality of Active Substance**.			
1	**Change and/or additional manufacturer of active substance**	1. Not include NCE, Biological product and Drug which is need bioequivalence test. 2. Manufacturer of active substances are listed on the AeRO / Web registration database NAFDC 3. The specification of the active substance are unchanged. 4. The specification of released and shelf-life of drug are unchanged. 5. Shelf life of drug of new active substances maximum 24 months, excluded if supported by qualified data.	**A. Quality Documents** 1. GMP Certificate manufacturer which is still valid. 2. Certificate of analysis of active substance. 3. Comparative batch analyses active substance from current and new manufacturer (special for Biological Product Batch analysis of minimally three (3) batches consecutive pilot/production scale). 4. Comparative batch analysis of drug of two (2) batches drug from curent and new manufacturer active substance (special for Biological Product Batch analysis of minimally three (3) batches consecutive pilot/production scale). 5. Stability Study Report of Drug Product and Commitment to continue stability study until the proposed shelf-life.	**247**
2	**Additional test on specification released active substance**	1. Changes are not caused due to recurrent events occurring during manufacturing process or . (for example, new contaminants are not eligible or changes to the total of contamination limits). 2. The addition of parameters is not intended to test new contaminants.	**A. Quality Documents** 1. Specification of active substance 2. Analytical Method of active substance 3. Analytical Method Validation Report	**247**
3	**Change in the manufacturer of starting material /reagent/ intermediate used in the manufacturing process of the active substance or change in the manufacturer active**	1. Not include NCE, Biological product and Drug which is need bioequivalence test. 2. For starting materials / reagen / intermediate	A. Quality documents 1. If sourced from animals accompanied by animal source information and certificate free of BSE / TSE. 2. Comparison of batch analysis data of active substances from the current and new	**247-248**

	substance(including quality control testing site)	specifications (including in process controls, methods of analysis of all materials) are identical to those already approved. 3. Methods of preparation and route of synthesis of intermediate products and active substances (including batch sizes) are identical to those already approved. 4. The Specification of particle size of active substance and analytical method are unchanged.	manufacturer (minimum two batch pilot scale / production).	
4 -	**Change name and/or adress manufacturer of active substance**	1. Manufacturing site of Active substance are unchanged.	**A. Product Information and labelling** 1. Supporting document of change name and/or adress of manufacturing of active substance.	**248**
5	**Update Ph.Eur. Certificate of Suitability (CEP)**	1. Not include Biological Product. 2. The specification of released and shelf-life of drug are unchanged. 3. Impurity Specification remain unchange. 4. No any source from human/ animal which need viral safety data in the manufacturing process of active substance.	**A. Quality Document** 1. New Certificate of Suitability (Ph Eur)	**248**
6	**Tightening of specification limit of active substance/intermediate product**	1. Change specification of active substance/inter-mediate product should be within the range of currently approved limits. 2. No any specification active substance oversight the range of currently approved limits. 3. No change in impurity profile active substance oversight the range of currently approved limits.	**A. Quality Document** 1. The proposed Quality Information and test of active substance/intermediate product. 2. Summary analytical procedure, if used new analytical procedure.	**248**
7	**Change of Pharmacopoea edition for active substance**	1. Method Analysis of .active substance remain unchanged. 2. The specification of active substance and drug product are remain unchanged.	**A. Quality Documents** 1. Related Pharmacopoea references.	**248**
8	**Tightening specification limits of active substance**	1.Any change should be within the range of currently approved limits. 2. The test procedure remains the same.	**A. Quality Documents** 1. The New specification of active substance 2. Certificate of Analysis of active substance with new specification.	**248**
9	**Change of the specification of active substance to fullfil the criteria of new pharmacopoeia**	1. The specification of released and shelf-life of drug are unchanged. 2. Specification of impurity and active substance specification remain unchanged (particle size	**A. Quality Documents** 1. Specification and test method of active substance 2 Certificate of Analysis of active substance. 3. Batch analysis result from two (2) batches production scale for all test in new specification.	**248**

		profile, polymorphism form). 3. Additional of validation from new method of pharmacopoeia.or change is not necessary.	4. Relevant refrence Pharmacopea.	
10	**Change specification of active substance non pharmacopoea to fullfilment the requirement of pharmacopoea.**	1. Has been done Verification Method Analysis. 2. The specification of Impurity and active substance are unchanged (such as profile particle size , Polimorfisme form). 3. No any significant change on Qualitative and Quantitative , except Tightening specification. 4. Not necessary additional Validation from new or change pharmacopoea.	**A. Quality Document** 1. Specification and Analytical Method of active substance. 2. Certificate of Analysis of active substance 3. Result of batch analysis of 2 batches of active substance of production scales for all analysis in new specification. 4. Comparative Batch analysis of 2 batches production scale active Substance which has fullfilment latest Specification and 2 batches production scale active substance proposed specification. 5. Minimum 1 batch of Dissolution profile drug product (if needed) 6. References of relevant pharmacopoeia.	**248-249**
11	**Additional of analytical parameters and limit of specification in process control of manufacturing process of active substance**	1. The change is not due to the affect to drug manufacture process. 2-. The specification of active substance are unchanged 3. Validation test method has been done.	**A. Quality Document** 1. Manufacturing procedure 2. Comparative current and new in-process test during manufacturing process. 3. Detail of analytical procedure and validation data of new analytical method/procedure 4. Batch analysis data using 3 batches of active substances for all study in new specification	**249**
12	**Minor Change on analytical procedure of active substance**	1. The Method of analsyis are unchanged (e.g.a change in column length or temperature, but not a different type of column and method) 2. Study of revalidation has been conducted conform-ed to the protocol study. 3. Result of validation analytical method appointed that new analytical procedure is similar/equivalent with the former procedure 4. The specification of released and shelf-life of drug are unchanged. 5. Not valid for additional analytical procedure.	**A. Quality Document** 1. Specification and analytical method of active Substance. 2. Certificate of Analysis of active substance 3. Comparison of validation result or comparison of the result of drug analysis that the new and the former analytical procedure are similar/equivalent.	**249**
13	**Change of analytical method to determine the concentration of active substance conformed to fulfill the criteria of Pharmacopoeia**	1. The specification of active substance are unchanged. 2. The specification of released and shelf- life are unchanged.	**A. Quality Documents** 1. Analytical Method of active substance . 2. Verification analytical procedure of active substance 3 Certificate of Analysis of active substance . 4. Reference standard	**249**
14	**Change of storage condition of active substance**	1. Result of stability studies specification still fulfill formmerly approved criteria 2. Change not as result of unexpected event during manufacturing process or stability case.	**A. Quality Documents** 1. Stability report of active substance **.** 2. Specification of active substance. .	**249**

		3. No change of repeated study period of active substance.		
15	Increase / decrease batch size (including range of batch size) active substances or intermediates used in the process production the active substance until 10 fold	1. Not including biological products 2. Changes do not affect the specification of the active substance / intermediates; should report any changes to the way the process of manufacture and / or control is made to changes related to batch size eg use of a device of a different size. 3. The validation results of the process according to the previous approved batch. 4. Changes do not affect the reproducibility and / or consistency of active substances or intermediates. 5. The change does not result from unexpected events arising during manufacture.	**A. Quality Documents** 1. Comparative of current and new batch analysis. 2. Statement letter contains that: a. change does not give a negative change to the reproducibility of the process; b. changes made are not a result of unexpected events when production or stability issues; c. the specification of active substance are unchanged	**249-250**
16	Making new WCB	1. New cell bank obtained from MCB / MSL previously approved. 2. New cell bank is at the level of the passage that has been approved beforehand. 3. New cell bank is issued based on a previously approved process protocol.	A. Quality Documents 1. Qualifying cell bank or seed lot based on approved procedure by NAFDC. 2. Characterization information and testing of MCB / WCB and cells produced (end of production) or postproduction (postproduction passage).	**250**
17	Changing seed lot: new generation WSL	1. New Seed Lot obtained from MSL previously approved. 2. The new Seed lot is at the approved release level. 3. New Seed Lot is issued based on protocol / process previously approved or as depicted in original license.	**A. Quality document** 1. Comparability of approved and proposed active substances in terms of physicochemical characterization, biological activity and impurity profile. 2. Quality control test results as quantitative data in table format for new proposed seed lot. 3. Commitment to submit studies on the stability of active substances produced using the proposed seed and report to NAFDC if there are unqualified results.	**250**
18	Reduced limit expired date of active substance	1. The change does not result from unexpected events arising during manufacture or stability case. 2. The specification of released and shelf-life of drug are unchanged.	A. Quality Documents 1. Stability report of Active Substances.	**250**
19	The removal of in-process test in the active substance production which an insignificant	1. Removed parameters are not critical parameters including but not limited to levels, contamination, and particle size. 2. The change does not result from unexpected	A. Quality Documents 1. The control information carried out at the critical stage of production and on the intermediate product of the active ingredient being submitted. 2. Justification / risk assessment that attributes are insignificant.	**250**

		events arising during manufacture or stability case. 3. The test does not concern critical parameter such as: composition, impurities, any critical physical characteristic or microbial impurity		
C	**Change related to Quality of Drug Product**			
1	**Minor change in manufacturing process of drug product**	1. Not include Biological and Sterile Product . 2. Principle of manufacturing process of drug product remain unchange. 3. New manufacturing process produces similar product from quality aspect (has been validated), drug product specification, efficacy and safety. 4. No any significant change on qualitative and quantitative on Physicochemical / Impurities profile. 5. The specification of Intermediate and Drug Product are remain unchanged. 6. Specification limit in Process control Manufacturing process are remain unchanged. 7. Stability studies of drug product has been done 3 months from 1 batch pilot/production scale . 8. Site Production is remain unchange. 9. Change not have any worst impact to quality safety and efficacy of drug product. 10. Dissolution profile are remain unchange.	**A. Quality Document** 1. Manufacturing Process of Drug Product. 2. Batch analysis of Drug Product . 3. For oral solid dosage form, Comparative dissolution profile of one batch production scale representative with new manufacturing process with 3 batches latest production scale from current manufacturing process. 4. Stability Studies Report of Drug Product and Commitment to undertake Stability Drug Product if Stability Study report uncomplete/on going 5. Justification not conduct BE test .	**251**
2	**Tightening limit specification batch release of drug product**	1 Any change still in the range of approved Specification limit . 2. Test procedure are remain unchange, or only minor change at test procedure. .	**A. Quality documents** 1. Matrix current and new limit batch release specification. 2. New Certificate of Analysis of drug product.	**251**
3	**Change of released and shelf-life specification to fulfill Pharmacopeia requirement**	1. The change is not a consequence of previous assessments. 2. The change does not result from unexpected events arising during manufacture.	A. Quality document 1. specification (release and shelf life) new drugs. 2. Comparative specifications (release and shelf life) new and current drugs 3. Batch drug analysis data for all tests on the new specification (two batches)	**251**

		3. Any change should be within the range of currently approved limits. 4. The test procedure remain the same, or changes in the test procedure are minor. 5. There is no qualitative and quantitative change from impurity profile / physicochemical or dissolution properties		
4	**Additional of parameters of analysis and limit of specification or process control in drug manufacturing process.**	1. This change does not result from unexpected events arising during manufacture. 2. The specification of drug are remain unchanged 3. Validation of analytical method has been conducted.	**A. Quality Document** 1. Manufacturing procedure 2. Details of analytical procedure and validation data of new analytical method/procedure 3. Batch Analysis data using 3 batches of active substances for all study in the specification of new drug.	**251**
5	**Tightening the limit specification of in-process control during drug manufacturing process**	1. The change is not a consequence of previous assessment 2. No change of impurities Profiles of drug out of range of currently approved limits. 3 The change does not result from unexpected events arising during manufacture or stability case. 4. The specification of released and shelf-life of drug are unchanged. 5. Any change should be within the range of currently approved limits. 6. The test procedure remain the same, or changes in the test procedure are minor.	**A. Quality Document** 1. In – process control specification during new manufacturing process . 2. Matrix in –process control specification during current and new manufacturing process . .	**251-252**
6	**Delete in-process test which not significant**	1.There is no change on impurities out of the range of currently approved limits. 2. The change does not result from unexpected events arising during manufacture or stability case. 3. The test does not concern critical parameter such as: assay, volume, impurities, any critical physical characteristic or microbial impurity.	A. Quality documents 1. Justification/risk assessment showing that the parameter is non-significant.	**252**
7	**Change located of IPC test**	1. There is no change on product specification out of the range of currently approved limits. 2. No change of impurities Profiles of drug out of range of currently approved limits	A. Administrative documents 1. GMP Certificate B. Quality document 1. Data batch analysis of three batches of Drugs. 2. Report transfer method of analysis	**252**

		3. The change does not result from unexpected events arising during manufacture or stability case. 4. The proposed analytical procedure shall be fixed or tightened precision, accuracy, specificity and sensitivity, if practicable. 5. There are no changes on the IPC out of the range of currently approved limits		
8	**Additional parameter of test drug product**	1. The change does not result from unexpected events arising during manufacture. 2. Only add additional test parameter in the drug product specification.	**A. Quality Document** 1. The specification of drug product . 2. The Analytical Procedure of drug product 3. Batch analysis of drug product (2 batches) 4. Validation Report of Method Analysis (if needed)	**252**
9	**Change analytical procedure refer to Pharmacopeia Monograph**	1. Not include Biological products 2. There is no qualitative and quantitative change from the impurity / physicochemical profile. 3. The analytical method are unchanged.	A. Quality document 1. The specification and method of drug testing 2. Data batch analysis of drugs with current and proposed analysis procedures 3. Validation results / verification of analytical methods	**252**
10	**Change and/or additional manufacturer of excipients**	1. Not include Biological products 2. The specifications of excipient are unchanged 3. The specification of release and shelf-life of drug are unchanged. 4. Raw materials that used fulfill the criteria of pharmaceutical grade or food grade	A. Quality documents 1. Certificate of Analysis Excipient	**252-253**
11	**Tightening limit specification of excipient**	1. The change is not an impact of previous assessment. 2. These change does not result from unexpected events arising during manufacture. 3. Any change should be within the range of currently approved limits . 4. The test procedure remain unchanged. 5. Acceptance criteria of residual solvent within range of approved limit (e.g. for resdidual solvent Class 3 or Pharmacopea Requirement.)	**A. Quality Document** 1. New specification at excipient . 2. Certificate of Analysis of excipient with new specification .	**253**
12	**Minor change at analytical procedure of excipient**	1. The method of analysis should remain the same (e.g. a change in column or temperature , but not a different type of column or method). 2. Analytical procedure is	**A. Quality Documents** 1. Specification and Analytical Method of excipient . 2. Certificate of analysis of excipient.	**253**

		not biological/ imunologi / imunochemistry analyti-cal procedure or analytical procedure with using biological reagent .		
13	**Change in method analysis of excipient following Pharmacopoea or other relevant monograph**	1. The specification of excipient are remain unchange (for ex. particle size , polimorph form.)	**A. Quality Document** 1. The specification of excipiemt. 2. Analytical Procedure of excipient. 3. Certificate of Analysis of excipient . 4. Pharmacopoea references or related supporting documents.	**253**
14	**Additional test parameter at specification of excipient**	1. Not include adjuvant excipient for Biological Product. 2. Change not as an impact of manufacturing Process.	**A. Quality Document** 1. Specification and Test Method of excipient. 2. Comparative batch analysis of excipient with current and proposed specification .	**253**
15	**Change at analytical procedure of excipient, include replace test method**	1. Re-validation study has been done following Protocol. 2. Validation report showing new analytical procedure is similar / equivalent with current procedure. 3. The specification of released and shelf-life of drug are unchanged.	**A. Quality Document** 1. Specification and Test Method of excipient 2. Revise of Impurity specification (if available) 3. Comparative validation result which showing new and current analytical procedure eqivalent.	**253**
16	**Change an excipient specification to fullfilment Pharmacopoea requirement**	1. New test method was verified with the result has fullfilment the requirement. 2. The specification of released and shelf-life of drug are unchanged.	**A. Quality Document** 1. Specification and Test Method of excipient 2. Certificate of Analysis of excipient . 3. Drug product specification. 4. Comparative batch analysis drug product from 2 batches production scale 5. Related Pharmacopoea references .	**253-254**
17	**Change in source of an excipient or reagen with Transmisible Spongiform Encephalophaties (TSE) / Bovine Spongiform Encephalophaties (BSE)**	1. The specification of released and shelf-life of drug are unchanged. 2. Not for excipient or reagent which used for manufacturing of biological product or drug product which contain biological active substance .	**A. Quality Document** 1. Declaration from the manufacturer of excipient or reagent that the source of excipient purely vegetable / animal/ synthethic origin . 2. Certificate free of BSE/TSE	**254**
18	**Change in weigh of coating tablets or capsule shell in oral immediate release dosage form**	1. The dissolution profile of new weight coated tablet or new weight capsule shell (miniml 2 batches pilot scales) equivalent with current drug product . 2. Change only weight and Dimension on drug product specification . 3. Stability studies of drug product has been done following protocol with minimal 2 batches pilot/production scale and minimal 3 months stability result has been fullfilment the	**A. Quality Document** 1. Description and formula 2. Drug Specifiation 3. Comparative batch analysis of drug product with current and proposed weigh coating tablet or capsule shell . 4. Comparative dissolution profle test of minimal 1 batch pilot scale between proposed formula and current formula drug product 5. Stability Studies Report of Drug Product and Commitment to undertake Stability Drug Product if Stability Studies report uncomplete/on going	**254**

		specification requirement. 4. Coating not as critical factor for mechanism release of drug product.		
19	**Increase, addition , deletion or replacement of the flavouring and/or colouring system .**	1. The specification of Released and shelf-life are unchanged (except colour and/or flavour). 2. No change in functional characteristics of the pharmaceutical form e.g. disintegration time , disollution profile . 3. Any new colouring and/ or flavouring does not include not allowed to be used in pharmaceu-tical . 4. Any new colouring and/ or flavouring does not include the use of materials of human or animal origin for which assessment is required of viral safety . 5. These change does not result from unexpected events arising during manufacture or stability case. 6. Stability study of drug product has been done following protocol with minimal 2 batches pilot/production scale and at least 3 months stability result has been fulfill the specification requirement.	**A. Quality Document** 1. Description and formula 2. Batch formula 3. Manufacturing process and in-process control 4. New specification of flavouring and/or colouring 5. New test procedure of flavouring and/or colouring 6. Certificate of Analysis of new flavouring and/or colouring . 7. The specification of drug product. 8. Batch analysis of drug product . 9. Comparative batch analysis drug product from 2 batches production scale of current and proposed formula . 10. Certificate of free BSE/TSE (if needed). 11. Stability Studies Report of Drug Product and Commitment to undertake Stability Drug Product if Stability Studies report uncomplete/on going.	**254**
20	**Reduction or deletion one or more components of flavouring and /or colouring**	1. The specification of released and shelf-life of drug are unchanged (except for colour and/or odour) 2. Stability study of drug product has been done following protocol with minimal 2 batches pilot/production scale and minimal 6 months stability result has been fullfilment the specification requirement.	**A. Quality Document** 1. Description and formula 2. Batch formula 3. The Manufacturing process of drug product 4. The specification of drug product . 5. Batch analysis of drug product (2 batches production scale). 6. Stability Studies Report of Drug Product and Commitment to undertake Stability Drug Product if Stability Studies report uncomplete/on going. .	**254-255**
21	**Change or addition of imprints , bossing or other markings (except breakline) on tablets or capsule printed , including replacement, or addition of inks used for product marking .**	1. The specification of released and shelf-life of drug are unchanged (except for appearance). 2. Any ink must comply with the relevant pharmaceutical legislation. 3. New Appearance not make confused with registered drug product.	**A. Quality Document** 1. The specification of drug product 2. Certificate of Analysis of ink or printing material 3. Product Information (if needed)	**255**

22	**Change of colour shield capsules**	1. The specification of capsule shell are unchanged except colour Shield capsules 2. The specification of release and shelf-life of drug are unchanged except colour shield capsules. 3. There is no change in functional characteristics of the capsule shell (eg crushed time, dissolution profile). 4. The change does not result from unexpected events arising during manufacture or stability case. 5. Stability tests have been carried out according to protocols with at least two batches of pilot or production scales with at least three months of data providing results that fulfill specifications	A. Quality documents 1. Description 2. The specification of drug 3. Certificate of free BSE / TSE. 4. Information source of gelatin as raw material of capsule shells 5. The specification of capsule shells. 6. Certificate of analysis capsule shells. 7. Batch analysis results of drug with current and new capsule shells. 8. Stability Studies Rports of Drug Product and Commitments to undertake if the drug stability report uncomplete	**255**
23	**Change in synthesis of excipients (non Pharmacopoea)**	1. Not include excipient of Biological Product . 2. Not include adjuvant Substance. 3. No any influence to the Specification of Excipient. 4. No any significant change on qualitative and quantitative on Physicochemical / Impurity profile. 5. Synthetic route and specification of excipient are similar and no change in qualitative and quantitative on impurities profile	**A. Quality Document** 1 Comparative batch analysis excipients from at least 2 batches pilot scale between current and new manufacturing process of excipient . 2. Comparative dissolution profile drug product from minimal 2 batches pilot scales .	**255**
24	**Change of excipient specification non pharmacopeia for fulfill criteria pharmacopeia**	1. The specification of excipient are remain unchanged (for: particle size and polymorphism shape). 2. The specifications of drug are unchanged	A. Quality documents 1. The specification and method of excipient testing. 2. Report of analysis excipient 3. Related pharmacopoeia references.	**255**
25	**Replacement or addition of secondary packaging site of drug product/**	1. Latest 2 years of Inspection Resport which have statisfied result	**A. Product Information and Labelling** 1. GMP Certificate of manufacturer of Secondary packaging.. 2. Photos secondary packaging from all angle and sample of commercial Product Information (if needed)	**255-256**
26	**Tightening of specification limits of primary packaging of drug product**	1. The change is not a consequence of any previous assessment . 2. Any change should be within the range of currently standard approved.	**A. Quality Document** 1. Specification of packaging 2. Certificate of analysis of packaging.	**256**

		3. The test procedure remains the same, or changes in the test procedure are minor.		
27	**Change Qualitative and Quantitative Composition in primary packaging of drug product (for all oral dosage form) .**	1. Not include Biological Product and Sterile Product. 2. Changes only on type and packaging material similar. 3. Proposed raw material Similar/equivalent with formerly approved. 4. Stability study of drug product has been done following protocol with minimal 2 batches pilot/production scale and minimal 6 months stability result has been fullfilment the specification requirement.	**A. Quality Document** 1. The specification and Test Method of packaging material . 2. Certificate of Analysis of Packaging. 2. Stability Studies Report of Drug Product and Commitment to undertake Stability Drug Product if Stability Study report uncomplete/on going. 3. There is no any interaction between drug product with proposed type/ packaging material in solution and semi solid dosage form	**256**
28	**Addition or replacement measure device which not as a part of primary packaging (not include spacer device for metered dose inhaler).**	1. Proposed measure device should get accurate dose which needed following approved posology and it supported with appropiate test procedure. 2. New measure device is compatible with drug product 3. The changes not have an impact on Product Information.	**A. Product Information and Label** 1. Photo measure device, primary and secondary packaging from all angle and sample of commercial product which stated new label including Product Information (if necessary) **B. Quality Document** 1. The specification and analytical procedure of packaging material. 2. Calibration report of measure devices .	**256**
29	**Minor change in analytical procedure of primary packaging of drug product**	1. Validation report showing new analytical procedure is similar / equivalent with current procedure 2. The method of analysis should remain the same (e.g. a change in column or temperature , but not a different type of column or method).	**A. Quality Document** 1. The specification and analytical procedure of packaging material **.**	**256**
30	**Change in test procedure of primary packaging of drug product , include replacement or additioomn test procedure .**	1. Validation report showing new analytical procedure is similar / equivalent with current procedure 2. Proposed Analytical Method not used new non technical standard or technical standard with new method.	**A. Quality Document** 1. The specification and analytical procedure of packaging material .	**256**
31	**Change or addition of supplier of packaging component or measure device which attached In drug product , not include spacer devices supplier for Metered dose inhaler.**	1. The specification of Packaging Material or measure device are remain unchanged.	**A. Product Informationand Labelling** 1. Declaration Letter of replacement or addition Supplier. **B. Quality Documents** 1. Registration number of medical devices. 2. The specification of packaging material 3. Certificate of analysis of medical devices	**256-257**

			4. Special for Biological Product attached with Comparative test result (control) packaging Component or medical devices from current and new supplier which include in the drug	
32	**Reduce of supplier of packaging component or measure device which attached in drug product , not include spacer devices supplier for Metered dose inhaler.**	1. No any deletion packaging component or measure device with attached drug product.	**A. Product Informationand Labelling** 1. Declaration Letter of reduction Supplier.	**257**
33	**Addition of parameters of analytical method of primary packaging of drug.**	1. Change not as an impact on manufacturing process.	**A. Quality Document** 1. Specification and Analytical Procedure of Packaging material. 2. Test result of primary packaging fullfil Requirement.	**257**
34	**Change of secondary packaging material**	1. Label remain unchanged.	**A. Product Information and Labelling** 1. The specification and analytical procedure secondary packaging material.	**257**
35	**Change of claim drug storage (redactional)**	1. The specification of released and shelf-life of drug are unchanged. 2. These changes does not result from unexpected events arising during manufacture or stability case.	**A. Product Information and Labelling** **1.** Photos of primary and secondary packaging from all angle and sample of commercial packaging (include Product Information).	**257**
36	**Reduce limit expiry date of drug product : as packaged not yet opened.**	1. The specification of released and shelf-life of drug are unchanged. 2. Stability studies has been Conducted conformed to the approved study protocol and the result fulfill the criteria of specification.	**A. Product Information and Labelling** 1. Photos and sample of commercial Product Information (if necessary). **B. Quality Documents** 1. The specification of drug product, 2. Stability Report of drug product	**257**
37	**Reduction of the limit of drug expiration: after the package has been opened or reconsti-tution .**	1. The specification of released and shelf-life of drug are unchanged. 2. Stability studies has been conducted conformed to the approved study protocol and the result fulfill the criteria of specification.	**A. Product Information and Labelling** 1. Photos and sample of commercial Product Information (if necessary). **B. Quality Documents** 1. Drug Product Specification . 2. Stability Report of Drug Product after Package opening or after recons titution.	**257**

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II

(Information)

INFORMATION FROM EUROPEAN UNION INSTITUTIONS, BODIES, OFFICES AND AGENCIES

EUROPEAN COMMISSION

Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures

(2013/C 223/01)

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1. INTRODUCTION

Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products [1] ('the Variations Regulation') governs the procedure for the variation of marketing authorisations. It has been amended by Commission Regulation (EU) No 712/2012 [2].

Article 4(1) of the Variations Regulation charges the Commission with the task of drawing up guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of that Regulation as well as on the documentation to be submitted pursuant to these procedures.

These guidelines apply to the variations of marketing authorisations for medicinal products for human use and veterinary medicinal products granted in accordance with Regulation (EC) No 726/2004 of the European Parliament and of the Council [3], Directives 2001/82/EC [4] and 2001/83/EC [5] of the European Parliament and of the Council, and Council Directive 87/22/EEC [6]. They are intended to facilitate the interpretation and application of the Variations Regulation. They provide details on the application of the relevant procedures, including a description of all the relevant steps from the submission of an application for a variation to the final outcome of the procedure on the application.

In addition, the Annex to these guidelines provides details of the classification of variations into the following categories as defined in Article 2 of the Variations Regulation: minor variations of Type IA, minor variations of Type IB and major variations of Type II and provides further details, where appropriate, on the scientific data to be submitted for specific variations and how this data should be documented. The Annex to these guidelines will be regularly updated, taking into account the recommendations provided in accordance with Article 5 of the Variations Regulation as well as scientific and technical progress.

Definitions relevant to these guidelines are provided in Directive 2001/82/EC, Directive 2001/83/EC, and Regulation (EC) No 726/2004 as well as in the Variations Regulation. In addition, for the purpose of these guidelines, marketing authorisation holders belonging to the same mother company or group of companies and marketing authorisation holders having concluded agreements or exercising concerted practices concerning the placing on the market of the relevant medicinal product have to be taken as the same marketing authorisation holder [7] ('holder').

Reference in these guidelines to the 'centralised procedure' is to be understood as the procedure for granting marketing authorisations set out in Regulation (EC) No 726/2004. Reference to the 'mutual recognition procedure' is to be understood as the procedure for granting marketing authorisations set out in Directive 87/22/EEC, Articles 32 and 33 of Directive 2001/82/EC, and Articles 28 and 29 of Directive 2001/83/EC. Marketing authorisations granted following a referral under Articles 36, 37 and 38 of Directive 2001/82/EC or Articles 32, 33 and 34 of Directive 2001/83/EC that has led to complete harmonisation are to be considered as marketing authorisations granted under the mutual recognition procedure also. Reference to the 'purely national procedure' is to be understood as the procedure for granting marketing authorisations by a Member State in accordance with the *acquis* outside the mutual recognition procedure.

Reference in this guideline to 'Member States concerned', in accordance with Article 2(6) of the Variations Regulation, is to be understood as each Member State whose competent authority has granted a marketing authorisation for the medicinal product in question. Reference to 'concerned Member States' is to be understood as all Member States concerned except the reference Member State. Reference to 'national competent authority' is to be understood as the authority that has granted a marketing authorisation under a purely national procedure.

Reference in these guidelines to the Agency means the European Medicines Agency.

2. PROCEDURAL GUIDANCE ON THE HANDLING OF VARIATIONS

A marketing authorisation lays down the terms under which the marketing of a medicinal product is authorised in the EU. A marketing authorisation is composed of:

(i) a decision granting the marketing authorisation issued by the relevant authority; and

(ii) a technical dossier with the data submitted by the applicant in accordance with Article 12(3) to Article 14 of Directive 2001/82/EC and Annex I thereto, Article 8(3) to Article 11 of Directive 2001/83/EC and Annex I thereto, Articles 6(2) and 31(2) of Regulation (EC) No 726/2004, or Article 7 of Regulation (EC) No 1394/2007.

The Variations Regulation governs the procedures for the amendment of the decision granting the marketing authorisation and of the technical dossier.

However, in the case of medicinal products for human use, the introduction of changes to the labelling or package leaflet that is not connected with the summary of product characteristics is not governed by the procedures of the Variations Regulation. In accordance with Article 61(3) of Directive 2001/83/EC, these changes are to be notified to the relevant competent authorities and they may be implemented if the competent authority has not objected within 90 days.

[1] OJ L 334, 12.12.2008, p. 7.
[2] OJ L 209, 4.8.2012, p. 4.
[3] OJ L 136, 30.4.2004, p. 1.
[4] OJ L 311, 28.11.2001, p. 1.
[5] OJ L 311, 28.11.2001, p. 67.
[6] OJ L 15, 17.1.1987, p. 38.
[7] OJ C 229, 22.7.1998, p. 4.

These guidelines cover the following categories of variations, defined in Article 2 of the Variations Regulation:

— Minor variations of Type IA

— Minor variations of Type IB

— Major variations of Type II

— Extensions

— Urgent safety restriction

The reference Member State, the national competent authority or the Agency [1] is available to address any questions which holders may have regarding a particular upcoming variation. Where appropriate, a pre-submission discussion may be organised with the reference Member State, the national competent authority or the Agency in order to obtain further regulatory and procedural advice.

It must be noticed that where a group of variations consists of different types of variations, the group must be submitted and will be handled according to the 'highest' variation type included in the group. For instance, a group consisting of an extension and a major variation of Type II will be handled as an extension application; a group consisting of minor variations of Type IB and Type IA will be handled as a Type IB notification.

Where reference is made in these guidelines to the submission of variations' notifications or applications, the number of copies to be submitted will be made public for each type of procedure by the Agency as regards the centralised procedure; by the coordination groups established by Article 31 of Directive 2001/82/EC as regards veterinary medicinal products and Article 27 of Directive 2001/83/EC as regards medicinal products for human use ('the coordination group') as regards the mutual recognition procedure, and by the national competent authority as regards the purely national procedure.

The application form for variations to a marketing authorisation for medicinal products (human and veterinary) is available at http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm

Any information related to the implementation of a given variation should be immediately provided by the holder upon the request of the relevant authority.

2.1. **Minor variations of Type IA**

Hereby guidance is provided on the application of Articles 7, 8, 11, 13a, 13d, 13e, 14, 17, 23 and 24 of the Variations Regulation to minor variations of Type IA.

The Variations Regulation and the Annex to these guidelines set out a list of changes to be considered as minor variations of Type IA. Such minor variations do not require any prior approval, but must be notified by the holder within 12 months following implementation ('Do and Tell' procedure). However, certain minor variations of Type IA require immediate notification after implementation, in order to ensure the continuous supervision of the medicinal product.

The Annex to these guidelines clarifies the conditions which must be met in order for a change to follow a Type IA notification procedure, and specifies which minor variations of Type IA must be notified immediately following implementation.

2.1.1. *Submission of Type IA notifications*

Minor variations of Type IA do not require prior examination by the authorities before they can be implemented by the holder. However, at the latest within 12 months from the date of the implementation, the holder must submit simultaneously to all Member States concerned, to the national competent authority, or to the Agency (as appropriate) a notification of the relevant variation(s). It is possible for a holder to include a minor variation of Type IA which is not subject to immediate notification in the submission of a minor variation of Type IA for immediate notification or with any other variation. The conditions laid down in Article 7(2)(a), 7(2)(b), 7(2)(c), 13d(2)(a), 13d(2)(b) or 13d(2)(c) of the Variations Regulation (as appropriate) should be fulfilled.

The holder may group several minor variations of Type IA under a single notification, as established in Articles 7(2) and 13d(2) of the Variations Regulation. Specifically, two possibilities exist for the grouping of variations of Type IA:

(1) The holder may group several minor variations of Type IA regarding the terms of one single marketing authorisation provided that they are notified at the same time to the same relevant authority.

(2) The holder may group one or more minor variations of Type IA to the terms of several marketing authorisations under a single notification provided that the variations are the same for all marketing authorisations concerned and they are notified at the same time to the same relevant authority.

The 12 months deadline to notify minor variations of Type IA allows holders to collect Type IA variations for their medicinal products during a year. However, the notification of these variations in a single submission is only possible where the conditions for grouping apply (same variations for all medicinal products concerned). Therefore, it may be the case that the submission of variations implemented over a period of 12 months (so called 'annual report') requires several submissions; e.g. one referring to a single minor variation of Type IA, another referring to group of minor variations of Type

[1] In this context, where reference is made to 'reference Member State', this applies to products approved via the mutual recognition procedure; where reference is made to 'national competent authority', this applies to products approved via purely national procedure; and where reference is made to the Agency, this applies to products approved via the centralised procedure.

IA to the terms of one marketing authorisation, and another referring to group of the minor variations of Type IA to the terms of several marketing authorisations.

The notification must contain the elements listed in Annex IV to the Variations Regulation, presented as follows in accordance with the appropriate headings and numbering of 'The rules governing medicinal products in the European Union', Volume 2B, Notice to applicants ('EU-CTD') format or the Notice to applicants Volume 6B format (veterinary medicinal products when EU-CTD format is not available):

— Cover letter.

— The completed EU variation application form (published in the Notice to applicants), including the details of the marketing authorisation(s) concerned, as well as a description of all variations submitted together with their date of implementation as applicable. Where a variation is the consequence of, or related to, another variation, a description of the relation between these variations should be provided in the appropriate section of the application form.

— Reference to the variation code as laid down in the Annex to these guidelines, indicating that all conditions and documentation requirements are met or, where applicable, reference to a classification recommendation published in accordance with Article 5 of the Variation Regulation used for the relevant application.

— All documentation specified in the Annex to these guidelines.

— In case that the variations affect the summary of product characteristics, labelling or package leaflet: the revised product information presented in the appropriate format, as well as the relevant translations. Where the overall design and readability of the outer and immediate packaging or package leaflet is affected by the minor variation of Type IA, mock-ups or specimens should be provided to the reference Member State, the national competent authority or the Agency.

For variations in the mutual recognition procedure, the reference Member State should additionally receive the list of dispatch dates indicating the Type IA Variation procedure number, the dates on which the applications have been sent to each Member State concerned and confirmation that the relevant fees have been paid as required by the competent authorities concerned.

For variations in the purely national procedure confirmation that the relevant fee has been paid as required by the national competent authority.

For variations in the centralised procedure, the relevant fee for the minor variation(s) of Type IA, as provided for in Council Regulation (EC) No 297/95 [1], should be paid in accordance with the Agency's financial procedures.

For grouped minor variations of Type IA concerning several marketing authorisations from the same holder in accordance with Article 7 or 13d of the Variations Regulation, a common cover letter and application form should be submitted together with separate supportive documentation and revised product information (if applicable) for each medicinal product concerned. This will allow the relevant authorities to update the dossier of each marketing authorisation included in the group with the relevant amended or new information.

2.1.2. *Type IA variations review for mutual recognition procedure*

The reference Member State will review the Type IA notification within 30 days following receipt.

By Day 30, the reference Member State will inform the holder and concerned Member States of the outcome of its review. In case the marketing authorisation requires any amendment to the decision granting the marketing authorisation, all Member States concerned will update the decision granting the marketing authorisation within 6 months following the receipt of the outcome of the review sent by the reference Member State, provided that the documents necessary for the amendment of the marketing authorisation have been submitted to the Member States concerned.

Where one or several minor variations of Type IA are submitted as part of one notification, the reference Member State will inform the holder which variation(s) have been accepted or rejected following its review. The marketing authorisation holder must not implement the rejected variation(s).

While in the case of minor variations of Type IA, failure to provide all necessary documentation in the application will not necessarily lead to the immediate rejection of the variation if the holder provides any missing documentation immediately upon the request of the relevant authority, it should be highlighted that a minor variation of Type IA may in specific circumstances be rejected with the consequence that the holder must immediately cease to apply already implemented variations concerned.

2.1.3. *Type IA variations review for purely national procedure*

The national competent authority will review the Type IA notification within 30 days following receipt.

By Day 30, the national competent authority will inform the holder of the outcome of its review. In case the marketing authorisation requires any amendment to the decision granting the marketing authorisation, the national competent authority will update the decision granting the marketing authorisation within 6 months following the date of information to the holder of the outcome of the review, provided that the documents necessary for the amendment of the marketing authorisation have been submitted to the national competent authority.

Where one or several minor variations of Type IA are submitted as part of one notification, the national competent authority will inform the holder which variation(s) have been accepted or rejected following its review.

[1] OJ L 35, 15.2.1995, p. 1.

While in the case of minor variations of Type IA, failure to provide all necessary documentation in the application will not necessarily lead to the immediate rejection of the variation if the holder provides any missing documentation immediately on request of the relevant authority, it should be highlighted that a minor variation of Type IA may in specific circumstances be rejected with the consequence that the holder must immediately cease to apply already implemented variations concerned.

2.1.4. *Type IA variations review for centralised procedure*

The Agency will review the Type IA notification within 30 days following receipt, without involvement of the rapporteur for the product concerned appointed by the Committee for Medicinal Products for Human Use or by the Committee for Veterinary Medicinal Products. However, a copy of the Type IA notification will be submitted by the Agency to the rapporteur for information.

By Day 30, the Agency will inform the holder of the outcome of its review. Where the outcome of the assessment is favourable and the Commission decision granting the marketing authorisation requires any amendment, the Agency will inform the Commission and transmit the revised documentation. In such case, the Commission will update the decision granting the marketing authorisation at the latest within 12 months.

Where one or several minor variations of Type IA are submitted as part of one notification, the Agency will clearly inform the holder which variation(s) have been accepted or rejected following its review.

While in the case of minor variations of Type IA, failure to provide all necessary documentation in the application will not necessarily lead to the immediate rejection of the variation if the holder provides any missing documentation immediately on request of the Agency, it should be highlighted that a minor variation of Type IA may in specific circumstances be rejected with the consequence that the holder must cease to apply already implemented variations concerned.

2.2. **Minor variations of Type IB**

Hereby guidance is provided on the application of Articles 7, 9, 11, 13b, 13d, 13e, 15, 17, 23 and 24 of the Variations Regulation to minor variations of Type IB.

The Variations Regulation and the Annex to these guidelines set out a list of changes to be considered as minor variations of Type IB. Such minor variations must be notified before implementation. The holder must wait a period of 30 days to ensure that the notification is deemed acceptable by the relevant authorities before implementing the change ('Tell, Wait and Do' procedure).

2.2.1. *Submission of Type IB notifications*

Notifications for minor variations of Type IB must be submitted by the holder simultaneously to all Member States concerned, to the national competent authority or to the Agency (as appropriate).

Holders may group under a single notification the submission of several minor variations of Type IB regarding the same marketing authorisation, or group the submission of one or more minor variation(s) of Type IB with other minor variations regarding the same marketing authorisation, provided that this corresponds to one of the cases listed in Annex III of the Variations Regulation, or when this has been agreed previously with the reference Member State, the national competent, authority or the Agency (as appropriate).

In addition, for medicinal products authorised under purely national procedures, the holder may also group several minor variations of Type IB affecting several marketing authorisations in a single Member State, or one or more minor variation(s) of Type IB with other minor variations affecting several marketing authorisations in a single Member State provided that (i) the variations are the same for all the marketing authorisations concerned, (ii) the variations are submitted at the same time to the national competent authority, and (iii) the national competent authority has previously agreed to the grouping.

Furthermore, where the same minor variation of Type IB or the same group of minor variations (as explained above) affect several marketing authorisations owned by the same holder, the holder may submit these variations as one application for 'worksharing' (see section 3 on 'worksharing').

The notification must contain the elements listed in Annex IV to the Variations Regulation, presented as follows in accordance with the appropriate headings and numbering of the EU-CTD format or the Notice to applicants Volume 6B format (veterinary medicinal products when EU-CTD format is not available):

— Cover letter.

— The completed EU variation application form (published in the Notice to applicants), including the details of the marketing authorisations(s) concerned. Where a variation is the consequence of or related to another variation, a description of the relation between these variations should be provided in the appropriate section of the application form. Where a variation is considered unclassified, a detailed justification for its submission as a Type IB notification must be included.

— Reference to the variation code as laid down in the Annex to these guidelines, indicating that all conditions and documentation requirements are met or, where applicable, reference to a classification recommendation published in accordance with Article 5 of the Variation Regulation used for the relevant application.

— Relevant documentation in support of the proposed variation including any documentation specified in the Annex to these guidelines.

— For variations requested by the competent authority resulting from new data submitted, e.g. pursuant to post authorisation conditions or in the framework of pharmacovigilance obligations, a copy of the request should be annexed to the cover letter.

— In case that the variations affect the summary of product characteristics, labelling or package leaflet: the revised product information presented in the appropriate format, as well as the relevant translations. Where the overall design and readability of the outer and immediate packaging or package leaflet is affected by the minor variation of Type IB, mock-ups or specimens should be provided to the reference Member State, the national competent authority or the Agency.

For variations in the mutual recognition procedure, the reference Member State should additionally receive the list of dispatch dates indicating the Type IB Variation procedure number, the dates on which the applications have been sent to each Member States concerned and confirmation that the relevant fees have been paid as required by the competent authorities concerned.

For variations in the purely national procedure confirmation that the relevant fee has been paid as required by the national competent authority.

For variations in the centralised procedure, the relevant fee for the minor variation(s) of Type IB, as provided for in Council Regulation (EC) No 297/95, should be paid in accordance with the Agency's financial procedures.

2.2.2. *Type IB variations review for mutual recognition procedure*

Upon receipt of a Type IB notification, the notification will be handled as follows:

The reference Member State will check within 7 calendar days whether the proposed change can be considered a minor variation of Type IB, and whether the notification is correct and complete ('validation') before the start of the evaluation procedure.

When the proposed variation is not considered a minor variation of Type IB following the Annex to these guidelines or has not been classified as a minor variation of Type IB in a recommendation pursuant to Article 5 of the Variations Regulation, and the reference Member State is of the opinion that it may have a significant impact on the quality, safety or efficacy of the medicinal product, the reference Member State will inform the concerned Member States and the holder immediately.

If the concerned Member States do not disagree within further 7 calendar days, the holder will be requested to revise its application and to complete it in accordance with the requirements for a major variation of Type II application. Following receipt of the valid revised variation application, a Type II assessment procedure will be initiated (see section 2.3.2).

If the concerned Member States disagree with the reference Member State, the reference Member State must take the final decision on the classification of the proposed variation having taken into account the comments received.

When the reference Member State is of the opinion that the proposed variation can be considered a minor variation of Type IB, the holder will be informed of the outcome of the validation and of the start date of the procedure.

Within 30 days following the acknowledgement of receipt of a valid notification, the reference Member State will notify the holder of the outcome of the procedure. If the reference Member State has not sent the holder its opinion on the notification within 30 days following the acknowledgement of receipt of a valid notification, the notification will be deemed acceptable.

In case of an unfavourable outcome, the holder may amend the notification within 30 days to take due account of the grounds for the non-acceptance of the variation. If the holder does not amend the notification within 30 days as requested, the variation will be deemed rejected by all concerned Member States.

Within 30 days of receipt of the amended notification, the reference Member State will inform the holder of its final acceptance or rejection of the variation(s) (including the grounds for the unfavourable outcome). Concerned Member States will be informed accordingly.

Where a group of minor variations were submitted as part of one notification, the reference Member State will inform the holder and the concerned Member States which variation(s) have been accepted or rejected following its review.

Where necessary, the relevant authorities will update the marketing authorisation within 6 months following closure of the procedure by the reference Member State, provided that the documents necessary for the amendment of the marketing authorisation have been submitted to the Member States concerned. However, the accepted minor variations of Type IB variation may be implemented without awaiting the update of the marketing authorisation.

2.2.3. *Type IB variations review for purely national procedure*

Upon receipt of a Type IB notification, the notification will be handled as follows:

The national competent authority will check whether the proposed change can be considered a minor variation of Type IB, and whether the notification is correct and complete ('validation') before the start of the evaluation procedure.

When the proposed variation is not considered a minor variation of Type IB following the Annex to these guidelines or has not been classified as a minor variation of Type IB in a

recommendation pursuant to Article 5 of the Variations Regulation, and the national competent authority is of the opinion that it may have a significant impact on the quality, safety or efficacy of the medicinal product, the holder will be requested to revise its application and to complete it in accordance with the requirements for a major variation of Type II application. Following receipt of the valid revised variation application, a Type II assessment procedure will be initiated (see section 2.3.4).

When the national competent authority is of the opinion that the proposed variation can be considered a minor variation of Type IB, the holder will be informed of the outcome of the validation and of the start date of the procedure.

Within 30 days following the acknowledgement of receipt of a valid notification, the national competent authority will notify the holder of the outcome of the procedure. If the national competent authority has not sent the holder its opinion on the notification within 30 days following the acknowledgement of receipt of a valid notification, the notification will be deemed acceptable.

In case of an unfavourable outcome, the holder may amend the notification within 30 days to take due account of the grounds for the non-acceptance of the variation. If the holder does not amend the notification within 30 days as requested, the variation will be deemed rejected by the national competent authority.

Within 30 days of receipt of the amended notification, the national competent authority will inform the holder of its final acceptance or rejection of the variation(s) (including the grounds for the unfavourable outcome).

Where a group of minor variations were submitted as part of one notification, the national competent authority will inform the holder which variation(s) have been accepted or rejected following its review.

Where necessary, the national competent authority will update the marketing authorisation within 6 months following closure of the procedure, provided that the documents necessary for the amendment of the marketing authorisation have been submitted to the national competent authority. However, the accepted minor variations of Type IB may be implemented without awaiting the update of the marketing authorisation.

2.2.4. *Type IB variations review for centralised procedure*

Upon receipt of a Type IB notification, the Agency will handle the notification as follows:

The Agency will check within 7 calendar days whether the proposed change can be considered a minor variation of Type IB, and whether the notification is correct and complete ('validation') before the start of the evaluation procedure.

When the proposed variation is not considered a minor variation of Type IB following the Annex to these guidelines or has not been classified as a minor variation of Type IB in a recommendation pursuant to Article 5 of the Variations Regulation, and the Agency is of the opinion that it may have a significant impact on the quality, safety or efficacy of the medicinal product, the holder will be requested to revise its application and to complete it in accordance with the requirements for a major variation of Type II application. Following receipt of the valid revised variation application, a Type II assessment procedure will be initiated (see section 2.3.6).

When the Agency is of the opinion that the proposed variation can be considered a minor variation of Type IB, the holder will be informed of the outcome of the validation and of the start date of the procedure.

The rapporteur will be involved in the review of the Type IB notification.

Within 30 days following the acknowledgement of receipt of a valid notification, the Agency will notify the holder of the outcome of the procedure. If the Agency has not sent the holder its opinion on the notification within 30 days following the acknowledgement of receipt of a valid notification, the notification will be deemed acceptable.

In case of an unfavourable outcome, the holder may amend the notification within 30 days to take due account of the grounds for the non-acceptance of the variation. If the holder does not amend the notification within 30 days as requested, the notification will be rejected.

Within 30 days of receipt of the amended notification, the Agency will inform the holder of its final acceptance or rejection of the variation(s) (including the grounds for the unfavourable outcome).

Where a group of minor variations are submitted as part of one notification, the Agency will clearly inform the holder which variation(s) have been accepted or rejected following its review.

Where the opinion of the Agency is positive and the variation(s) affect(s) the terms of the Commission decision granting the marketing authorisation, the Agency will inform the Commission accordingly and transmit the relevant documentation. Where necessary, the Commission will update the marketing authorisation at the latest within 12 months. However, the accepted minor variation(s) of Type IB may be implemented without awaiting the update of the Commission decision granting the marketing authorisation and the agreed change(s) will be included in the annexes of any subsequent Regulatory Procedure.

2.3. **Major variations of Type II**

Hereby guidance is provided on the application of Articles 7, 10, 11, 13, 13c, 13d, 13e, 16, 17, 23 and 24 of the Variations Regulation to major variations of Type II.

The Variations Regulation and the Annex to these guidelines set out a list of changes to be considered as major variations of Type II. Such major variations require approval of the relevant competent authority before implementation.

2.3.1. *Submission of Type II applications*

Notifications for major variations of Type II must be submitted by the holder simultaneously to all Member States concerned, to the national competent authority or to the Agency (as appropriate).

Holders may group under a single notification the submission of several major variations of Type II regarding the same marketing authorisation, or group the submission of one or more major variation(s) of Type II with other minor variations regarding the same marketing authorisation, provided that this corresponds to one of the cases listed in Annex III of the Variations Regulation, or when this has been agreed previously with the reference Member State, the national competent, authority or the Agency (as appropriate).

In addition, for medicinal products authorised under purely national procedures, the holder may also group several major variations of Type II affecting several marketing authorisations in a single Member State, or one or more major variation(s) of Type II with other minor variations affecting several marketing authorisations in a single Member State, provided that (i) the variations are the same for all the marketing authorisations concerned, (ii) the variations are submitted at the same time to the national competent authority, and (iii) the national competent authority has previously agreed to the grouping.

Furthermore, where the same major variation of Type II or the same group of variations (as explained above) affect several marketing authorisations owned by the same holder, the holder may submit these variations as one application for 'worksharing' (see section 3 on 'worksharing').

The application must contain the elements listed in Annex IV to the Variations Regulation, presented as follows in accordance with the appropriate headings and numbering of the EU-CTD format or the Notice to applicants Volume 6B format (veterinary medicinal products when the EU-CTD format is not available):

— Cover letter.

— The completed EU variation application form (published in the Notice to Applicants), including the details of the marketing authorisation(s) concerned. Where a variation is the consequence of or related to another variation, a description of the relation between these variations should be provided in the appropriate section of the application form.

— Reference to the variation code as laid down in the Annex to these guidelines, indicating that all conditions and documentation requirements are met or, where applicable, reference to a classification recommendation published in accordance with Article 5 of the Variation Regulation used for the relevant application.

— Supporting data relating to the proposed variation(s).

— Update or Addendum to quality summaries, non-clinical overviews and clinical overviews (or expert reports for veterinary medicinal products) as relevant. When non-clinical or clinical study reports are submitted, even if only one, their relevant summary(ies) should be included in Module 2.

— For variations requested by the competent authority resulting from new data submitted, e.g. pursuant to post authorisation conditions or in the framework of pharmacovigilance obligations, a copy of the request should be annexed to the cover letter.

— In case that the variations affect the summary of product characteristics, labelling or package leaflet, the revised product information presented in the appropriate format, as well as the relevant translations. Where the overall design and readability of the outer and immediate packaging or package leaflet is affected by the major variation of Type II, mock-ups or specimens should be provided to the reference Member State, the national competent authority or the Agency.

For variations in the mutual recognition procedure, the reference Member State should additionally receive the list of dispatch dates indicating the Type II Variation procedure number, the dates on which the applications have been sent to each Member State concerned and confirmation that the relevant fee has been paid as required by the competent authorities concerned.

For variations in the purely national procedure confirmation that the relevant fee has been paid as required by the national competent authority.

For variations in the centralised procedure, the relevant fee for the Type II variation(s), as provided for in Council Regulation (EC) No 297/95, should be paid in accordance with the Agency's financial procedures.

2.3.2. *Type II variations assessment for mutual recognition procedure*

Upon receipt of a Type II application, the reference Member State will handle the application as follows:

If the application has been submitted simultaneously to all the Member States concerned and contains the elements listed in point 2.3.1, the reference Member State will acknowledge receipt of a valid application of a major variation of Type II. The procedure starts from the date of acknowledgement of the receipt of a valid application by the reference Member State. The holder and the concerned Member States will be informed of the timetable at the start of the procedure.

As a general rule, for major variations of Type II, a 60-day evaluation period will apply. This period may be reduced by the reference Member State having regard to the urgency of the matter, particularly for safety issues, or may be extended by the reference Member State to 90 days for variations listed in Part I of Annex V or for grouping of variations in accordance with Article 7(2)(c) of the Variations Regulation. For variations for veterinary medicinal products listed in Part 2 of Annex V of the Variations Regulation a 90-day period will apply.

The reference Member State will prepare a draft assessment report and a decision on the application according to the communicated timetable and will circulate them to the concerned Member States for comments as well as to the holder for information. The concerned Member States will send to the reference Member State their comments within the deadlines set out in the timetable.

Within the evaluation period, the reference Member State may request the marketing authorisation holder to provide supplementary information. The request for supplementary information will be sent to the holder together with a timetable stating the date by when the holder should submit the requested data and where appropriate the extended evaluation period. In general, a suspension of 1 month will typically apply. For longer suspension the holder should send a justified request to the reference Member State for agreement.

The procedure will be suspended until the receipt of the supplementary information. The evaluation of responses may take up to 30 or 60 days depending on the complexity and amount of data requested to the holder.

After receipt of the holder's response, the reference Member State will finalise the draft assessment report and the decision on the application and will circulate them to the concerned Member States for comments as well as to the holder for information.

2.3.3. *Outcome of Type II variations assessment for mutual recognition procedure*

By the end of the evaluation period, the reference Member State will finalise and submit the assessment report and its decision on the application to the concerned Member States.

Within 30 days following receipt of the assessment report and the decision, the concerned Member States will recognise the decision and inform the reference Member State accordingly, unless a potential serious risk to public health or a potential serious risk to human or animal health or to the environment (in the case of veterinary medicinal products) is identified that prevents a Member State from recognising the decision of the reference Member State. The Member State that, within 30 days following receipt of the assessment report and the decision of the reference Member State, identifies such a potential serious risk must inform the reference Member State and give a detailed statement of the reasons for its position.

The reference Member State will then refer the application to the corresponding coordination group for application of Article 33(3), (4) and (5) of Directive 2001/82/EC or Article 29(3), (4) and (5) of Directive 2001/83/EC to the matter of disagreement and will inform the holder and the concerned Member States accordingly. The holder is not entitled to trigger a referral.

Where an application concerning a grouping of variations that includes at least a variation Type II is referred to the coordination group, the decision on the variations not subject to the referral will be suspended until the referral procedure has concluded (including, where relevant, the referral to the Committee for Medicinal Products for Human Use under Articles 32 to 34 of Directive 2001/83/EC, or the Committee for Veterinary Medicinal Products pursuant to Articles 36 to 38 of Directive 2001/82/EC). However, only the variation(s) in respect of which a potential serious risk to human or animal health or to the environment has been identified will be discussed by the coordination group and eventually by the Committee for Medicinal Products for Human use or the Committee for Veterinary Medicinal Products, not the whole group.

The reference Member State will inform the concerned Member States and the holder about the approval or rejection of the variation(s) (including the grounds for the unfavourable outcome). Where several Type II variations, or a group of Type II variation(s) with other minor variations have been submitted as one application, the reference Member State will inform the holder and the concerned Member States which variation(s) have been accepted or rejected. The holder may withdraw single variations from the grouped application during the procedure (prior to the finalisation of the assessment of the reference Member State).

After a positive decision is communicated regarding variations with changes to the summary of product characteristics, labelling or package leaflet, the holder should submit, within 7 days, translations of the product information texts to all Member States concerned.

After approval of the variation(s), the competent authorities of the Member States concerned will, where necessary, amend the marketing authorisation to reflect the variation(s) within 2 months, provided that the documents necessary for the amendment of the marketing authorisation have been submitted to the Member States concerned.

The accepted major variation(s) of Type II can be implemented 30 days after the holder has been informed about the acceptance of the variation(s) by the reference Member State, provided that the necessary documents to amend the marketing authorisation have been submitted to the Member State concerned. In those cases where the application has been the object of a referral, the variation(s) must not be implemented until the referral procedure has concluded that the variation(s) is accepted. However, the variations in the group not subject to the referral may be implemented if so indicated by the reference Member State.

Variations related to safety issues must be implemented within a time-frame agreed between the reference Member State and the holder.

2.3.4. *Type II variations assessment for purely national procedure*

Upon receipt of a Type II application, the national competent authority will handle the application as follows:

If the application contains the elements listed in point 2.3.1, the national competent authority will acknowledge receipt of a valid application of a major variation of Type II. The procedure starts from the date of acknowledgement of the receipt of a valid application. The holder will be informed of the timetable at the start of the procedure.

As a general rule, for major variations of Type II, a 60-day evaluation timetable will apply. This period may be reduced by the national competent authority having regard to the urgency of the matter, particularly for safety issues, or may be extended to 90 days for variations listed in Part I of Annex V or for grouping of variations in accordance with Article 13d(2)(c) of the Variations Regulation. For variations for veterinary medicinal products listed in Part 2 of Annex V of the Variations Regulation a 90-day timetable will apply.

Within the evaluation period, the national competent authority may request the holder to provide supplementary information. The request for supplementary information will be sent to the holder together with a timetable stating the date by when the holder should submit the requested data and where appropriate the extended evaluation period.

The procedure will be suspended until the receipt of the supplementary information. As a general rule, a suspension of 1 month will apply. For longer suspension the holder should send a justified request to the national competent authority for agreement.

The evaluation of responses may take up to 30 or 60 days depending on the complexity and amount of data requested to the holder.

2.3.5. *Outcome of Type II variations assessment for purely national procedure*

By the end of the evaluation period, the national competent authority will finalise the evaluation including its decision on the application and inform the holder about the approval or rejection of the variation(s) (including the grounds for the unfavourable outcome).

Where several Type II variations, or a group of Type II variation(s) with other minor variations have been submitted as one application, the national competent authority will inform the holder which variation(s) have been accepted or rejected. The holder may withdraw single variations from the grouped application during the procedure (prior to the finalisation of the assessment by the national competent authority).

After approval of the variation(s), the national competent authorities will, where necessary, amend the marketing authorisation(s) to reflect the variation(s) within 2 months provided that the documents necessary for the amendment of the marketing authorisation have been submitted to the national competent authority.

The accepted major variation(s) of Type II can be implemented after the holder has been informed about the acceptance of the variation(s) by the national competent authority, provided that the necessary documents to amend the marketing authorisation(s) have been submitted.

Variations related to safety issues must be implemented within a time-frame agreed between the national competent authority and the holder.

2.3.6. *Type II variations assessment for centralised procedure*

Upon receipt of a Type II application, the Agency will handle the application as follows:

If the application submitted to the Agency contains the elements listed in point 2.3.1, the Agency will acknowledge receipt of a valid application of a major variation of Type II. By the date of acknowledgement of the receipt of a valid application, the Agency will start the procedure. The marketing authorisation holder will be informed of the adopted timetable at the start of the procedure.

As a general rule, for major variations of Type II, a 60-day evaluation timetable will apply. This period may be reduced by the Agency having regard to the urgency of the matter, particularly for safety issues, or may be extended by the Agency to 90 days for variations listed in Part I of Annex V or for grouping of variations in accordance with Articles 7(2)(c) of the Variations Regulation. For variations for veterinary medicinal products listed in Part 2 of Annex V of the Variations Regulation a 90-day timetable will apply.

Within the evaluation period, the Committee for Medicinal Products for Human Use or the Committee for Veterinary Medicinal Products may request supplementary information. The request for supplementary information or follow-on request will be sent to the holder together with the timetable stating the date by when the holder should submit the requested data and where appropriate the extended evaluation period.

The procedure will be suspended until the receipt of the supplementary information. In general, a suspension of up to 1 month will typically apply. For suspension longer than 1 month the holder should send a justified request to the Agency for agreement by the corresponding Committee. For any follow-on request for supplementary information, an additional procedural suspension of up to 1 month will be applied in general; a maximum of 2 months may be applied when justified.

The Committee assessment of responses may take up to 30 or 60 days depending on the complexity and amount of data to be requested to the marketing authorisation holder.

An oral explanation to the Committee for Medicinal Products for Human Use or the Committee for Veterinary Medicinal Products may be held at the request of the Committee or the holder, where appropriate.

2.3.7. *Outcome of Type II variations assessment in centralised procedure*

Upon adoption of an opinion of the Committee for Medicinal Products for Human Use or the Committee for Veterinary Medicinal Products, the Agency will inform the marketing authorisation holder within 15 days as to whether the opinion is favourable or unfavourable (including the grounds for the unfavourable outcome).

Where several Type II variations, or a group of Type II variation(s) with other minor variations have been submitted as one application, the Agency will issue an opinion reflecting the final outcome of the procedure. Such opinion will also list any variations which are not considered approvable. The holder may withdraw single variations from the grouped application during the procedure (prior to the finalisation of the opinion of the Agency).

The re-examination procedure set-out in Articles 9(2) and 34(2) of Regulation (EC) No 726/2004 also applies to the opinions adopted for major variations of Type II applications.

Where the final opinion of the Agency is favourable and the variation(s) affects the terms of the Commission decision granting the marketing authorisation, the Agency will transmit to the Commission its opinion and the grounds for its opinion as well as the necessary documents to amend the marketing authorisation.

Upon receipt of the final opinion and the relevant information, the Commission will, where necessary, amend the marketing authorisation within 2 months in the following cases:

(i) variations related to the addition of a new therapeutic indication or to the modification of an existing one;

(ii) variations related to the addition of a new contraindication;

(iii) variations related to a change in posology;

(iv) variations related to the addition of a non-food producing target species or the modification of an existing one for veterinary medicinal products;

(v) variations concerning the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine;

(vi) variations related to changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;

(vii) variations related to changes to the withdrawal period for a veterinary medicinal product;

(viii) other type II variations that are intended to implement changes to the decision granting the marketing authorisation due to a significant public health concern or significant animal health or environmental concern in the case of veterinary medicinal products.

In the case of other variations, the Commission will, where necessary, amend the decision granting the marketing authorisation at the latest within 12 months.

The approved major variation(s) of Type II requiring amendment of the Commission decision granting the marketing authorisation within 2 months may only be implemented once the holder has been informed by the Commission accordingly. Where amendment of the decision granting the marketing authorisation is not required within 2 months, or where the approved variation(s) does not affect the terms of the Commission decision granting the marketing authorisation, the variation(s) may be implemented once the holder has been informed by the Agency that its opinion is favourable.

Variations related to safety issues must be implemented within a time-frame agreed between the Commission and the holder.

2.4. **Extensions**

Annex I of the Variations Regulation sets out a list of changes to be considered as extensions. As established in Article 19 of the Variations Regulation, such applications will be evaluated in accordance with the same procedure as for the granting of the initial marketing authorisation to which it relates. The extension can either be granted as a new marketing authorisation or will be included in the initial marketing authorisation to which it relates.

2.4.1. *Submission of Extensions applications*

Extension applications must be submitted to all Member States concerned, to the national competent authority, or to the Agency (as appropriate).

Holders may group under a single notification the submission of several extensions, or one or more extensions with one or more other variations, regarding the same marketing authorisation provided that this corresponds to one of the cases listed in Annex III of the Variations Regulation, or when this has been agreed previously with the reference Member State, the national competent, authority or the Agency (as appropriate). However, no worksharing of extensions applications is foreseen in the Variations Regulation.

The application must be presented as follows, in accordance with the appropriate headings and numbering of the EU-CTD format or the Notice to applicants Volume 6B format (veterinary medicinal products when the EU-CTD format is not available):

— Cover letter.

— The completed EU application form (published in the Notice To Applicants)

— Supporting data relating to the proposed extension. Some guidance on the appropriate additional studies required for extension applications is available in Appendix IV to Chapter 1 of Volume 2A or 6A of the Notice to applicants.

— A full Module 1 (Part 1 for veterinary medicinal products) should be provided, with justifications for absence of data or documents included in the relevant section(s) of Module 1 or Part 1.

— Update or Addendum to quality summaries, non-clinical overviews and clinical overviews (or expert reports for veterinary medicinal products) as relevant. When non-clinical or clinical study reports are submitted, even if only one, their relevant summary(ies) should be included in Module 2.

— In case that the extension affects the summary of product characteristics, labelling or package leaflet: the revised product information, presented in the appropriate format.

For extension applications in the mutual recognition procedure, the reference Member State should additionally receive the list of dispatch dates indicating the procedure number, the dates on which the applications have been sent to each Member State concerned and confirmation that the relevant fees have been paid as required by the competent authorities concerned.

For extension applications in the purely national procedure confirmation that the relevant fee has been paid as required by the national competent authority.

For extension applications in the centralise procedure, the relevant fee for the extension(s), as provided for in Council Regulation (EC) No 297/95, should be paid in accordance with the Agency's financial procedures.

2.4.2. *Extension assessment for national procedure*

Upon receipt of an extension application under the mutual recognition or the purely national procedure, it will be handled as an initial marketing authorisation application in accordance with Directive 2001/82/EC or Directive 2001/83/EC.

2.4.3. *Extension assessment for centralised procedure*

Upon receipt of an extension application, the Agency will handle the application as for an initial marketing authorisation application in accordance with Regulation (EC) No 726/2004.

2.5. **Human influenza vaccines**

Hereby guidance is provided on the application of Articles 12, 13f and 18 of the Variations Regulation to the annual update of human influenza vaccines.

Because of the specificities inherent in the manufacturing of human influenza vaccines, a special 'fast track' variation procedure is applicable for the annual change in active substance for the purpose of the annual update of a human influenza vaccine in order to meet the EU recommendation for human influenza virus strain(s) vaccine composition for the coming season. In addition, a special urgent procedure is foreseen in Article 21 of the Variations Regulation for cases of pandemic situation.

Any other variations to human influenza vaccines follow the variation procedures foreseen in other sections of these Guidelines.

The 'fast track' procedure consists of two steps. The first step concerns the assessment of the administrative and quality data elements (summary of product characteristics, labelling and package leaflet, and the chemical, pharmaceutical and biological documentation). The second step concerns the assessment of additional data where necessary.

Marketing authorisation holders are advised to discuss the annual update submissions in advance with the reference Member State, the national competent authority or the Agency.

2.5.1. *Submission of variations for annual update of human influenza vaccines applications*

Variations concerning changes to the active substance for the annual update of human influenza vaccines applications must be submitted to the reference Member State and to all concerned Member States, to the national competent authority or to the Agency (as appropriate).

The application must be presented in accordance with the appropriate headings and numbering of the EU-CTD format:

— Cover letter.

— The completed EU application form (published in the Notice to applicants)

— Update or Addendum to quality summaries, non-clinical overviews and clinical overviews as relevant. When non-clinical or clinical study reports are submitted, even if only one, their relevant summary(ies) should be included in Module 2.

— Supporting data relating to the proposed variation(s).

— The revised product information, presented in the appropriate format.

In the case of applications for the annual update of human influenza vaccines under the mutual recognition procedure, the reference Member State should additionally receive the list of dispatch dates indicating the procedure number, the dates on which the applications have been sent to each Member States concerned and confirmation that the relevant fees have been paid as required by the competent authorities concerned.

In the case of applications for the annual update of human influenza vaccines under the purely national procedure confirmation that the relevant fee has been paid as required by the national competent authority.

In the case of applications for the annual update of human influenza vaccines under the centralised procedure, the relevant fee for the variation as provided for in Council Regulation (EC) No 297/95 should be paid in accordance with the Agency's financial procedures.

2.5.2. *Variations assessment for mutual recognition procedure*

Upon receipt of an application for the annual update, the reference Member State will handle the application as follows:

The reference Member State will acknowledge receipt of a valid application within 7 days and inform the holder and the Member States concerned of the start of the procedure.

The reference Member State will prepare an assessment report and a decision on the application. To this end, the reference Member State will consider first the administrative and quality data. As the reference Member State must sent the assessment and the draft Decision within the maximum deadline of 45 days foreseen in the Regulation, it is expected that, in order to allow for sufficient time for the assessment of additional data (notably clinical and stability data) where necessary, the reference Member State will typically conclude its assessment of the administrative and quality data within 30 days of the reception of a valid application.

The reference Member State may request the holder to submit additional information (notably clinical or stability data); in such a case, it will inform the concerned Member States. When a request for additional information is sent to the holder, the 45 days deadline is stopped until the requested information has been submitted by the holder.

The reference Member State will transmit its assessment report and draft Decision to the concerned Member States. Within 12 days from the reception date, the concerned Member States will adopt a decision accordingly and inform the holder and the reference Member State thereof.

2.5.3. *Variations assessment for purely national procedure*

Upon receipt of an annual variation human influenza vaccines application, the national competent authority will handle the application as follows:

The national competent authority will acknowledge receipt of a valid application of an annual variation human influenza vaccine and inform the holder accordingly.

Within the evaluation period, the national competent authority may send the holder a request for supplementary information (notably clinical or stability data); in such a case, the 45 days deadline is stopped until the requested information has been submitted by the holder.

Within 45 days from the receipt of a valid application, the national competent authority will finalise the evaluation including its decision on the application and inform the holder about the approval or rejection of the variation(s) (including the grounds for the unfavourable outcome).

2.5.4. *Variations assessment in centralised procedure*

Upon receipt of an annual variation human influenza vaccines application, the Agency will handle the application as follows:

The Agency will acknowledge receipt of a valid application of an annual variation human influenza vaccine within 7 days and inform the holder of the start of the procedure.

The Committee for Medicinal Products for Human Use has a maximum of 55 days from the start of the procedure to assess the application. The Committee may request the holder to submit additional information (notably clinical or stability data); in such a case, the 55 days deadline is stopped until the requested information has been submitted by the holder.

Where necessary and based on the final opinion from the Committee, the Commission will amend the decision granting the marketing authorisation and update the Community Register of Medicinal Products.

2.6. **Urgent Safety Restrictions**

Article 22 of the Variations Regulation foresees that in the event of a risk to public health in the case of medicinal products for human use or in the event of a risk to human or animal health or to the environment in the case of veterinary medicinal products, the holder may take provisional 'urgent safety restrictions'.

Urgent safety restrictions concern interim change(s) in the terms of the marketing authorisation due to new information having a bearing on the safe use of the medicinal product. These urgent changes must be subsequently introduced via a corresponding variation in the marketing authorisation.

The holder must immediately notify all Member States concerned, the national competent authority or the Agency (as appropriate) of the restrictions to be introduced.

If no objections have been raised by the relevant authority or the Agency (for centrally authorised medicinal products) within 24 hours following receipt of that information, the urgent safety restrictions are deemed accepted. They must be implemented within a time frame agreed between the reference Member State, the national competent authority or the Agency (as appropriate) and the holder.

Urgent safety restrictions may also be imposed by the Commission (for centrally authorised medicinal products) or by the national competent authorities (for nationally authorised medicinal products) in the event of a risk to public health in the case of medicinal products for human use or in the event of a risk to human or animal health in the case of veterinary medicinal products.

The corresponding variation application reflecting the urgent safety restrictions (whether requested by the holder or imposed by the Commission or the national competent authorities) must be submitted by the holder as soon as possible within 15 days.

2.7. **Statement of compliance under the Paediatric Regulation**

Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 [1] ('Paediatric Regulation') provides for rewards:

— Under Article 36(1) of Regulation (EC) No 1901/2006, the holder of a patent or supplementary protection certificate is entitled to a 6-month extension of the period referred to in Article 13(1) and (2) of Regulation (EEC) No 1768/92 [2] (now: Regulation (EC) No 469/2009) under certain conditions, including the addition to the marketing authorisation of the statement referred to in Article 28(3) of the Paediatric Regulation ('compliance statement').

— Under Article 37 of Regulation (EC) No 1901/2006, the holder of a marketing authorisation for an orphan medicinal product is entitled to an extension of the 10-year period referred to in Article 8(1) of Regulation (EC) No 141/2000 to 12 years under certain conditions, including the addition of the compliance statement to the marketing authorisation.

It follows that, for the purposes of benefiting from the rewards provided for under Articles 36 and 37 of the Paediatric Regulation, a variation to add the compliance statement in the marketing authorisation may be required.

Article 23a of the Variations Regulation simplifies the procedure to add the compliance statement in the marketing authorisation so that the rewards foreseen under Regulation (EC) No 1901/2006 may be sought as soon as possible once the requirements foreseen in the Paediatric Regulation have been complied with. Specifically, in order to include the compliance statement holders should submit a variation request to the relevant authority. After verification that all relevant conditions are met, the compliance statement is to be included by the relevant authority in the technical dossier of the marketing authorisation.

For the purposes of legal certainty, the relevant authority will provide the holder with a confirmation that the compliance statement has been included in the technical dossier within 30 days after the relevant assessment has been concluded. In the case of marketing authorisations granted under the centralised procedure, the confirmation that the compliance statement has been included in the marketing authorisation will be issued by the European Medicines Agency.

[1] OJ L 378, 27.12.2006, p. 1.

[2] From 6 July 2009, this Regulation has been repealed by Regulation (EC) No 469/2009.

3. **PROCEDURAL GUIDANCE ON WORKSHARING**

Article 20 of the Variations Regulation allows a holder to submit in one application the same Type IB, the same Type II variation, or the same group of variations corresponding to one of the cases listed in Annex III of the Regulation or agreed with the reference Member State, the national competent authority or the Agency (as appropriate) which does not contain any extension affecting

(i) more than one purely national marketing authorisation of the same holder in more than one Member State; or

(ii) more than one mutual recognition marketing authorisation of the same holder; or

(iii) more than one centralised marketing authorisation of the same holder; or

(iv) one or several purely national marketing authorisation(s) and one or several centralised marketing authorisation(s) of the same holder; or

(v) one or several purely national marketing authorisation(s) and one or several mutual recognition marketing authorisation(s) of the same holder; or

(vi) one or several mutual recognition marketing authorisation(s) and one or several centralised marketing authorisation(s) of the same holder; or

(vii) one or several purely national marketing authorisation(s), one or several mutual recognition marketing authorisation(s) and one or several centralised marketing authorisation(s) of the same holder.

In order to avoid duplication of work in the evaluation of such variations, a worksharing procedure has been established under which one authority (the 'reference authority'), chosen amongst the competent authorities of the Member States and the Agency, will examine the variation on behalf of the other concerned authorities.

Where at least one of the concerned marketing authorisations has been authorised via the centralised procedure, the Agency will be the reference authority (section 3.4). In all other cases, a national competent authority chosen by the coordination group, taking into account the recommendation of the holder, will act as the reference authority (section 3.2).

In order to facilitate the planning of the procedure, holders are encouraged to inform the Agency or the coordination group and the proposed reference authority in advance of the submission of a variation or group of variations to be subject to a worksharing procedure.

In order to benefit from a worksharing procedure, it is necessary that the same change(s) will apply to the different medicinal products concerned with no need (or limited need) for assessment of a potential product-specific impact. Therefore, where the 'same' change(s) to different marketing authorisations require the submission of individual supportive data for specific medicinal products concerned or separate product-specific assessment, such changes cannot benefit from worksharing.

3.1. Submission of variation(s) application under worksharing

A variation or group of variations presented for worksharing must be submitted as explained in sections 2.2-2.3 above and must be transmitted as one integrated submission package covering all variations for all medicinal products. This must include a common cover letter and application form, together with separate supportive documentation for each medicinal product concerned and revised product information (if applicable) for each medicinal product concerned. This will allow the Agency and the national competent authorities to update the dossier of each marketing authorisation included in the worksharing procedure with the relevant amended or new information.

The worksharing application must be submitted to all relevant authorities, i.e. all Member States where the products concerned are authorised and the Agency (for the centralised procedure).

3.2. Worksharing assessment not involving medicinal products authorised under the centralised procedure

When the holder informs the coordination group of an upcoming worksharing procedure that does not affect any centralised marketing authorisation, the coordination group will at the next meeting decide on the reference authority, taking into account the proposal of the holder and, if applicable pursuant to the third subparagraph of Article 20(3) of the Variations Regulation, another relevant authority to assist the reference authority. The holder will be informed by the coordination group of the decision of which national competent authority will act as reference authority.

Upon receipt of a worksharing application, the reference authority will handle the application as follows:

The reference authority will acknowledge receipt of a valid application for worksharing. Immediately after acknowledging receipt of a valid application, the reference authority will start the procedure. The holder and the Member States concerned will be informed of the timetable at the start of the procedure.

As a general rule, worksharing procedures will follow a 60-day period or a 90-day evaluation period for variations listed in Part 2 of Annex V of the Variations Regulation. This period may however be reduced by the reference authority having regard to the urgency of the matter, particularly for safety issues, or may be extended to 90 days for variations listed in Part 1 of Annex V or for grouping of variations in accordance with Article 7(2)(c) or 13d(2)(c) of the Variations Regulation.

The reference authority will prepare an opinion according to the communicated timetable and will circulate it to the concerned Member States for comments as well as to the holder for information. Concerned Member States will send their comments within the deadlines set out in the timetable.

Within the evaluation period, the reference Member State may request the marketing authorisation holder to provide supplementary information. The request for supplementary information will be sent to the holder together with a timetable stating the date by when the holder should submit the requested data and, where appropriate, the extended evaluation period. In general, a suspension of 1 month will typically apply. For longer suspension the holder should send a justified request to the reference Member State for agreement.

The procedure will be suspended until the receipt of the supplementary information. The assessment of responses may take up to 30 or 60 days depending on the complexity and amount of data requested to the holder.

After receipt of the holder's response, the reference Member State will finalise the draft opinion and will circulate it to the concerned Member States for comments as well as to the holder for information.

3.3. Outcome of the worksharing assessment not involving medicinal products authorised under the centralised procedure

By the end of the evaluation period, the reference authority will issue its opinion on the application and inform the concerned Member States and the holder.

In case of a favourable opinion, the list of variations that are not considered approvable should be attached in the Opinion (if applicable). Variations may be considered approvable for some of the concerned products only. In case of an unfavourable outcome, the grounds for the unfavourable outcome should be explained.

Within 30 days following receipt of the opinion, the concerned Member States will recognise the opinion and inform the reference Member State accordingly, unless a potential serious risk to public health or a potential serious risk to human or animal health or to the environment (in the case of veterinary medicinal products) is identified that prevents a Member State from recognising the opinion of the reference Member State. The Member State that, within 30 days following receipt of the opinion of the reference Member State, identifies such a potential serious risk should inform the reference Member State and give a detailed statement of the reasons for its position.

The reference authority will then refer the application to the coordination group for application of Article 33(3), (4) and (5) of Directive 2001/82/EC or Article 29(3), (4) and (5) of Directive 2001/83/EC to the matter of disagreement and will inform the holder and the Member States concerned accordingly. The holder is not entitled to trigger a referral.

Where a referral to the coordination group is made, the procedure concerning the decision on the worksharing application will be suspended until a decision has been adopted on the referral procedure (including, where relevant, the referral to the Committee for Medicinal Products for Human Use under Articles 32 to 34 of Directive 2001/83/EC, or the Committee for Veterinary Medicinal Products pursuant to Articles 36 to 38 of Directive 2001/82/EC).

After a positive opinion is communicated regarding variations with changes to the summary of product characteristics, labelling or package leaflet, the holder should submit, within 7 days, translations of the product information texts to all Member States concerned.

Within 30 days following the approval of the opinion or, where a referral has been triggered, the notification of the agreement of the coordination group or the Commission decision (as applicable), the Member States concerned will amend the marketing authorisation(s) accordingly, provided that the documents necessary for the amendment of the marketing authorisation have been submitted to the Member States concerned.

Minor variation(s) of Type IB approved via a worksharing procedure, may be implemented upon receipt of the favourable opinion of the reference authority.

Major variation(s) of Type II (including those which contain grouped minor variation(s) of Type IB) approved via a worksharing procedure may be implemented 30 days after receipt of the favourable opinion from the reference authority provided that the necessary documentation to amend the marketing authorisation has been submitted to the Member States concerned. In those cases where the application has been the object of a referral, the variation(s) must not be implemented until the referral procedure has concluded that the variation(s) is accepted.

Variations related to safety issues must be implemented within a time-frame agreed between the marketing authorisation holder and the reference authority.

3.4. Worksharing assessment involving medicinal products authorised under the centralised procedure

Upon receipt of a worksharing application that affects at least one centralised marketing authorisation, the Agency will handle the application as follows:

The Agency will acknowledge receipt of a valid worksharing application. Immediately after acknowledging the receipt of a valid application, the Agency will start the procedure. The holder will be informed of the adopted timetable at the start of the procedure.

The Agency will appoint a rapporteur (and in some cases also a co-rapporteur) to lead the assessment procedure.

In general, worksharing procedures will follow a 60-day evaluation timetable or a 90-day evaluation timetable for variations listed in Part 2 of Annex V of the Variations Regulation. This period may however be reduced by the reference authority having regard to the urgency of the matter, particularly for safety issues, or may be extended to 90 days for variations listed in Part 1 of Annex V or for grouping of variations in accordance with Article 7(2)(c) or 13d(2)(c).

Within the evaluation period, the Committee for Medicinal Products for Human Use or the Committee for Veterinary Medicinal Products may request supplementary information. The request for supplementary information or follow-on request will be sent to the holder together with the timetable stating the date by when the holder should submit the requested data and where appropriate the extended evaluation period.

The procedure will be suspended until the receipt of the supplementary information. In general, a suspension of up to 1 month will typically apply. For suspension longer than 1 month the holder should send a justified request to the Agency for agreement by the Committee for Medicinal Products for Human or the Committee for Veterinary Medicinal Products.

For any follow-on request for supplementary information, an additional clock-stop of up to 1 month will be applied in general; a maximum of 2 months may be applied when justified.

The Committee assessment of responses may take up to 30 or 60 days depending on the complexity and amount of data provided by the marketing authorisation holder.

An oral explanation to the Committee for Medicinal Products for Human Use or the Committee for Veterinary Medicinal Products can be held at the request of the relevant Committee or the marketing authorisation holder, where appropriate.

3.5. Outcome of the worksharing assessment involving medicinal products authorised under the centralised procedure

By the end of the evaluation period, the Agency will adopt an opinion on the application, including the assessment report. The Agency will inform the holder and Member States concerned (if applicable). In case of disagreement with the opinion, holders may request a re-examination thereof in accordance with the procedure set out in Articles 9(2) and 34(2) of Regulation (EC) No 726/2004.

Where the opinion of the Agency is favourable and the variation(s) affects the terms of the Commission decision(s) granting the marketing authorisation, the Agency will transmit to the Commission its opinion and the grounds for its opinion as well as the necessary documents to amend the marketing authorisation.

If the Agency considers that some variations are not approvable, the list of variations that are not considered approvable should be attached in the Opinion. Variations may be considered approvable for some of the concerned products only.

Upon receipt of a favourable opinion by the Member States concerned or the Commission, the following steps apply:

— For medicinal products authorised under the mutual recognition procedure or purely national procedures, the Member States concerned must approve the opinion, inform the Agency accordingly and, where necessary, amend the national marketing authorisations within 60 days provided that the necessary documents to amend the marketing authorisation(s) have been submitted.

Minor variation(s) of Type IB (with the exception of those grouped with major variation(s) of Type II) may be implemented upon receipt of the favourable opinion of the Agency.

Major variation(s) of Type II (and those minor variation(s) of Type IB grouped with the Type II variation) may be implemented 30 days after receipt of the favourable opinion from the Agency provided that (i) the documents necessary for the amendment of the marketing authorisation(s) have been submitted to the Member States concerned, and (ii) the application has not been the object of a referral.

— For centrally authorised products, the Commission will, where necessary and provided that the necessary documents to amend the marketing authorisation(s) have been submitted, amend the relevant authorisation(s) within 2 months in the following cases:

(i) variations related to the addition of a new therapeutic indication or to the modification of an existing one;

(ii) variations related to the addition of a new contraindication;

(iii) variations related to a change in posology;

(iv) variations related to the addition of a non-food producing target species or the modification of an existing one for veterinary medicinal products;

(v) variations concerning the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine;

(vi) variations related to changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;

(vii) variations related to changes to the withdrawal period for a veterinary medicinal product;

(viii) other type II variations that are intended to implement changes to the decision granting the marketing authorisation due to a significant public health concern or significant animal health or environmental concern in the case of veterinary medicinal products.

In the case of other variations, the Commission will amend the decision granting the marketing authorisation at the latest within 12 months.

Minor variation(s) of Type IB (with the exception of those grouped with major variation(s) of Type II) may be implemented upon receipt of the favourable opinion of the Agency.

Major variation(s) of Type II (and those minor variation(s) of Type IB grouped with the Type II variation), with the exception of variations that require the adoption of a Commission decision within 2 months, may be implemented 30 days after receipt of the favourable opinion from the Agency, provided that the necessary documents to amend the marketing authorisation(s) have been submitted.

4. **ANNEX**

This Annex consists of four chapters classifying variations related to: A) Administrative changes; B) Quality changes; C) Safety, Efficacy and Pharmacovigilance changes and D) Specific changes to Plasma Master Files and Vaccine Antigen Master Files.

Where reference has to be made to specific variations in this Annex, the variation in question should be quoted using the following structure: X.N.x.n ('variation code').

— X refers to the capital letter of the chapter in this Annex where the variation is included (e.g. A, B, C or D)

— N refers to the roman number of the section inside a chapter where the variation is included (e.g. I, II, III, etc.)

— x refers to the letter of the subsection inside a chapter where the variation is included (e.g. a, b, c, etc.)

— n refers to the number given in this Annex to a specific variation (e.g. 1, 2, 3, etc.)

For each chapter this Annex contains:

— A list of variations which should be classified as minor variations of Type IA or major variations of Type II in accordance with the definitions of Article 2 and Annex II to the Variations Regulation. It is also indicated which minor variations of Type IA require immediate notification as established in Article 8(1) of the Variations Regulation

— A list of variations that should be considered as minor variations of Type IB,. It is noted that, in accordance with Article 3 of the Variations Regulation, this category applies by default. Accordingly, this Annex does not attempt to establish an exhaustive list for this category of variations.

This Annex does not deal with the classification of extensions as they are exhaustively listed in Annex I of the Variations Regulation. All changes specified in Annex I of the Variations Regulation must be considered extensions of the marketing authorisations; any other change can not be classified as such.

When one or more of the conditions established in this Annex for a minor variation of Type IA are not met, the concerned change may be submitted as a Type IB variation ('Type IB by default') unless the change is specifically classified as a major variation of Type II in this Annex or in a recommendation pursuant to Article 5 of the Variations Regulation, or unless the applicant considers that the changes may have a significant impact on the quality, safety or efficacy of the medicinal product.

If the competent authority considers that a variation submitted as a Type IB by default may have a significant impact on the quality, safety or efficacy of the medicinal product, it may request that the application be upgraded and processed as a Type II variation.

For the purpose of this Annex 'test procedure' has the same meaning as 'analytical procedure'; 'limits' has the same meaning as 'acceptance criteria'. 'Specification parameter' means the quality attribute for which a test procedure and limits are set, e.g. assay, identity, water content. The addition or deletion of a specification parameter therefore includes its corresponding test method and limits.

When several minor changes are taking place (e.g. to the same method or process or material) at the same time or in cases of a major update of the quality information for the active substance or the finished product, the applicant should take into account the overall impact of these changes on the quality, safety or efficacy of the medicinal product when considering the appropriate classification and submit them accordingly.

Specific supporting data for Type IB and Type II variations will depend on the specific nature of the change.

Furthermore, if a variation leads to a revision of the summary of product characteristics, labelling or package leaflet (jointly referred to as 'the product information'), this change is considered part of that variation. In such cases updated product information has to be submitted as part of the application with the relevant translations. Mock-ups or specimens should be provided to the reference Member State, the national competent authority or the Agency.

There is no need to notify the competent authorities of an updated monograph of the European pharmacopoeia or a national pharmacopoeia of a Member State in the case that reference is made to the 'current edition' in the dossier of an authorised medicinal product. Applicants are reminded that compliance with the updated monograph should be implemented within 6 months.

Any change to the content of the dossier that supports a European Pharmacopoeia Certificate of Suitability, should be submitted to the European Directorate for the Quality of Medicines (EDQM). However, if the certificate is revised following EDQM evaluation of this change, any marketing authorisation concerned must be updated accordingly.

With reference to Part III point 1 of Annex I of Directive 2001/83/EC, changes to Plasma Master Files (hereinafter PMFs) and Vaccine Antigen Master Files (VAMFs) follow the evaluation procedures for variations set-out in the Variations Regulation. Therefore, Chapter D in this guideline provides a list of variations which are specific to such PMFs or VAMFs. Following review of these variations, any marketing authorisation concerned must be updated in accordance with Chapter B.V of this guideline. In case the documentation of the human plasma used as starting material for a plasma derived medicinal product is not submitted as a PMF, variations to this starting material as described in the marketing authorisation dossier should also be handled in accordance with this Annex.

References in this Annex to changes to the marketing authorisation dossier mean addition, replacement or deletion, unless specifically indicated. If amendments to the dossier only concern editorial changes, such changes should generally not be submitted as a separate variation, but they can be included in a variation concerning that part of the dossier. In such cases the changes should be clearly identified in the application form as editorial changes and a declaration that the content of the concerned part of the dossier has not been changed by the editorial changes beyond the scope of the variation submitted should be provided. It should be noted that editorial changes include the removal of obsolete or redundant text but not the removal of specification parameters or manufacturing descriptions.

ANNEX

A. **ADMINISTRATIVE CHANGES**

A.1 Change in the name and/or address of the marketing authorisation holder	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1	**1, 2**	**IA_{IN}**

Conditions

1. The marketing authorisation holder must remain the same legal entity.

Documentation

1. A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or new address is mentioned.

2. Revised product information.

A.2 Change in the (invented) name of the medicinal product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) for Centrally Authorised products	**1**	**1, 2**	**IA_{IN}**
b) for Nationally Authorised Products		**2**	**IB**

Conditions

1. The check by the EMA on the acceptability of the new name has been finalised and was positive.

Documentation

1. Copy of the EMA letter of acceptance of the new (invented) name.

2. Revised product information.

A.3 Change in name of the active substance or of an excipient	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1, 2	**1, 2**	**IA_{IN}**

Conditions

1. The active substance/excipient must remain the same.

2. For veterinary medicinal products for food-producing species, the new name has been published in Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council before implementation of this change.

Documentation

1. Proof of acceptance by WHO or copy of the INN list. If applicable, proof that the change is in line with the Ph. Eur. For herbal medicinal product, declaration that the name is in accordance with the Note for Guidance on Quality of Herbal Medicinal Products, and with the guideline on declaration of herbal substances and herbal preparations in (traditional) herbal medicinal products.

2. Revised product information

A.4 Change in the name and/or address of: a manufacturer (including where relevant quality control testing sites); or an ASMF holder; or a supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the technical dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier; or a manufacturer of a novel excipient (where specified in the technical dossier)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1	**1, 2, 3**	**IA**

Conditions

1. The manufacturing site and all manufacturing operations must remain the same.

Documentation

1. A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name and/or address is mentioned.
2. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).
3. In case of change in the name of the holder of the Active Substance Master File holder, updated 'letter of access'.

A.5 Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) The activities for which the manufacturer/importer is responsible include batch release	**1**	**1, 2**	**IA_{IN}**
b) The activities for which the manufacturer/importer is responsible do not include batch release	**1**	**1, 2**	**IA**

Conditions

1. The manufacturing site undergoing the name and/or address change and all manufacturing operations must remain the same.

Documentation

1. Copy of the modified manufacturing authorisation, if available; or a formal document from a relevant official body (e.g. Chamber of Commerce, or if not available, from a Regulatory Agency) in which the new name and/or address is mentioned.
2. If applicable, amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including revised product information as appropriate.

A.6 Change in ATC Code/ATC Vet Code	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1	**1, 2**	**IA**

Conditions

1. Change following granting of or amendment to ATC Code by WHO/ATC Vet Code.

Documentation

1. Proof of acceptance (by WHO) or copy of the ATC (Vet) Code list.
2. Revised product information

A.7 Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier) (*)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1, 2	**1, 2**	**IA**

Conditions

1. There should at least remain one site/manufacturer, as previously authorised, performing the same function as the one(s) concerned by the deletion. Where applicable at least one manufacturer responsible for batch release that is able to certify the product testing for the purpose of batch release within the EU/EEA remains in the EU/EEA.

2. The deletion should not be due to critical deficiencies concerning manufacturing.

Documentation

1. The variation application form should clearly outline the 'present' and 'proposed' manufacturers as listed in section 2.5 of the application form for marketing authorisations.

2. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including revised product information as appropriate.

(*) *Note:* where notice has been given by the authorities of the intention to perform an inspection, the deletion of the relevant site shall be notified immediately.

A.8 Changes to date of the audit to verify GMP compliance of the manufacturer of the active substance (*)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			IA

Documentation

1. Written confirmation from the manufacturer of the finish product stating verification of compliance of the manufacturer of the active substance with principles and guidelines of good manufacturing practices.

(*) *Note:* this variation does not apply when the information has been otherwise transmitted to the authorities (e.g. through the so-called 'QP declaration').

B. **QUALITY CHANGES**

B.I ACTIVE SUBSTANCE

B.I.a) *Manufacture*

B.I.a.1 Change in the manufacturer of a starting material/ reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	**1, 2, 3**	**1, 2, 3, 4, 5, 6, 7**	**IA_{IN}**
b) Introduction of a manufacturer of the active substance supported by an ASMF			**II**
c) The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions, which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability			**II**
d) New manufacturer of material for which an assessment is required of viral safety and/or TSE risk			**II**

e) The change relates to a biological active substance or a starting material/reagent/intermediate used in the manufacture of a biological/immunological product			**II**
f) Changes to quality control testing arrangements for the active substance-replacement or addition of a site where batch control/testing takes place	**2, 4**	**1, 5**	**IA**
g) Introduction of a new manufacturer of the active substance that is not supported by an ASMF and requires significant update to the relevant active substance section of the dossier			**II**
h) Addition of an alternative sterilisation site for the active substance using a Ph.Eur. method		**1, 2, 4, 5, 8**	**IB**
i) Introduction of a new site of micronisation	**2, 5**	**1, 4, 5, 6**	**IA**
j) Changes to quality control testing arrangements for a biological active substance: replacement or addition of a site where batch control/testing including a biological/immunological/immuno-chemical method takes place			**II**
k) New storage site of Master Cell Bank and/or Working Cell Banks		**1, 5**	**IB**

Conditions

1. For starting materials and reagents the specifications (including in process controls, methods of analysis of all materials), are identical to those already approved. For intermediates and active substances the specifications (including in process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed route of synthesis are identical to those already approved.

2. The active substance is not a biological/immunological substance or sterile.

3. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with the current *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products*.

4. Method transfer from the old to the new site has been successfully completed.

5. The particle size specification of the active substance and the corresponding analytical method remain the same.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), if applicable.

2. A declaration from the marketing authorisation holder or the ASMF holder, where applicable, that the synthetic route (or in case of herbal medicinal products, where appropriate the method of preparation, geographical source, production of herbal drug and manufacturing route) quality control procedures and specifications of the active substance and of the starting material/reagent/intermediate in the manufacturing process of the active substance (if applicable) are the same as those already approved.

3. Either a TSE Ph. Eur. Certificate of Suitability for any new source of material or, where applicable, documentary evidence that the specific source of the TSE risk material has previously been assessed by the competent authority and shown to comply with the current *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products*. The information should include the following: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, its use and previous acceptance. For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant).

4. Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the active substance from the current and proposed manufacturers/sites.

5. The variation application form should clearly outline the 'present' and 'proposed' manufacturers as listed in section 2.5 of the application form for marketing authorisation.

6. A declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application where the active substance is used as a starting material and a declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application as responsible for batch release. These declarations should state that the active substance manufacturer(s) referred to in the application operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances — see the note under variation No B.II.b.1.

7. Where relevant, a commitment of the manufacturer of the active substance to inform the MA holder of any changes to the manufacturing process, specifications and test procedures of the active substance.

8. Proof that the proposed site is appropriately authorised for the pharmaceutical form or product or manufacturing operation concerned, i.e.:

   For a manufacturing site within the EU/EEA: a copy of the current manufacturing authorisation. A reference to the EudraGMP database will suffice.

   For a manufacturing site outside the EU/EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a GMP certificate issued within the last 3 years by the relevant competent authority.

   For a manufacturing site outside the EU/EEA where no such mutual recognition agreement exists: a GMP certificate issued within the last 3 years by an inspection service of one of the Member States of the EU/EEA. A reference to the EudraGMP database will suffice.

B.I.a.2 Changes in the manufacturing process of the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Minor change in the manufacturing process of the active substance	**1, 2, 3, 4, 5, 6, 7**	**1, 2, 3**	**IA**
b) Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product			**II**
c) The change refers to a biological/immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological substance, which may have a significant impact on the quality, safety and efficacy of the medicinal product and is not related to a protocol			**II**
d) The change relates to a herbal medicinal product and there is a change to any of the following: geographical source, manufacturing route or production			**II**
e) Minor change to the restricted part of an Active Substance Master File		**1, 2, 3, 4**	**IB**

Conditions

1. No adverse change in qualitative and quantitative impurity profile or in physico-chemical properties.

2. The synthetic route remains the same, i.e. intermediates remain the same and there are no new reagents, catalysts or solvents used in the process. In the case of herbal medicinal products, the geographical source, production of the herbal substance and the manufacturing route remain the same.

3. The specifications of the active substance or intermediates are unchanged.

4. The change is fully described in the open ('applicant's') part of an Active Substance Master File, if applicable.

5. The active substance is not a biological/immunological substance.

6. The change does not refer to the geographical source, manufacturing route or production of a herbal medicinal product.

7. The change does not refer to the restricted part of an Active Substance Master File.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), and of the approved Active Substance Master File (where applicable), including a direct comparison of the present process and the new process.

2. Batch analysis data (in comparative tabular format) of at least two batches (minimum pilot scale) manufactured according to the currently approved and proposed process.

3. Copy of approved specifications of the active substance.

4. A declaration from the marketing authorisation holder or the ASMF Holder, where applicable, that there is no change in qualitative and quantitative impurity profile or in physico-chemical properties, that the synthetic route remains the same and that the specifications of the active substance or intermediates are unchanged.

Note: for B.I.a.2.b), for chemical active substances, this refers to substantial changes to the synthetic route or manufacturing conditions which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability.

B.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Up to 10-fold increase compared to the originally approved batch size	**1, 2, 3, 4, 6, 7, 8**	**1, 2, 5**	**IA**
b) Downscaling down to 10-fold	**1, 2, 3, 4, 5**	**1, 2, 5**	**IA**
c) The change requires assessment of the comparability of a biological/immunological active substance			**II**
d) More than 10-fold increase compared to the originally approved batch size		**1, 2, 3, 4**	**IB**
e) The scale for a biological/immunological active substance is increased/decreased without process change (e.g. duplication of line)		**1, 2, 3, 4**	**IB**

Conditions

1. Any changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment.

2. Test results of at least two batches according to the specifications should be available for the proposed batch size.

3. The product concerned is not a biological/immunological medicinal product.

4. The change does not adversely affect the reproducibility of the process.

5. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.

6. The specifications of the active substance/intermediates remain the same.

7. The active substance is not sterile.

8. The batch size is within the 10-fold range of the batch size foreseen when the marketing authorisation was granted or following a subsequent change not agreed as a Type IA variation.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

2. The batch numbers of the tested batches having the proposed batch size.

3. Batch analysis data (in a comparative tabulated format) on a minimum of one production batch of the active substance or intermediate as appropriate, manufactured to both the currently approved and the proposed sizes. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorisation holder if outside specification (with proposed action).

4. Copy of approved specifications of the active substance (and of the intermediate, if applicable).

5 A declaration from the marketing authorisation holder or the ASMF holder as appropriate that the changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment, that the change does not adversely affect the reproducibility of the process, that it is not the result of unexpected events arising during manufacture or because of stability concerns and that the specifications of the active substance/intermediates remain the same.

B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Tightening of in-process limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new in-process test and limits	**1, 2, 5, 6**	**1, 2, 3, 4, 6**	**IA**
c) Deletion of a non-significant in-process test	**1, 2, 7**	**1, 2, 5**	**IA**
d) Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the active substance			**II**
e) Deletion of an in-process test which may have a significant effect on the overall quality of the active substance			**II**
f) Addition or replacement of an in-process test as a result of a safety or quality issue		**1, 2, 3, 4, 6**	**IB**

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).

2. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.

3. Any change should be within the range of currently approved limits.

4. The test procedure remains the same, or changes in the test procedure are minor.

5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

6. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods).

7. The specification parameter does not concern a critical parameter for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics, e.g. particle size, bulk or tapped density, identity test, water, any request for changing the frequency of testing.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

2. Comparative table of current and proposed in-process tests.

3. Details of any new non-pharmacopoeial analytical method and validation data, where relevant.

4. Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the active substance for all specification parameters.

5. Justification/risk assessment from the marketing authorisation holder or the ASMF Holder, as appropriate, that the in-process tests are non-significant, or that the in-process tests are obsolete.

6. Justification from the MAH or ASMF Holder as appropriate for the new in-process test and limits.

B.I.a.5 Changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Replacement of the strain(s) in a seasonal, pre-pandemic or a pandemic vaccine against human influenza			**II**

B.I.b) *Control of active substance*

B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Tightening of specification limits for medicinal products subject to Official Control Authority Batch Release	**1, 2, 3, 4**	**1, 2**	**IA_{IN}**
b) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
c) Addition of a new specification parameter to the specification with its corresponding test method	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 5, 7**	**IA**
d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	**1, 2, 8**	**1, 2, 6**	**IA**
e) Deletion of a specification parameter which may have a significant effect on the overall quality of the active substance and/or the finished product			**II**
f) Change outside the approved specifications limits range for the active substance			**II**

g) Widening of the approved specifications limits for starting materials/intermediates, which may have a significant effect on the overall quality of the active substance and/or the finished product			**II**
h) Addition or replacement (excluding biological or immunological substance) of a specification parameter with its corresponding test method as a result of a safety or quality issue		**1, 2, 3, 4, 5, 7**	**IB**
i) Where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State for the active substance, a change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country		**1, 2, 3, 4, 5, 7**	**IB**

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).

2. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.

3. Any change should be within the range of currently approved limits.

4. The test procedure remains the same, or changes in the test procedure are minor.

5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

6. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeia microbiological methods).

7. For any material, the change does not concern a genotoxic impurity. If it involves the final active substance, other than for residual solvents which must be in line with ICH/VICH limits, any new impurity control should be in line with the Ph. Eur. or National Pharmacopoeia of a Member State.

8. The specification parameter does not concern a critical parameter, for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics, e.g. particle size, bulk or tapped density, identity test, water, any request for skip testing.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

2. Comparative table of current and proposed specifications.

3. Details of any new analytical method and validation data, where relevant.

4. Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the relevant substance for all specification parameters.

5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the active substance complying with the current and proposed specification. For herbal medicinal products, comparative disintegration data may be acceptable.

6. Justification/risk assessment from the marketing authorisation holder or the ASMF Holder, as appropriate, that the in-process parameter is non-significant, or that the in-process parameter is obsolete.

7. Justification from the MAH or ASMF Holder as appropriate of the new specification parameter and the limits.

B.I.b.2 Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Minor changes to an approved test procedure	**1, 2, 3, 4**	**1, 2**	**IA**
b) Deletion of a test procedure for the active substance or a starting material/reagent/intermediate, if an alternative test procedure is already authorised.	7	**1**	**IA**
c) Other changes to a test procedure (including replacement or addition) for a reagent, which does not have a significant effect on the overall quality of the active substance	**1, 2, 3, 5, 6**	**1, 2**	**IA**
d) Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological active substance			**II**
e) Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate		**1, 2**	**IB**

Conditions

1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.

2. There have been no changes of the total impurity limits; no new unqualified impurities are detected.

3. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).

4. The test method is not a biological/immunological/immunochemical method, or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods).

5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

6. The active substance is not biological/immunological.

7 An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA/IA(IN) notification.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).

2. Comparative validation results, or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.I.c) *Container closure system*

B.I.c.1 Change in immediate packaging of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Qualitative and/or quantitative composition	**1, 2, 3**	**1, 2, 3, 4, 6**	**IA**

b) Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological active substances			**II**
c) Liquid active substances (non-sterile)		**1, 2, 3, 5, 6**	**IB**

Conditions

1. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.

2 Relevant stability studies have been started under ICH/VICH conditions and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least 3 months satisfactory stability data are at the disposal of the applicant at time of implementation. However, if the proposed packaging is more resistant than the existing packaging, the 3 months' stability data do not yet have to be available. These studies must be finalised and the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the shelf-life/retest period (with proposed action).

3 Sterile, liquid and biological/immunological active substances are excluded.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

2. Appropriate data on the new packaging (e.g. comparative data on permeability, e.g. for O_2, CO_2 moisture), including a confirmation that the material complies with relevant pharmacopoeial requirements or legislation of the Union on plastic materials and objects in contact with foodstuffs.

3. Where appropriate, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack), including confirmation that the material complies with relevant pharmacopoeia requirements or legislation of the Union on plastic material and objects in contact with foodstuffs.

4. A declaration from the marketing authorisation holder or the ASMF holder as appropriate that the required stability studies have been started under ICH/VICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

5. The results of stability studies that have been carried out under ICH/VICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved retest period (with proposed action).

6. Comparison of the current and proposed immediate packaging specifications, if applicable.

B.I.c.2 Change in the specification parameters and/or limits of the immediate packaging of the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new specification parameter to the specification with its corresponding test method	**1, 2, 5**	**1, 2, 3, 4, 6**	**IA**
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	**1, 2**	**1, 2, 5**	**IA**
d) Addition or replacement of a specification parameter as a result of a safety or quality issue		**1, 2, 3, 4, 6**	**IB**

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure) unless it has been previously assessed and agreed as part of a follow-up measure.

2. The change does not result from unexpected events arising during manufacture of the packaging material or during storage of the active substance.

3. Any change should be within the range of currently approved limits.

4. The test procedure remains the same, or changes in the test procedure are minor.

5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

2. Comparative table of current and proposed specifications.

3. Details of any new analytical method and validation data, where relevant.

4. Batch analysis data on two batches of the immediate packaging for all specification parameters.

5 Justification/risk assessment from the marketing authorisation holder or the ASMF Holder, as appropriate, that the in-process parameter is non-significant, or that the in-process parameter is obsolete.

6. Justification from the marketing authorisation holder or the ASMF Holder, as appropriate, of the new specification parameter and the limits.

B.I.c.3 Change in test procedure for the immediate packaging of the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Minor changes to an approved test procedure	**1, 2, 3,**	**1, 2**	**IA**
b) Other changes to a test procedure (including replacement or addition)	**1, 3, 4**	**1, 2**	**IA**
c) Deletion of a test procedure if an alternative test procedure is already authorised	**5**	**1**	**IA**

Conditions

1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.

2. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).

3. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

4. The active substance/finished product is not biological/immunological.

5. There is still a test procedure registered for the specification parameter and this procedure has not been added through a IA/IA(IN) notification.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a description of the analytical methodology, a summary of validation data.

2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.I.d) *Stability*

B.I.d.1 Change in the retest period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Retest period/storage period			
1. Reduction	**1**	**1, 2, 3**	**IA**
2. Extension of the retest period based on extrapolation of stability data not in accordance with ICH/VICH guidelines (*)			**II**
3. Extension of storage period of a biological/immunological active substance not in accordance with an approved stability protocol			**II**
4. Extension or introduction of a retest period/storage period supported by real time data		**1, 2, 3**	**IB**
b) Storage conditions			
1. Change to more restrictive storage conditions of the active substance	**1**	**1, 2, 3**	**IA**
2. Change in storage conditions of biological/immunological active substances, when the stability studies have not been performed in accordance with a currently approved stability protocol			**II**
3. Change in storage conditions of the active substance		**1, 2, 3**	**IB**
c) Change to an approved stability protocol	**1, 2**	**1, 4**	**IA**

Conditions

1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.

2. The changes do not concern a widening of the acceptance criteria in the parameters tested, a removal of stability indicating parameters or a reduction in the frequency of testing.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate). This must contain results of appropriate real time stability studies,

conducted in accordance with the relevant stability guidelines on at least two (three for biological medicinal products) pilot or production scale batches of the active substance in the authorised packaging material and covering the duration of the requested retest period or requested storage conditions.

2. Confirmation that stability studies have been done to the currently approved protocol. The studies must show that the agreed relevant specifications are still met.

3. Copy of approved specifications of the active substance.

4. Justification for the proposed changes.

(*) *Note:* Retest period not applicable for biological/immunological active substance.

B.I.e) *Design Space and post-approval change management protocols*

B.I.e.1 Introduction of a new design space or extension of an approved design space for the active substance, concerning:	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) One unit operation in the manufacturing process of the active substance including the resulting in-process controls and/or test procedures		**1, 2, 3**	**II**
b) Test procedures for starting materials/reagents/intermediates and/or the active substance		**1, 2, 3**	**II**

Documentation

1. The design space has been developed in accordance with the relevant European and international scientific guidelines. Results from product, process and analytical development studies (e.g. interaction of the different parameters forming the design space have to be studied, including risk assessment and multivariate studies, as appropriate) demonstrating where relevant that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the active substance has been achieved.

2. Description of the Design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges.

3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

B.I.e.2 Introduction of a post approval change management protocol related to the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
		1, 2, 3	**II**

Documentation

1. Detailed description for the proposed change.

2. Change management protocol related to the active substance.

3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

B.I.e.3 Deletion of an approved change management protocol related to the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1	**1, 2**	**IA_{IN}**

Conditions

1. The deletion of the approved change management protocol related to the active substance is not a result of unexpected events or out of specification results during the implementation of the change(s) described in the protocol and does not have any effect on the already approved information in the dossier.

Documentation

1. Justification for the proposed deletion.
2. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

B.I.e.4 Changes to an approved change management protocol	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Major changes to an approved change management protocol			**II**
b) Minor changes to an approved change management protocol that do not change the strategy defined in the protocol		**1**	**IB**

Documentation

1. Declaration that any change should be within the range of currently approved limits. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.

B.I.e.5 Implementation of changes foreseen in an approved change management protocol	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) The implementation of the change requires no further supportive data	**1**	**1, 2, 4**	**IA_{IN}**
b) The implementation of the change requires further supportive data		**1, 2, 3, 4**	**IB**
c) Implementation of a change for a biological/immunological medicinal product		**1, 2, 3, 4, 5**	**IB**

Conditions

1. The proposed change has been performed fully in line with the approved change management protocol.

Documentation

1. Reference to the approved change management protocol.
2. Declaration that the change is in accordance with the approved change management and that the study results meet the acceptance criteria specified in the protocol. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.
3. Results of the studies performed in accordance with the approved change management protocol.
4. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).
5. Copy of approved specifications of the active substance.

B.II. FINISHED PRODUCT

B.II.a) *Description and composition*

B.II.a.1 Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Changes in imprints, bossing or other markings	**1, 2, 3, 4**	**1, 2**	**IA_{IN}**

b) Changes in scoring/break lines intended to divide into equal doses		**1, 2, 3**	**IB**

Conditions

1. Finished product release and end of shelf life specifications have not been changed (except for appearance).

2. Any ink must comply with the relevant pharmaceutical legislation.

3. The scoring/break lines are not intended to divide into equal doses.

4. Any product markings used to differentiate strengths should not be completely deleted.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a detailed drawing or written description of the current and new appearance, and including revised product information as appropriate.

2. Samples of the finished product where applicable (see NTA, Requirements for samples in the Member States).

3 Results of the appropriate Ph. Eur tests demonstrating equivalence in characteristics/correct dosing.

B.II.a.2 Change in the shape or dimensions of the pharmaceutical form	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Immediate release tablets, capsules, suppositories and pessaries	**1, 2, 3, 4**	**1, 4**	**IA_{IN}**
b) Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets intended to be divided into equal doses		**1, 2, 3, 4, 5**	**IB**
c) Addition of a new kit for a radiopharmaceutical preparation with another fill volume			**II**

Conditions

1. If appropriate, the dissolution profile of the reformulated product is comparable to the old one. For herbal medicinal products, where dissolution testing may not be feasible, the disintegration time of the new product compared to the old one.

2. Release and end of shelf-life specifications of the product have not been changed (except for dimensions).

3. The qualitative or quantitative composition and mean mass remain unchanged.

4. The change does not relate to a scored tablet that is intended to be divided into equal doses.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a detailed drawing of the current and proposed situation, and including revised product information as appropriate.

2. Comparative dissolution data on at least one pilot batch of the current and proposed dimensions (no significant differences regarding comparability see the relevant (Human or Veterinary) guidance on Bioavailability). For herbal medicinal product comparative disintegration data may be acceptable.

3. Justification for not submitting a new bioequivalence study according to the relevant (Human or Veterinary) guidance on Bioavailability.

4. Samples of the finished product where applicable (see NTA, Requirements for samples in the Member States).

5. Results of the appropriate Ph. Eur tests demonstrating equivalence in characteristics/correct dosing.

Note: for B.II.a.2.c), applicants are reminded that any change to the 'strength' of the medicinal product requires the submission of an Extension application.

B.II.a.3 Changes in the composition (excipients) of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Changes in components of the flavouring or colouring system			
1. Addition, deletion or replacement	**1, 2, 3, 4, 5, 6, 7, 9, 11**	**1, 2, 4, 5, 6**	**IA_{IN}**
2. Increase or reduction	**1, 2, 3, 4, 11**	**1, 2, 4**	**IA**
3. Biological veterinary medicinal products for oral use for which the colouring or flavouring agent is important for the uptake by target animal species			**II**
b) Other excipients			
1. Any minor adjustment of the quantitative composition of the finished product with respect to excipients	**1, 2, 4, 8, 9, 10**	**1, 2, 7**	**IA**
2. Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the medicinal product			**II**
3. Change that relates to a biological/immunological product			**II**
4. Any new excipient that includes the use of materials of human or animal origin for which assessment is required of viral safety data or TSE risk			**II**
5. Change that is supported by a bioequivalence study			**II**
6. Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level		**1, 3, 4, 5, 6, 7, 8, 9, 10**	**IB**

Conditions

1. No change in functional characteristics of the pharmaceutical form, e.g. disintegration time, dissolution profile.

2. Any minor adjustment to the formulation to maintain the total weight should be made by an excipient which currently makes up a major part of the finished product formulation.

3. The finished product specification has only been updated in respect of appearance/odour/taste and if relevant, deletion of an identification test.

4. Stability studies have been started under ICH/VICH conditions (with indication of batch numbers) and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least 3 months satisfactory stability data are at the disposal of the applicant (at time of implementation for Type IAs

and at time of notification for Type IBs) and that the stability profile is similar to the currently registered situation. Assurance is given that these studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action). In addition, where relevant, photo-stability testing should be performed.

5. Any new proposed components must comply with the relevant Directives (e.g. Directive 94/36/EC of the European Parliament and of the Council [1] and Commission Directive 2008/128/EC [2] for colours for use in foodstuffs and Council Directive 88/388/EEC [3] for flavours).

6. Any new component does not include the use of materials of human or animal origin for which assessment is required of viral safety data or compliance with the current *Note For Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products*.

7. Where applicable, the change does not affect the differentiation between strengths and does not have a negative impact on taste acceptability for paediatric formulations.

8. The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one (no significant differences regarding comparability, see the relevant (Human or Veterinary) guidance on Bioavailability). For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one.

9. The change is not the result of stability issues and/or should not result in potential safety concerns, i.e. differentiation between strengths.

10. The product concerned is not a biological/immunological medicinal product.

11. For veterinary medicinal products for oral use, the change does not affect the uptake by target animal species.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including identification method for any new colorant, where relevant, and including revised product information as appropriate.

2. A declaration that the required stability studies have been started under ICH/VICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

3. The results of stability studies that have been carried out under ICH/VICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

4. Sample of the new product, where applicable (see Notice to Applicants Requirements for samples in the Member States).

5. Either a Ph. Eur. Certificate of Suitability for any new component of animal susceptible to TSE risk or where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by the competent authority and shown to comply with the scope of the current *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathies via Human and Veterinary Medicinal Products*. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use.

   For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant).

6. Data to demonstrate that the new excipient does not interfere with the finished product specification test methods, if appropriate.

7 Justification for the change/choice of excipients etc. must be given by appropriate development pharmaceutics (including stability aspects and antimicrobial preservation where appropriate).

8. For solid dosage forms, comparative dissolution profile data of at least two pilot scale batches of the finished product in the new and old composition. For herbal medicinal products, comparative disintegration data may be acceptable.

9. Justification for not submitting a new bioequivalence study according to the current *Note for Guidance on The Investigation of Bioavailability and Bioequivalence*.

10. For veterinary medicines intended for use in food producing animal species, proof that the excipient is classified according to Article 14(2)(c) of Regulation (EC) No 470/2009 or, if not, justification that the excipient does not have pharmacological activity at the dose at which it is administered to the target animal.

(1) OJ L 237, 10.9.1994, p. 13.
(2) OJ L 6, 10.1.2009, p. 20.
(3) OJ L 184, 15.7.1988, p. 61.

B.II.a.4 Change in coating weight of oral dosage forms or change in weight of capsule shells	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Solid oral pharmaceutical forms	**1, 2, 3, 4**	**1, 2**	**IA**
b) Gastro-resistant, modified or prolonged release pharmaceutical forms where the coating is a critical factor for the release mechanism			**II**

Conditions

1. The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one. For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one.

2. The coating is not a critical factor for the release mechanism.

3. The finished product specification has only been updated in respect of weight and dimensions, if applicable.

4. Stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or industrial scale batches and at least 3 months satisfactory stability data are at the disposal of the applicant at the time of implementation and assurance that these studies will be finalised. Data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

2. A declaration that the required stability studies have been started under ICH/VICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). In addition, where relevant, photo-stability testing should be performed.

B.II.a.5 Change in concentration of a single-dose, total use parenteral product, where the amount of active substance per unit dose (i.e. the strength) remains the same	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II

B.II.a.6 Deletion of the solvent/diluent container from the pack	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2	IB

Documentation

1. Justification for the deletion, including a statement regarding alternative means to obtain the solvent/diluent as required for the safe and effective use of the medicinal product.

2. Revised product information.

B.II.b) *Manufacture*

B.II.b.1 Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Secondary packaging site	**1, 2**	**1,3, 8**	**IA_{IN}**
b) Primary packaging site	**1, 2, 3, 4, 5**	**1, 2, 3, 4, 8, 9**	**IA_{IN}**
c) Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products, or for pharmaceutical forms manufactured by complex manufacturing processes			**II**
d) Site which requires an initial or product specific inspection			**II**
e) Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products		**1, 2, 3, 4, 5, 6, 7, 8, 9**	**IB**
f) Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/immunological medicinal products		**1, 2, 3, 4, 5, 6, 7, 8**	**IB**

Conditions

1. Satisfactory inspection in the last 3 years by an inspection service of one of the Member States of the EU/EEA or of a country where an operational Good Manufacturing Practice (GMP) mutual recognition agreement (MRA) exists between the country concerned and the EU.

2. Site appropriately authorised (to manufacture the pharmaceutical form or product concerned).

3. Product concerned is not a sterile product.

4. Where relevant, for instance for suspensions and emulsions, validation scheme is available or validation of the manufacture at the new site has been successfully carried out according to the current protocol with at least three production scale batches.

5. Product concerned is not a biological/immunological medicinal product.

Documentation

1. Proof that the proposed site is appropriately authorised for the pharmaceutical form or product concerned, i.e.:

   For a manufacturing site within the EU/EEA: a copy of the current manufacturing authorisation. A reference to the EudraGMP database will suffice;

For a manufacturing site outside the EU/EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a GMP certificate issued within the last 3 years by the relevant competent authority;

For a manufacturing site outside the EU/EEA where no such mutual recognition agreement exists: a GMP certificate issued within the last 3 years by an inspection service of one of the Member States of the EU/EEA. A reference to the EudraGMP database will suffice.

2. Where relevant, the batch numbers, corresponding batch size and the manufacturing date of batches (≥ 3) used in the validation study should be indicated and the validation data presented, or validation protocol (scheme) to be submitted.

3. The variation application form should clearly outline the 'present' and 'proposed' finished product manufacturers as listed in section 2.5 of the application form.

4. Copy of approved release and end-of-shelf life specifications if relevant.

5. Batch analysis data on one production batch and two pilot-scale batches simulating the production process (or two production batches) and comparative data on the last three batches from the previous site; batch data on the next two production batches should be available on request or reported if outside specifications (with proposed action).

6. For semisolid and liquid formulations in which the active substance is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology or any other appropriate imaging technique.

7. i) If the new manufacturing site uses the active substance as a starting material — A declaration by the Qualified Person (QP) at the site responsible for batch release that the active substance is manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the Union.

   ii) In addition, if the new manufacturing site is located within the EU/EEA and uses the active substance as a starting material — A declaration by the Qualified Person (QP) of the new manufacturing site that the active substance used is manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the Union.

8. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

9. If the manufacturing site and the primary packaging site are different, conditions of transport and bulk storage should be specified and validated.

Notes:

In case of a change in or a new manufacturing site in a country outside the EU/EEA without an operational GMP mutual recognition agreement with the EU, marketing authorisation holders are advised to consult the relevant competent authorities first before making the submission of the notification and to provide information about any previous EU/EEA inspection in the last 2-3 years and/or any planned EU/EEA inspection(s) including inspection dates, product category inspected, Supervisory Authority and other relevant information. This will facilitate the arrangement for a GMP inspection by an inspection service of one of the Member States if needed.

QP Declarations in relation to active substances

Manufacturing authorisation holders are obliged to only use as starting materials active substances that have been manufactured in accordance with GMP so a declaration is expected from each of the manufacturing authorisation holders that use the active substance as a starting material. In addition, as the QP responsible for batch certification takes overall responsibility for each batch, a further declaration from the QP responsible for batch certification is expected when the batch release site is a different site from the above.

In many cases only one manufacturing authorisation holder is involved and therefore only one declaration will be required. However, when more than one manufacturing authorisation holder is involved rather than provide multiple declarations it may be acceptable to provide a single declaration signed by one QP. This will be accepted provided that:

The declaration makes it clear that it is signed on behalf of all the involved QPs.

The arrangements are underpinned by a technical agreement as described in Chapter 7 of the GMP Guide and the QP providing the declaration is the one identified in the agreement as taking specific responsibility for the GMP compliance of the active substance manufacturer(s). Note: these arrangements are subject to inspection by the competent authorities.

Applicants are reminded that a Qualified Person is at the disposal of a manufacturing authorisation holder according to Article 41 of Directive 2001/83/EC and Article 45 of Directive 2001/82/EC and located in the EU/EEA. Therefore declarations from personnel employed by manufacturers in third countries, including those located within MRA partner countries are not acceptable.

According to Article 46a(1) of Directive 2001/83/EC and Article 50a(1) of Directive 2001/82/EC, manufacture includes complete or partial manufacture, import, dividing up, packaging or presentation prior to its incorporation into a medicinal product, including repackaging or relabeling as carried out by a distributor.

A declaration is not required for blood or blood components they are subject to the requirements of Directive 2002/98/EC of the European Parliament and of the Council [1].

[1] OJ L 33, 8.2.2003, p. 30.

B.II.b.2 Change to importer, batch release arrangements and quality control testing of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Replacement or addition of a site where batch control/testing takes place	**2, 3, 4, 5**	**1, 2, 5**	**IA**
b) Replacement or addition of a site where batch control/testing takes place for a biological/immunological product and any of the test methods performed at the site is a biological/immunological method			**II**
c) Replacement or addition of a manufacturer responsible for importation and/or batch release			
1. Not including batch control/testing	**1, 2,5**	**1, 2, 3, 4, 5**	**IA_{IN}**
2. Including batch control/testing	**1, 2, 3, 4, 5**	**1, 2, 3, 4, 5**	**IA_{IN}**
3. Including batch control/testing for a biological/immunological product and any of the test methods performed at that site is a biological/immunological/immunochemical method			**II**

Conditions

1. The manufacturer responsible for batch release must be located within the EU/EEA. At least one batch release site remains within the EU/EEA that is able to certify the product testing for the purpose of batch release within the EU/EEA.

2. The site is appropriately authorised.

3. The product is not a biological/immunological medicinal product.

4. Method transfer from the old to the new site or new test laboratory has been successfully completed.

5. At least one batch control/testing site remains within the EU/EEA or in a country where an operational and suitably scoped GMP mutual recognition agreement (MRA) exists between the country concerned and the EU, that is able to carry out product testing for the purpose of batch release within the EU/EEA.

Documentation

1. For a site within the EU/EEA: Attach copy of manufacturing authorisation(s) or where no manufacturing authorisation exists a certificate of GMP compliance issued within the last 3 years by the relevant competent authority.

For a manufacturing site outside the EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a GMP certificate, issued within the last 3 years by the relevant competent authority. Where no such agreement exists a GMP certificate issued within the last 3 years by a EU/EEA competent authority.

2. The variation application form should clearly outline the 'present' and 'proposed' finished product manufacturers, importer, batch control/testing and batch release sites as listed in section 2.5 of the application form for marketing authorisation.

3. For centralised procedure only: contact details of new contact person in the EU/EEA for product defects and recalls, if applicable.

4. A declaration by the Qualified Person (QP) responsible for batch certification stating that the active substance manufacturer(s) referred to in the marketing authorisation operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances — see the note under variation No B.II.b.1.

5 Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including revised product information as appropriate.

B.II.b.3 Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Minor change in the manufacturing process	**1, 2, 3, 4, 5, 6, 7**	**1, 2, 3, 4, 5, 6, 7, 8**	**IA**
b) Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product			**II**
c) The product is a biological/immunological medicinal product and the change requires an assessment of comparability			**II**
d) Introduction of a non-standard terminal sterilisation method			**II**
e) Introduction or increase in the overage that is used for the active substance			**II**
f) Minor change in the manufacturing process of an aqueous oral suspension		**1, 2, 4, 6, 7,8**	**IB**

Conditions

1. No change in qualitative and quantitative impurity profile or in physico-chemical properties.

2. Either the change relates to an immediate release solid oral dosage form/oral solution and the medicinal product concerned is not a biological/immunological or herbal medicinal product;

   or the change relates to process parameter(s) that, in the context of a previous assessment, have been considered to have no impact on the quality of the finished product (regardless of the type of product and/or dosage form).

3. The manufacturing principle including the single manufacturing steps remain the same, e.g. processing intermediates and there are no changes to any manufacturing solvent used in the process.

4 The currently registered process has to be controlled by relevant in-process controls and no changes (widening or deletion of limits) are required to these controls.

5. The specifications of the finished product or intermediates are unchanged.

6. The new process must lead to an identical product regarding all aspects of quality, safety and efficacy.

7. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or industrial scale batch and at least 3 months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a direct comparison of the present process and the new process.

2. For semi-solid and liquid products in which the active substance is present in non-dissolved form: appropriate validation of the change including microscopic imaging of particles to check for visible changes in morphology; comparative size distribution data by an appropriate method.

3. For solid dosage forms: dissolution profile data of one representative production batch and comparative data of the last three batches from the previous process; data on the next two full production batches should be available on request or reported if outside specification (with proposed action). For herbal medicinal products, comparative disintegration data may be acceptable.

4. Justification for not submitting a new bioequivalence study according to the relevant (Human or Veterinary) guidance on Bioavailability.

5. For changes to process parameter(s) that have been considered to have no impact on the quality of the finished product, declaration to this effect reached in the context of the previously approved risk assessment.

6. Copy of approved release and end-of-shelf life specifications.

7. Batch analysis data (in a comparative tabulated format) on a minimum of one batch manufactured to both the currently approved and the proposed process. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorisation holder if outside specification (with proposed action).

8. Declaration that relevant stability studies have been started under ICH/VICH conditions, as appropriate, (with indication of the batch numbers concerned) and relevant stability parameters have been assessed in at least one pilot scale or industrial scale batch and at least 3 months satisfactory stability data are at the disposal of the applicant at time of notification and that the stability profile is similar to the currently registered situation. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

B.II.b.4 Change in the batch size (including batch size ranges) of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Up to 10-fold compared to the originally approved batch size	**1, 2, 3, 4, 5, 7**	**1, 4**	**IA**
b) Downscaling down to 10-fold	**1, 2, 3, 4, 5, 6**	**1, 4**	**IA**
c) The change requires assessment of the comparability of a biological/immunological medicinal product or the change in batch size requires a new bioequivalence study			**II**
d) The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes			**II**

e) More than 10-fold increase compared to the originally approved batch size for immediate release (oral) pharmaceutical forms		**1, 2, 3, 4, 5, 6**	**IB**
f) The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)		**1, 2, 3, 4, 5, 6**	**IB**

Conditions

1. The change does not affect reproducibility and/or consistency of the product.

2. The change relates to conventional immediate release oral pharmaceutical forms or to non-sterile liquid based pharmaceutical forms.

3. Any changes to the manufacturing method and/or to the in-process controls are only those necessitated by the change in batch-size, e.g. use of different sized equipment.

4. Validation scheme is available or validation of the manufacture has been successfully carried out according to the current protocol with at least three batches at the proposed new batch size in accordance with the relevant guidelines.

5. The product concerned is not a biological/immunological medicinal product.

6. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.

7. The batch size is within the 10-fold range of the batch size foreseen when the marketing authorisation was granted or following a subsequent change not agreed as a Type IA variation.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

2. Batch analysis data (in a comparative tabulated format) on a minimum of one production batch manufactured to both the currently approved and the proposed sizes. Batch data on the next two full production batches should be made available upon request and reported by the MAH if outside specifications (with proposed action).

3. Copy of approved release and end-of-shelf life specifications.

4. Where relevant the batch numbers, corresponding batch size and the manufacturing date of batches (≥ 3) used in the validation study should be indicated or validation protocol (scheme) be submitted.

5. The validation results should be provided

6. The results of stability studies that have been carried out under ICH/VICH conditions, on the relevant stability parameters, on at least one pilot or industrial scale batch, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). For biologicals/immunologicals: a declaration that an assessment of comparability is not required.

B.II.b.5 Change to in-process tests or limits applied during the manufacture of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Tightening of in-process limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new test(s) and limits	**1, 2, 5, 6**	**1, 2, 3, 4, 5, 7**	**IA**
c) Deletion of a non-significant in-process test	**1, 2, 7**	**1, 2, 6**	**IA**

d) Deletion of an in-process test which may have a significant effect on the overall quality of the finished product			**II**
e) Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product			**II**
f) Addition or replacement of an in-process test as a result of a safety or quality issue		**1, 2, 3, 4, 5, 7**	**IB**

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).

2. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.

3. Any change should be within the range of currently approved limits.

4. The test procedure remains the same, or changes in the test procedure are minor.

5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

6. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods).

7. The in-process test does not concern the control of a critical parameter, e.g.:

   assay,

   impurities (unless a particular solvent is definitely not used in the manufacture)

   any critical physical characteristics (particle size, bulk, tapped density, etc.)

   identity test (unless there is a suitable alternative control already present)

   microbiological control (unless not required for the particular dosage form)

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

2. Comparative table of current and proposed in-process tests and limits.

3. Details of any new analytical method and validation data, where relevant.

4. Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the finished product for all specification parameters.

5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch manufactured using the current and new in-process tests. For herbal medicinal products, comparative disintegration data may be acceptable.

6 Justification/risk assessment showing that the in-process test is non-significant or that it is obsolete.

7. Justification of the new in-process test and limits.

B.II.c) *Control of excipients*

B.II.c.1 Change in the specification parameters and/or limits of an excipient	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new specification parameter to the specification with its corresponding test method	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 6, 8**	**IA**
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	**1, 2, 8**	**1, 2, 7**	**IA**
d) Change outside the approved specifications limits range			**II**
e) Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product			**II**
f) Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method, as a result of a safety or quality issue		**1, 2, 3, 4, 5, 6, 8**	**IB**
g) Where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State for the excipient, a change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country		**1, 2, 3, 4, 5, 6, 8**	**IB**

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).

2. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.

3. Any change should be within the range of currently approved limits.

4. The test procedure remains the same, or changes in the test procedure are minor.

5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

6. The test method is not a biological/immunological/immunochemical method, or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods)

7. The change does not concern a genotoxic impurity.

8. The specification parameter does not concern the control of a critical parameter, e.g.:

   impurities (unless a particular solvent is definitely not used in the manufacture of the excipient)

   any critical physical characteristics (particle size, bulk, tapped density, etc.)

   identity test (unless there is a suitable alternative control already present)

   microbiological control (unless not required for the particular dosage form)

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

2. Comparative table of current and proposed specifications.

3. Details of any new analytical method and validation data, where relevant.

4. Batch analysis data on two production batches (3 production batches for biological excipients) of the excipient for all specification parameters.

5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the excipient complying with the current and proposed specification. For herbal medicinal products comparative disintegration data may be acceptable.

6. Justification for not submitting a new bioequivalence study according to the relevant (Human, Veterinary) Guideline on *Bioavailability,* if appropriate.

7. Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.

8. Justification of the new specification parameter and the limits.

B.II.c.2 Change in test procedure for an excipient	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Minor changes to an approved test procedure	**1, 2, 3, 4**	**1, 2**	**IA**
b) Deletion of a test procedure if an alternative test procedure is already authorised	**5**	**1**	**IA**
c) Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent			**II**
d) Other changes to a test procedure (including replacement or addition)		**1, 2**	**IB**

Conditions

1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.

2. There have been no changes of the total impurity limits; no new unqualified impurities are detected.

3. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).

4. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods).

5. An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA/IA(IN) notification.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).

2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.II.c.3 Change in source of an excipient or reagent with TSE risk	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) From TSE risk material to vegetable or synthetic origin			
1. For excipients or reagents not used in the manufacture of a biological/immunological active substance or in a biological/immunological medicinal product	**1**	**1**	**IA**
2. For excipients or reagents used in the manufacture of a biological/immunological active substance or in a biological/immunological medicinal product		**1, 2**	**IB**
b) Change or introduction of a TSE risk material or replacement of a TSE risk material from a different TSE risk material, not covered by a TSE certificate of suitability			**II**

Conditions

1. Excipient and finished product release and end of shelf life specifications remain the same.

Documentation

1. Declaration from the manufacturer or the marketing authorisation holder of the material that it is purely of vegetable or synthetic origin.

2. Study of equivalence of the materials and the impact on production of the final material and impact on behaviour (e.g. dissolution characteristics) of the finished product.

B.II.c.4 Change in synthesis or recovery of a non-pharmacopoeial excipient (when described in the dossier) or a novel excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Minor change in synthesis or recovery of a non-pharmacopoeial excipient or a novel excipient	**1, 2**	**1, 2, 3, 4**	**IA**
b) The specifications are affected or there is a change in physico-chemical properties of the excipient which may affect the quality of the finished product.			**II**
c) The excipient is a biological/immunological substance			**II**

Conditions

1. The synthetic route and specifications are identical and there is no change in qualitative and quantitative impurity profile (excluding residual solvents, provided they are controlled in accordance with ICH/VICH limits), or in physico-chemical properties.

2. Adjuvants are excluded.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

2. Batch analysis data (in a comparative tabulated format) of at least two batches (minimum pilot scale) of the excipient manufactured according to the old and the new process.

3. Where appropriate, comparative dissolution profile data for the finished product of at least two batches (minimum pilot scale). For herbal medicinal products, comparative disintegration data may be acceptable.

4. Copy of approved and new (if applicable) specifications of the excipient.

B.II.d) *Control of finished product*

B.II.d.1 Change in the specification parameters and/or limits of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Tightening of specification limits for medicinal products subject to Official Control Authority Batch Release	**1, 2, 3, 4**	**1, 2**	**IA_{IN}**
c) Addition of a new specification parameter to the specification with its corresponding test method	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 5, 7**	**IA**
d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter such as odour and taste or identification test for a colouring or flavouring material)	**1, 2, 9**	**1, 2, 6**	**IA**
e) Change outside the approved specifications limits range			**II**
f) Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product			**II**
g) Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method as a result of a safety or quality issue		**1, 2, 3, 4, 5, 7**	**IB**
h) Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur for the finished product (*)	**1, 2, 3, 4, 7, 8**	**1, 2**	**IA_{IN}**
i) Ph. Eur. 2.9.40 Uniformity of dosage units is introduced to replace the currently registered method, either Ph. Eur. 2.9.5 (Uniformity of mass) or Ph. Eur. 2.9.6 (Uniformity of content)	**1, 2,10**	**1, 2, 4**	**IA**

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure), unless the supporting documentation has been already assessed and approved within another procedure.

2. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.

3. Any change should be within the range of currently approved limits.

4. The test procedure remains the same, or changes in the test procedure are minor.

5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

6. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance.

7. The change does not concern any impurities (including genotoxic) or dissolution.

8. The change concerns the updating of the microbial control limits to be in line with the current Pharmacopoeia, and the currently registered microbial control limits (present situation) are in line with the pre January 2008 (non-harmonised) situation and does not include any additional specified controls over the Pharmacopoeia requirements for the particular dosage form and the proposed controls are in line with the harmonised monograph.

9. The specification parameter or proposal for the specific dosage form does not concern a critical parameter for example:

   assay,

   impurities (unless a particular solvent is definitely not used in the manufacture of the finished product)

   any critical physical characteristics (hardness or friability for uncoated tablets, dimensions, etc.)

   a test that is required for the particular dosage form in accordance with the general notices of the Ph. Eur.;

   any request for skip testing.

10. The proposed control is fully in line with the Table 2.9.40.-1 of Ph. Eur. 2.9.40 monograph, and does not include the alternative proposal for testing uniformity of dosage units by Mass Variation instead of Content Uniformity when the latter is specified in Table 2.9.40.-1.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

2. Comparative table of current and proposed specifications.

3. Details of any new analytical method and validation data, where relevant.

4. Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the finished product for all specification parameters

5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch complying with the current and proposed specification. For herbal medicinal products, comparative disintegration data may be acceptable.

6 Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.

7. Justification of the new specification parameter and the limits

(*) *Note:* there is no need to notify the competent authorities of an updated monograph of the European pharmacopoeia or a national pharmacopoeia of a Member State in the case that reference is made to the 'current edition' in the dossier of an authorised medicinal product. This variation therefore applies to cases where no reference to the updated monograph of the pharmacopoeia was contained in the technical dossier and the variation is made to make reference to the updated version.

B.II.d.2 Change in test procedure for the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Minor changes to an approved test procedure	**1, 2, 3, 4,**	**1,2**	**IA**
b) Deletion of a test procedure if an alternative method is already authorised	**4**	**1**	**IA**

c) Substantial change to, or replacement of, a biological/immunological/immunochemical test method or a method using a biological reagent or replacement of a biological reference preparation not covered by an approved protocol			**II**
d) Other changes to a test procedure (including replacement or addition)		**1, 2**	**IB**
e) Update of the test procedure to comply with the updated general monograph in the Ph. Eur.	**2, 3, 4, 5**	**1**	**IA**
f) To reflect compliance with the Ph.Eur. and remove reference to the outdated internal test method and test method number (*)	**2, 3, 4, 5**	**1**	**IA**

Conditions

1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.

2. There have been no changes of the total impurity limits; no new unqualified impurities are detected

3. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method);

4. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods).

5. The registered test procedure already refers to the general monograph of the Ph. Eur. and any changes are minor in nature and require update of the technical dossier.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).

2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent.; This requirement is not applicable in case of an addition of a new test procedure.

(*) *Note*: there is no need to notify the competent authorities of an updated monograph of the European pharmacopoeia in the case that reference is made to the 'current edition' in the dossier of an authorised medicinal product.

B.II.d.3 Variations related to the introduction of real-time release or parametric release in the manufacture of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II

B.II.e) *Container closure system*

B.II.e.1 Change in immediate packaging of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Qualitative and quantitative composition			
1. Solid pharmaceutical forms	**1, 2, 3**	**1, 2, 3, 4, 6**	**IA**

2. Semi-solid and non-sterile liquid pharmaceutical forms		**1, 2, 3, 5, 6**	**IB**
3. Sterile medicinal products and biological/immunological medicinal products.			**II**
4. The change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life.			**II**
b) Change in type of container or addition of a new container			
1. Solid, semi-solid and non-sterile liquid pharmaceutical forms		**1, 2, 3, 5, 6, 7**	**IB**
2. Sterile medicinal products and biological/immunological medicinal products			**II**
3. Deletion of an immediate packaging container that does not lead to the complete deletion of a strength or pharmaceutical form	**4**	**1, 8**	**IA**

Conditions

1. The change only concerns the same packaging/container type (e.g. blister to blister).

2. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.

3. Relevant stability studies have been started under ICH/VICH conditions and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least 3 months satisfactory stability data are at the disposal of the applicant at time of implementation. However, if the proposed packaging is more resistant than the existing packaging, e.g. thicker blister packaging, the 3 months' stability data do not yet have to be available. These studies must be finalised and the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

4. The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including revised product information as appropriate.

2. Appropriate data on the new packaging (comparative data on permeability, e.g. for O_2, CO_2 moisture).

3. Where appropriate, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack), including confirmation that the material complies with relevant pharmacopoeial requirements or legislation of the Union on plastic material and objects in contact with foodstuffs.

4. A declaration that the required stability studies have been started under ICH/VICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

5. The results of stability studies that have been carried out under ICH/VICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

6. Comparative table of the current and proposed immediate packaging specifications, if applicable.

7. Samples of the new container/closure where applicable (see NTA, Requirements for samples in the Member States/EMA).

8. Declaration that the remaining pack-size(s) is/are consistent with the dosage regimen and duration of treatment and adequate for the dosing instructions as approved in the summary of product characteristics.

Note: for B.II.e.1.b), applicants are reminded that any change which results in a 'new pharmaceutical form' requires the submission of an Extension application.

B.II.e.2 Change in the specification parameters and/or limits of the immediate packaging of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new specification parameter to the specification with its corresponding test method	**1, 2, 5**	**1, 2, 3, 4, 6**	**IA**
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	**1, 2**	**1, 2, 5**	**IA**
d) Addition or replacement of a specification parameter as a result of a safety or quality issue		**1, 2, 3, 4, 6**	**IB**

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).

2. The change does not result from unexpected events arising during manufacture

3. Any change should be within the range of currently approved limits.

4. The test procedure remains the same, or changes in the test procedure are minor.

5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

2. Comparative table of current and proposed specifications.

3. Details of any new analytical method and validation data, where relevant.

4. Batch analysis data on two batches of the immediate packaging for all specification parameters.

5. Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.

6. Justification of the new specification parameter and the limits.

B.II.e.3 Change in test procedure for the immediate packaging of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Minor changes to an approved test procedure	**1, 2, 3**	**1, 2**	**IA**

b) Other changes to a test procedure (including replacement or addition)	**1, 3, 4**	**1, 2**	**IA**
c) Deletion of a test procedure if an alternative test procedure is already authorised	**5**	**1**	**IA**

Conditions

1. Appropriate validation studies have been performed in accordance with the relevant guidelines and validation studies show that the updated test procedure is at least equivalent to the former test procedure.

2. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).

3. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

4. The active substance/finished product is not biological/immunological.

5. An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA/IA(IN) notification.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a description of the analytical methodology, a summary of validation data.

2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.II.e.4 Change in shape or dimensions of the container or closure (immediate packaging)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Non-sterile medicinal products	**1, 2, 3**	**1, 2, 4**	**IA**
b) The change in shape or dimensions concerns a fundamental part of the packaging material, which may have a significant impact on the delivery, use, safety or stability of the finished product			**II**
c) Sterile medicinal products		**1, 2, 3, 4**	**IB**

Conditions

1. No change in the qualitative or quantitative composition of the container.

2. The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the finished product.

3. In case of a change in the headspace or a change in the surface/volume ratio, stability studies in accordance with the relevant guidelines have been started and relevant stability parameters have been assessed in at least two pilot scale (three for biological/immunological medicinal products) or industrial scale batches and at least 3 months (6 months for biological/immunological medicinal products) stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including description, detailed drawing and composition of the container or closure material, and including revised product information as appropriate.

2. Samples of the new container/closure where applicable (see NTA, Requirements for samples in the Member States).

3. Revalidation studies have been performed in case of sterile products terminally sterilised. The batch numbers of the batches used in the revalidation studies should be indicated, where applicable.

4. In case of a change in the headspace or a change in the surface/volume ratio, a declaration that the required stability studies have been started under ICH/VICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation for a Type IA notification and time of submission of a Type IB notification, and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

B.II.e.5 Change in pack size of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Change in the number of units (e.g. tablets, ampoules, etc.) in a pack			
1. Change within the range of the currently approved pack sizes	**1, 2**	**1, 3**	**IA_{IN}**
2. Change outside the range of the currently approved pack sizes		**1, 2, 3**	**IB**
b) Deletion of pack size(s)	**3**	**1, 2**	**IA**
c) Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products			**II**
d) Change in the fill weight/fill volume of non-parenteral multi-dose (or single-dose, partial use) products		**1, 2, 3**	**IB**

Conditions

1. New pack size should be consistent with the posology and treatment duration as approved in the Summary of Product Characteristics.

2. The primary packaging material remains the same.

3. The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the Summary of Product Characteristics.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate) including revised product information as appropriate.

2. Justification for the new/remaining pack-size, showing that the new/remaining size is/are consistent with the dosage regimen and duration of treatment as approved in the summary of product characteristics

3. Declaration that stability studies will be conducted in accordance with the relevant guidelines for products where stability parameters could be affected. Data to be reported only if outside specifications (with proposed action).

Note: for B.II.e.5.c) and d), applicants are reminded that any changes to the 'strength' of the medicinal product require the submission of an Extension application.

B.II.e.6 Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used))	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Change that affects the product information	1	1	IA_{IN}
b) Change that does not affect the product information	1	1	IA

Conditions

1. The change does not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished product.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including revised product information as appropriate.

B.II.e.7 Change in supplier of packaging components or devices (when mentioned in the dossier)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Deletion of a supplier	1	1	IA
b) Replacement or addition of a supplier	1, 2, 3, 4	1, 2, 3	IA
c) Any change to suppliers of spacer devices for metered dose inhalers			II

Conditions

1. No deletion of packaging component or device.

2. The qualitative and quantitative composition of the packaging components/device and design specifications remain the same.

3. The specifications and quality control method are at least equivalent.

4. The sterilisation method and conditions remain the same, if applicable.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

2. For devices for medicinal products for human use, proof of CE marking.

3. Comparative table of current and proposed specifications, if applicable.

B.II.f) *Stability*

B.II.f.1 Change in the shelf-life or storage conditions of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Reduction of the shelf life of the finished product			
1. As packaged for sale	1	1, 2, 3	IA_{IN}

2. After first opening	**1**	**1, 2, 3**	**IA_{IN}**
3. After dilution or reconstitution	**1**	**1, 2, 3**	**IA_{IN}**
b) Extension of the shelf life of the finished product			
1. As packaged for sale (supported by real time data)		**1, 2, 3**	**IB**
2. After first opening (supported by real time data)		**1, 2, 3**	**IB**
3. After dilution or reconstitution (supported by real time data)		**1, 2, 3**	**IB**
4. Extension of the shelf-life based on extrapolation of stability data not in accordance with ICH/VICH guidelines (*)			**II**
5. Extension of the shelf-life of a biological/immunological medicinal product in accordance with an approved stability protocol.		**1, 2, 3**	**IB**
c) Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol			**II**
d) Change in storage conditions of the finished product or the diluted/reconstituted product		**1, 2, 3**	**IB**
e) Change to an approved stability protocol	**1, 2**	**1, 4**	**IA**

Conditions

1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.

2. The change does not concern a widening of the acceptance criteria in the parameters tested, a removal of stability indicating parameters or a reduction in the frequency of testing.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate). This must contain results of appropriate real time stability studies (covering the entire shelf life) conducted in accordance with the relevant stability guidelines on at least two pilot scale batches [1] of the finished product in the authorised packaging material and/or after first opening or reconstitution, as appropriate; where applicable, results of appropriate microbiological testing should be included.

2. Revised product information

3. Copy of approved end of shelf life finished product specification and where applicable, specifications after dilution/reconstitution or first opening.

4. Justification for the proposed change(s).

(*) *Note:* extrapolation not applicable for biological/immunological medicinal product.

[1] Pilot scale batches can be accepted with a commitment to verify the shelf life on production scale batches.

B.II.g) *Design Space and post approval change management protocol*

B.II.g.1 Introduction of a new design space or extension of an approved design space for the finished product, concerning:	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) One or more unit operations in the manufacturing process of the finished product including the resulting in-process controls and/or test procedures		**1, 2, 3**	**II**
b) Test procedures for excipients/intermediates and/or the finished product.		**1, 2, 3**	**II**

Documentation

1. Results from product and process development studies (including risk assessment and multivariate studies, as appropriate) demonstrating that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the finished product has been achieved.

2. Description of the design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges.

3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

B.II.g.2 Introduction of a post approval change management protocol related to the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
		1, 2, 3	**II**

Documentation

1. Detailed description for the proposed change.

2. Change management protocol related to the finished product.

3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

B.II.g.3 Deletion of an approved change management protocol related to the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1	**1, 2**	**IA_{IN}**

Conditions

1. The deletion of the approved change management protocol related to the finish product is not a result of unexpected events or out of specification results during the implementation of the change(s) described in the protocol and does not have any effect on the already approved information in the dossier.

Documentation

1. Justification for the proposed deletion.

2. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

B.II.g.4 Changes to an approved change management protocol	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Major changes to an approved change management protocol			**II**

b) Minor changes to an approved change management protocol that do not change the strategy defined in the protocol		**1**	**IB**

Documentation

1. Declaration that any change should be within the range of currently approved limits. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.

B.II.g.5 Implementation of changes foreseen in an approved change management protocol	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) The implementation of the change requires no further supportive data	**1**	**1, 2, 4**	**IA_{IN}**
b) The implementation of the change requires further supportive data		**1, 2, 3, 4**	**IB**
c) Implementation of a change for a biological/immunological medicinal product		**1, 2, 3, 4, 5**	**IB**

Conditions

1. The proposed change has been performed fully in line with the approved change management protocol, which requires its immediate notification following implementation.

Documentation

1. Reference to the approved change management protocol.
2. Declaration that the change is in accordance with the approved change management and that the study results meet the acceptance criteria specified in the protocol. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.
3. Results of the studies performed in accordance with the approved change management protocol.
4. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).
5. Copy of approved specifications of the finished product.

B.II.h *Adventitious Agents Safety*

B.II.h.1 Update to the 'Adventitious Agents Safety Evaluation' information (section 3.2.A.2)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Studies related to manufacturing steps investigated for the first time for one or more adventitious agents			**II**
b) Replacement of obsolete studies related to manufacturing steps and adventitious agents already reported in the dossier			
1) with modification of risk assessment			**II**
2) without modification of risk assessment		**1, 2, 3**	**IB**

Documentation

1. Amendment of the relevant section(s) of the dossiers including the introduction of the new studies to investigate the capability of manufacturing steps to inactivate/reduce adventitious agents.

2. Justification that the studies do not modify the risk assessment.

3. Amendment of product information (where applicable).

B.III CEP/TSE/MONOGRAPHS

B.III.1 Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability:	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
For an active substance **For a starting material/reagent/intermediate used in the manufacturing process of the active substance** **For an excipient**			
a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.			
1. New certificate from an already approved manufacturer	**1, 2, 3, 4, 5, 8, 11**	**1, 2, 3, 4, 5**	**IA_{IN}**
2. Updated certificate from an already approved manufacturer	**1, 2, 3, 4, 8**	**1, 2, 3, 4, 5**	**IA**
3. New certificate from a new manufacturer (replacement or addition)	**1, 2, 3, 4, 5, 8, 11**	**1, 2, 3, 4, 5**	**IA_{IN}**
4. Deletion of certificates (in case multiple certificates exist per material)	**10**	**3**	**IA**
5. New certificate for a non-sterile active substance that is to be used in a sterile medicinal product, where water is used in the last steps of the synthesis and the material is not claimed to be endotoxin free		**1, 2, 3, 4, 5, 6**	**IB**
b) European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/intermediate/or excipient			
1. New certificate for an active substance from a new or an already approved manufacturer	**3, 5, 6, 11**	**1, 2, 3, 4, 5**	**IA_{IN}**
2. New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer	**3, 6, 9**	**1, 2, 3, 4, 5**	**IA**
3. Updated certificate from an already approved manufacturer	**7, 9**	**1, 2, 3, 4, 5**	**IA**
4. Deletion of certificates (in case multiple certificates exist per material)	**10**	**3**	**IA**
5. New/updated certificate from an already-approved/new manufacturer using materials of human or animal origin for which an assessment of the risk with respect to potential contamination with adventitious agents is required			**II**

Conditions

1. The finished product release and end of shelf life specifications remain the same.

2. Unchanged (excluding tightening) additional (to Ph. Eur.) specifications for impurities (excluding residual solvents, provided they are in compliance with ICH/VICH) and product specific requirements (e.g. particle size profiles, polymorphic form), if applicable.

3. The manufacturing process of the active substance, starting material/reagent/intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.

4. For active substance only, it will be tested immediately prior to use if no retest period is included in the Ph. Eur. Certificate of Suitability or if data to support a retest period is not already provided in the dossier.

5. The active substance/starting material/reagent/intermediate/excipient is not sterile.

6. The substance is not included in a veterinary medicinal product for use in animal species susceptible to TSE

7. For veterinary medicinal products: there has been no change in the source of material.

8. For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.

9. If Gelatine manufactured from bones is to be used in a medicinal product for parenteral use, it should **only** be manufactured in compliance with the relevant country requirements.

10. At least one manufacturer for the same substance remains in the dossier.

11. If the active substance is a not a sterile substance but is to be used in a sterile medicinal product then according to the CEP it must not use water during the last steps of the synthesis or if it does the active substance must also be claimed to be free from bacterial endotoxins.

Documentation

1. Copy of the current (updated) Ph. Eur. Certificate of Suitability.

2. In case of an addition of a manufacturing site, the variation application form should clearly outline the 'present' and 'proposed' manufacturers as listed in section 2.5 of the application form.

3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).

4. Where applicable, a document providing information of any materials falling within the scope of the *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products* including those which are used in the manufacture of the active substance/excipient. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use.

   For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant).

5. Where applicable, for active substance, a declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application where the active substance is used as a starting material and a declaration by the QP of each of the manufacturing authorisation holders listed in the application as responsible for batch release. These declarations should state that the active substance manufacturer(s) referred to in the application operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances — see the note under variation No B.II.b.1. The manufacture of intermediates also require a QP declaration, while as far as any updates to certificates for active substances and intermediates are concerned, a QP declaration is only required if, compared to the previously registered version of the certificate, there is a change to the actual listed manufacturing sites.

6. Suitable evidence to confirm compliance of the water used in the final steps of the synthesis of the active substance with the corresponding requirements on quality of water for pharmaceutical use.

B.III.2 Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Change of specification(s) of a former non-EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State			
1. Active substance	**1, 2, 3, 4, 5**	**1, 2, 3, 4**	**IA_{IN}**
2. Excipient/active substance starting material	**1, 2,4**	**1, 2, 3, 4**	**IA**
b) Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	**1, 2, 4, 5**	**1, 2, 3, 4**	**IA**
c) Change in specifications from a national pharmacopoeia of a Member State to the Ph. Eur.	**1, 4, 5**	**1, 2, 3, 4**	**IA**

Conditions

1. The change is made exclusively to fully comply with the pharmacopoeia. All the tests in the specification need to correspond to the pharmacopoeial standard after the change, except any additional supplementary tests.

2. Additional specifications to the pharmacopoeia for product specific properties are unchanged (e.g. particle size profiles, polymorphic form or, e.g. bioassays, aggregates).

3. No significant changes in qualitative and quantitative impurities profile unless the specifications are tightened

4. Additional validation of a new or changed pharmacopoeial method is not required

5. For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

2. Comparative table of current and proposed specifications.

3. Batch analysis data (in a comparative tabulated format) on two production batches of the relevant substance for all tests in the new specification and additionally, where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch. For herbal medicinal products, comparative disintegration data may be acceptable.

4. Data to demonstrate the suitability of the monograph to control the substance, e.g. a comparison of the potential impurities with the transparency note of the monograph.

Note: there is no need to notify the competent authorities of an updated monograph of the European pharmacopoeia or a national pharmacopoeia of a Member State in the case that reference is made to the 'current edition' in the dossier of an authorised medicinal product.

B.IV MEDICAL DEVICES

B.IV.1 Change of a measuring or administration device	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Addition or replacement of a device which is not an integrated part of the primary packaging			
1. Device with CE marking	**1, 2, 3, 6, 7**	**1, 2, 4**	**IA_{IN}**
2. Device without CE marking for veterinary products only		**1, 3, 4**	**IB**
3. Spacer device for metered dose inhalers or other device which may have a significant impact on the delivery of the active substance in the product (e.g. nebuliser)			**II**
b) Deletion of a device	**4, 5**	**1, 5**	**IA_{IN}**
c) Addition or replacement of a device which is an integrated part of the primary packaging			**II**

Conditions

1. The proposed measuring or administration device must accurately deliver the required dose for the product concerned in line with the approved posology and results of such studies should be available.

2. The new device is compatible with the medicinal product.

3. The change should not lead to substantial amendments of the product information.

4. The medicinal product can still be accurately delivered.

5. For veterinary medicinal products, the device is not crucial for the safety of the person administering the product.

6. The medical device is not used as a solvent of the medicinal product.

7. If a measuring function is intended the CE marking should cover the measuring function.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including description, detailed drawing and composition of the device material and supplier where appropriate, and including revised product information as appropriate.

2. Proof of CE marking and if a measuring function is intended the proof of CE marking should also include the 4 digit notified body number.

3. Data to demonstrate accuracy, precision and compatibility of the device.

4. Samples of the new device where applicable (see NTA, Requirements for samples in the Member States).

5. Justification for the deletion of the device.

Note: for B.IV.1.c), applicants are reminded that any change which results in a 'new pharmaceutical form' requires the submission of an Extension application.

B.IV.2 Change in specification parameters and/or limits of a measuring or administration device for veterinary medicinal products	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Tightening of specification limits	1, 2, 3, 4	1, 2	IA
b) Addition of a new specification parameter to the specification with its corresponding test method	1, 2, 5	1, 2, 3, 4, 6	IA
c) Widening of the approved specifications limits, which has a significant effect on the overall quality of the device			II
d) Deletion of a specification parameter that has a significant effect on the overall quality of the device			II
e) Addition of a specification parameter as a result of a safety or quality issue		1, 2, 3, 4, 6	IB
f) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	1, 2	1, 2, 5	IA

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure) unless the supporting documentation has been already assessed and approved within another procedure.

2. The change should not be the result of unexpected events arising during manufacture.

3. Any change should be within the range of currently approved limits.

4. The test procedure remains the same

5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

2. Comparative table of current and proposed specifications.

3. Details of any new analytical method and summary of validation data.

4. Batch analysis data on two production batches for all tests in the new specification.

5. Justification/risk assessment showing that the parameter is non-significant based or that it is obsolete.

6. Justification for the new specification parameter and the limits

B.IV.3 Change in test procedure of a measuring or administration device for veterinary medicinal products	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Minor change to an approved test procedure	1, 2	1, 2	IA

b) Other changes to a test procedure (including replacement or addition)	**1, 3**	**1, 2**	**IA**
c) Deletion of a test procedure if an alternative test procedure is already authorised	**4**	**1**	**IA**

Conditions

1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.

2. The method of analysis should remain the same.

3. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way

4. An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA/IA(IN) notification.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a description of the analytical methodology and a summary of validation data.

2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.V. CHANGES TO A MARKETING AUTHORISATION RESULTING FROM OTHER REGULATORY PROCEDURES

B.V.a) *PMF/VAMF*

B.V.a.1 Inclusion of a new, updated or amended Plasma Master File in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) First-time inclusion of a new Plasma Master File affecting the properties of the finished product			**II**
b) First-time inclusion of a new Plasma Master File not affecting the properties of the finished product		**1, 2, 3, 4**	**IB**
c) Inclusion of an updated/amended Plasma Master File when changes affect the properties of the finished product		**1, 2, 3, 4**	**IB**
d) Inclusion of an updated/amended Plasma Master File when changes do not affect the properties of the finished product	**1**	**1, 2, 3, 4**	**IA_{IN}**

Conditions

1. The updated or amended Plasma Master File has been granted a certificate of compliance with legislation of the Union in accordance with Annex I of Directive 2001/83/EC.

Documentation

1. Declaration that the PMF Certificate and Evaluation Report are fully applicable for the authorised product, PMF holder has provided the PMF Certificate, Evaluation report and PMF dossier to the MAH (where the MAH is different to the PMF holder), the PMF Certificate and Evaluation Report replace the previous PMF documentation for this Marketing Authorisation.

2. PMF Certificate and Evaluation Report.

3. An expert statement outlining all the changes introduced with the certified PMF and evaluating their potential impact on the finished products including product specific risk assessments.

4. The variation application form should clearly outline the 'present' and 'proposed' PMF EMA Certificate (code number) in the MA dossier. When applicable, the variation application form should clearly list also all the other PMFs to which the medicinal product refers even if they are not the subject of the application.

B.V.a.2 Inclusion of a new, updated or amended Vaccine Antigen Master File in the marketing authorisation dossier of a medicinal product. (VAMF 2nd step procedure)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) First-time inclusion of a new Vaccine Antigen Master File			**II**
b) Inclusion of an updated/amended Vaccine Antigen Master File, when changes affect the properties of the finished product		**1, 2, 3, 4**	**IB**
c) Inclusion of an updated/amended Vaccine Antigen Master File, when changes do not affect the properties of the finished product	**1**	**1, 2, 3, 4**	**IA_{IN}**

Conditions

1. The updated or amended Vaccine Antigen Master File has been granted a certificate of compliance with legislation of the Union in accordance with Annex I to Directive 2001/83/EC.

Documentation

1. Declaration that the VAMF Certificate and Evaluation Report are fully applicable for the authorised product, VAMF holder has submitted the VAMF Certificate, Evaluation report and VAMF dossier to the MAH (where the MAH is different to the VAMF holder), the VAMF Certificate and Evaluation Report replace the previous VAMF documentation for this Marketing Authorisation.

2. VAMF Certificate and Evaluation Report.

3. An expert statement outlining all the changes introduced with the certified VAMF and evaluating their potential impact on the finished products including product specific risk assessments.

4. The variation application form should clearly outline the 'present' and 'proposed' VAMF EMA Certificate (code number) in the MA dossier. When applicable, the variation application form should clearly list also all the other VAMFs to which the medicinal product refers even if they are not the subject of the application.

B.V.b) *Referral*

B.V.b.1 Update of the quality dossier intended to implement the outcome of a Union referral procedure	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) The change implements the outcome of the referral	**1**	**1, 2**	**IA_{IN}**
b) The harmonisation of the quality dossier was not part of the referral and the update is intended to harmonise it			**II**

Conditions

1. The outcome does not require further assessment.

Documentation

1. Attached to the cover letter of the variation application: A reference to the Commission Decision concerned.

2. The changes introduced during the referral procedure should be clearly highlighted in the submission.

C. **SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES**

C.I HUMAN AND VETERINARY MEDICINAL PRODUCTS

C.I.1 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union referral procedure	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) The medicinal product is covered by the defined scope of the procedure	**1**	**1, 2, 3**	**IA_{IN}**
b) The medicinal product is not covered by the defined scope of the procedure but the change(s) implements the outcome of the procedure and no new additional data is required to be submitted by the MAH		**1, 2, 3**	**IB**
c) The medicinal product is not covered by the defined scope of the procedure but the change(s) implements the outcome of the procedure with new additional data submitted by the MAH		**1, 3**	**II**

Conditions

1. The variation implements the wording requested by the authority and it does not require the submission of additional information and/or further assessment.

Documentation

1. Attached to the cover letter of the variation application: a reference to the Commission Decision concerned or to the agreement reached by the CMDh (as applicable) with the annexed Summary of Product Characteristics, Labelling or Package Leaflet.

2. A declaration that the proposed Summary of Product Characteristics, Labelling and Package Leaflet is identical for the concerned sections to that annexed to the Commission Decision or to the agreement reached by the CMDh (as applicable).

3. Revised product information.

C.I.2 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Implementation of change(s) for which no new additional data is required to be submitted by the MAH		**1, 2**	**IB**
b) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH (e.g. comparability)			**II**

Documentation

1. Attached to the cover letter of the variation application: EMA/NCA request, if applicable.

2. Revised product information.

C.I.3 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Article 45 or 46 of Regulation (EC) No 1901/2006	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Implementation of wording agreed by the competent authority	**1**	**1, 2**	**IA_{IN}**
b) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH		**2**	**II**

Conditions

1. The variation implements the wording requested by the competent authority and it does not require the submission of additional information and/or further assessment.

Documentation

1. Attached to the cover letter of the variation application: reference to the agreement/assessment of the competent authority.

2. Revised product information.

C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
			II

Note: this variation does not apply when the new data has been submitted under variation C.I.13. In such cases, the change(s) in the SmPC, labelling and/or package leaflet is covered by the scope of variation C.I.13.

C.I.5 Change in the legal status of a medicinal product for centrally authorised products	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) For generic/hybrid/biosimilar medicinal products following an approved legal status change of the reference medicinal product		**1, 2**	**IB**
b) All other legal status changes			**II**

Documentation

1. Attached to the cover letter of the variation application: proof of authorisation of the legal status change (e.g. reference to the Commission Decision concerned).

2. Revised product information.

Note: for Nationally Authorised Products approved via MRP/DCP, the change of the legal status is to be handled at national level (not via a MRP variation).

C.I.6 Change(s) to therapeutic indication(s)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Addition of a new therapeutic indication or modification of an approved one			**II**
b) Deletion of a therapeutic indication			**IB**

Note: where the change takes place in the context of the implementation of the outcome of a referral procedure, or — for a generic/hybrid/biosimilar product — when the same change has been done for the reference product, variations C.I.1 and C.I.2 apply, respectively.

C.I.7 Deletion of:	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) a pharmaceutical form		**1, 2**	**IB**
b) a strength		**1, 2**	**IB**

Documentation

1. Declaration that the remaining product presentation(s) are adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics.

2. Revised product information

Note: in cases where a given pharmaceutical form or strength has received a marketing authorisation which is separate to the marketing authorisation for other pharmaceutical forms or strengths, the deletion of the former will not be a variation but the withdrawal of the marketing authorisation.

C.I.8 Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use (*)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location		**1, 2**	**IA_{IN}**

Documentation

1. Summary of the pharmacovigilance system, or update of the relevant elements (as applicable):

   — Proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance and a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC.

   — Contact details of the QPPV, Member States in which the QPPV resides and carries out his/her tasks

   — PSMF location

2. PSMF number (if available)

Note: This variation covers the introduction of a PSMF irrespective of whether or not the technical dossier of the MA contained a DDPS.

Once the Article 57 database is functional, changes in QPPV, including contact details (telephone and fax numbers, postal address and e-mail address) and changes to the location of the PSMF (street, city, postcode, country) may be updated through the Article 57 database only (without the need for a variation).

Where the MAH makes use of the possibility to update the above information through the Article 57 database, the MAH must indicate in the marketing authorisation that the updated information of those particulars is included in the database.

(*) For introduction of a new pharmacovigilance system for veterinary medicinal products, please refer to C.II.7.

C.I.9 Change(s) to an existing pharmacovigilance system as described in the detailed description of the pharmacovigilance system (DDPS).	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Change in the QPPV and/or QPPV contact details and/or back-up procedure	**1**	**1**	**IA_{IN}**
b) Change(s) in the safety database and/or major contractual arrangements for the fulfilment of pharmacovigilance obligations, and/or change of the site undergoing pharmacovigilance activities	**1, 2, 3**	**1**	**IA_{IN}**
c) Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system (e.g. change of the major storage/archiving location, administrative changes)	**1**	**1**	**IA**
d) Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	**4**	**1, 2**	**IA_{IN}**

Conditions

1. The pharmacovigilance system itself remains unchanged.

2. The database system has been validated (when applicable).

3. Transfer of data from other database systems has been validated (when applicable).

4. The same changes to the DDPS are introduced for all medicinal products of the same MAH (same final DDPS version)

Documentation

1. Latest version of the DDPS and, where applicable, latest version of the product specific addendum. These should include for changes to the QPPV a) summary CV of the new QPPV, b) proof of QPPV EudraVigilance registration, and c) a new statement of the MAH and the QPPV regarding their availability and the means for notification of adverse reactions signed by the new QPPV and the MAH, and reflecting any other consequential changes, e.g. to the organisation chart.

   When the QPPV and/or QPPV contact details are not included in a DDPS or no DDPS exists, the submission of a revised DDPS version is not required and the application form is to be provided.

2. Reference of the application/procedure and product in which the change(s) were accepted.

Note: C.I.9 covers changes to an existing pharmacovigilance system 1) for veterinary medicinal products and 2) for human medicinal products that have not yet introduced a PSMF.

Note for a): Once the Article 57 database is functional, changes in QPPV, including contact details (telephone and fax numbers, postal address and e-mail address) may be updated through the Article 57 database only (without the need for a variation). Where the MAH makes use of the possibility to update this information through the Article 57 database, the MAH must indicate in the marketing authorisation that the updated information of those particulars is included in the database.

Note for d): The assessment of a DDPS submitted as part of a new MAA/Extension/Variation may give rise to changes at the request of the national competent authority/EMA in this DDPS. Where this occurs, the same change(s) can be introduced to the DDPS in other marketing authorisations of the same MAH by submitting a (grouped) Type IA_{IN} variation.

C.I.10 Change in the frequency and/or date of submission of periodic safety update reports (PSUR) for human medicinal products	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1, 2	IA_{IN}

Conditions

1. The change in the frequency and/or date of submission of the PSUR has been agreed by the CHMP/CMDh/NCA

Documentation

1. Attached to the cover letter of the variation application: A reference to the agreement of the competent authority (in the case of marketing authorisations granted under the centralised procedure, the CHMP).

2. Revised frequency and/or date of submission of the PSUR (for medicinal products authorised via the centralised procedure, the full set of annexes, including the revised Annex II should be provided).

Note: this variation applies only when the PSUR cycle is specified in the marketing authorisation by other means than a reference to the list of Union reference dates and where PSUR submission is required.

C.I.11 Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Implementation of wording agreed by the competent authority	1	1, 2	IA_{IN}
b) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment by the competent authority is required (*)			II

Conditions

1. The variation implements the action requested by the authority and it does not require the submission of additional information and/or further assessment.

Documentation

1. Attached to the cover letter of the variation application: A reference to the relevant decision of the competent authority.

2. Update of the relevant section of the dossier.

Note: this variation covers the situation where the only change introduced concerns the conditions and/or obligations of the marketing authorisation, including the risk management plan and the conditions and/or obligations of marketing authorisations under exceptional circumstances and conditional marketing authorisation.

(*) the introduction of a risk management plan requested by the competent authority always requires significant assessment.

C.I.12 Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1, 2	IA_{IN}

Conditions

1. The medicinal product is included or removed from the list of medicinal products that are subject to additional monitoring (as applicable)

Documentation

1. Attached to the cover letter of the variation application: A reference to the list of medicinal products that are subject to additional monitoring

2. Revised product information

Note: this variation covers the situation where the inclusion or deletion of the black symbol and explanatory statements is not done as part of another regulatory procedure (e.g. renewal or variation procedure affecting the product information).

C.I.13 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority (*)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II

Note: in cases where the assessment by the competent authority of the data submitted leads to a change of the Summary of Product Characteristics, Labelling or Package Leaflet, the relevant amendment to the Summary of Product Characteristics, Labelling or Package Leaflet is covered by the variation.

The inclusion of the Compliance Statement provided for under Article 28(3) of Regulation (EC) No 1901/2006 is likewise covered by this variation (provided that the requirements under Regulation (EC) No 1901/2006 have been met).

(*) This variation does not apply to variations that can be considered as Type IB by default under any other section of this Annex.

C.II VETERINARY MEDICINAL PRODUCT — SPECIFIC CHANGES

C.II.1 Variations concerning a change to or addition of a non-food producing target species.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II
C.II.2 Deletion of a food producing or non-food producing target species.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Deletion as a result of a safety issue			**II**
b) Deletion not resulting from a safety issue		**1, 2**	**IB**

Documentation

1. Justification for the deletion of the target species

2. Revised product information

C.II.3 Changes to the withdrawal period for a veterinary medicinal product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II
C.II.4 Variations concerning the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II
C.II.5 Variations concerning the replacement of a strain for a veterinary vaccine against equine influenza.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II

C.II.6 Changes to the labelling or the package leaflet which are not connected with the summary of product characteristics.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Administrative information concerning the holder's representative		1	IA_{IN}
b) Other changes		1	IB

Documentation

1. Revised product information.

C.II.7 Introduction of a new Pharmacovigilance system	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Which has not been assessed by the relevant national competent authority/EMA for another product of the same MAH			II
b) Which has been assessed by the relevant national competent authority/EMA for another product of the same MAH (*)		1, 2	IB

Documentation

1. The new Detailed Description of the Pharmacovigilance System (DDPS)

2. Reference to the application/procedure and product in which the DDPS was assessed previously

(*) *Note:* this variation covers the situation where the applicability of an already assessed Pharmacovigilance System will have to be assessed for the new MAs concerned (e.g. at time of transfer of MA)

C.II.8 Change in the frequency and/or date of submission of periodic safety update reports (PSUR)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA_{IN}

Conditions

1. The change in the frequency and/or date of submission of the PSUR has been agreed by the competent authority

Documentation

1. Attached to the cover letter of the variation application: The relevant decision of the competent authority

D. **PMF/VAMF**

D.1 Change in the name and/or address of the VAMF certificate holder	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA_{IN}

Conditions

1. The VAMF certificate holder must remain the same legal entity.

Documentation

1. A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or new address is mentioned.

D.2 Change in the name and/or address of the PMF certificate holder	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA_{IN}

Conditions

1. The PMF certificate holder must remain the same legal entity.

Documentation

1. A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or new address is mentioned.

D.3 Change or transfer of the current PMF certificate holder to a new PMF certificate holder, i.e. different legal entity	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2, 3, 4, 5, 6	IA_{IN}

Documentation

1. A document including the identification (name and address) of the current PMF Holder (transferor) and the identification (name and address) of the person to whom the transfer is to be granted (transferee) together with the proposed implementation date — signed by both companies.

2. Copy of the latest PMF Certificate page 'EMA Plasma Master File (PMF) Certificate of compliance with Community legislation'.

3. Proof of establishment of the new holder (Excerpt of the commercial register and the English translation of it) — signed by both companies.

4. Confirmation of the transfer of the complete PMF documentation since the initial PMF certification to the transferee — signed by both companies.

5. Letter of Authorisation including contact details of the person responsible for communication between the competent authority and the PMF holder — signed by the transferee.

6. Letter of Undertaking to fulfil all open and remaining commitments (if any) — signed by the transferee.

D.4 Change in the name and/or address of a blood establishment including blood/plasma collection centres	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1, 2	1, 2, 3	IA

Conditions

1. The blood establishment must remain the same legal entity.

2. The change must be administrative (e.g. merger, take over); change in the name of the blood establishment/collection centre provided the blood establishment must remain the same.

Documentation

1. Signed declaration that the change does not involve a change of the quality system within the blood establishment.

2. Signed declaration that there is no change in the list of the collection centres.

3. Updated relevant sections and annexes of the PMF dossier.

D.5 Replacement or addition of a blood/plasma collection centre within a blood establishment already included in the PMF	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2, 3	IB

Documentation

1. Epidemiological data for viral markers related to the blood/plasma collection centre covering the last 3 years. For newly opened centre(s) or in case no data are yet available, a declaration that epidemiological data will be provided at the time of the next annual update(s).

2. Statement that the centre is working under the same conditions as the other centres belonging to the blood establishment, as specified in the standard contract between blood establishment and PMF holder.

3. Updated relevant sections and annexes of the PMF dossier.

D.6 Deletion or change of status (operational/non-operational) of establishment(s)/centre(s) used for blood/plasma collection or in the testing of donations and plasma pools	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1, 2	**1**	**IA**

Conditions

1. The reason for deletion or change of status should not be related to a GMP issue.

2. The establishments(s)/centre(s) should comply with the legislation in terms of inspections in case of change of status from non-operational to operational.

Documentation

1. Updated relevant sections and annexes of the PMF dossier.

D.7 Addition of a new blood establishment for the collection of blood/plasma not included in the PMF	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II

D.8 Replacement or addition of a blood centre for testing of donations and/or plasma pools within an establishment already included in the PMF	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
		1, 2	**IB**

Documentation

1. Statement that the testing is performed following the same SOPs and/or test methods as already accepted.

2. Updated relevant sections and annexes of the PMF dossier.

D.9 Addition of a new blood establishment for testing of donations and/or plasma pool not included in the PMF	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II

D.10 Replacement or addition of a new blood establishment or centre(s) in which storage of plasma is carried out	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
		1, 2	**IB**

Documentation

1. Statement that the storage centre is working following the same SOPs as the already accepted establishment.

2. Updated relevant sections and annexes of the PMF dossier.

D.11 Deletion of a blood establishment or centre(s) in which storage of plasma is carried out	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA

Conditions

1. The reason for deletion should not be related to a GMP issues.

Documentation

1. Updated relevant sections and annexes of the PMF dossier.

D.12 Replacement or addition of an organisation involved in the transport of plasma.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1	IB

Documentation

1. Updated relevant sections and annexes of the PMF dossier, including a list of all the blood establishments using this transport organisation, a summary of the system in place to ensure that the transport is performed under appropriate conditions (time, temperature and GMP compliance) and confirmation that transport conditions are validated.

D.13 Deletion of an organisation involved in the transport of plasma	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA

Conditions

1. The reason for deletion should not be related to GMP issues.

Documentation

1. Updated relevant sections and annexes of the PMF dossier.

D.14 Addition of a CE-marked test kit to test individual donations as a new test kit or as a replacement of an existing test kit	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1, 2	IA

Conditions

1. The new test kit is CE-marked.

Documentation

1. List of testing site(s) where the kit is used.

2. Updated relevant sections and annexes of the PMF dossier, including updated information on testing as requested in the 'Guideline on the scientific data requirements for a PMF'.

D.15 Addition of a non-CE marked test kit to test individual donations as a new test kit or as a replacement of an existing test kit	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) The new test kit has not previously been approved in the PMF for any blood centre for testing of donations			II
b) The new test kit has been approved in the PMF for other blood centre(s) for testing of donations		1, 2	IA

Documentation

1. List of testing centre(s) where the kit is currently used and a list of testing centre(s) where the kit will be used.

2. Updated relevant sections and annexes of the PMF dossier, including updated information on testing as requested in the 'Guideline on the scientific data requirements for a PMF'.

D.16 Change of kit/method used to test pools (antibody or antigen or NAT test).	Conditions to be fulfilled	Documentation to be supplied	Procedure type
			II

D.17 Introduction or extension of inventory hold procedure.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	**1**	**IA**

Conditions

1. The inventory hold procedure is a more stringent procedure (e.g. release only after retesting of donors).

Documentation

1. Updated relevant sections of the PMF dossier, including the rationale for introduction or extension of inventory hold period, the sites where the inventory hold takes place and for changes to procedure, a decision tree including new conditions.

D.18 Removal of inventory hold period or reduction in its length.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1	**IB**

Documentation

1. Updated relevant sections of the PMF dossier

D.19 Replacement or addition of blood containers (e.g. bags, bottles)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) The new blood containers are CE-marked	**1, 2**	**1**	**IA**
b) The new blood containers are not CE-marked			**II**

Conditions

1. The container is CE-marked.

2. The quality criteria of the blood in the container remain unchanged.

Documentation

1. Updated relevant sections and annexes of the PMF dossier, including the name of container, manufacturer, anticoagulant solution specification, confirmation of CE-mark and the name of the blood establishments where the container is used.

D.20 Change in storage/transport	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) storage and/or transport conditions	**1**	**1**	**IA**
b) maximum storage time for the plasma	**1, 2**	**1**	**IA**

Conditions

1. The change should tighten the conditions and be in compliance with Ph. Eur. requirements for Human Plasma for Fractionation.

2. The maximum storage time is shorter than previously.

Documentation

1. Updated relevant sections and annexes of the PMF dossier, including detailed description of the new conditions, confirmation of validation of storage/transport conditions and the name of the blood establishment(s) where the change takes place (if relevant).

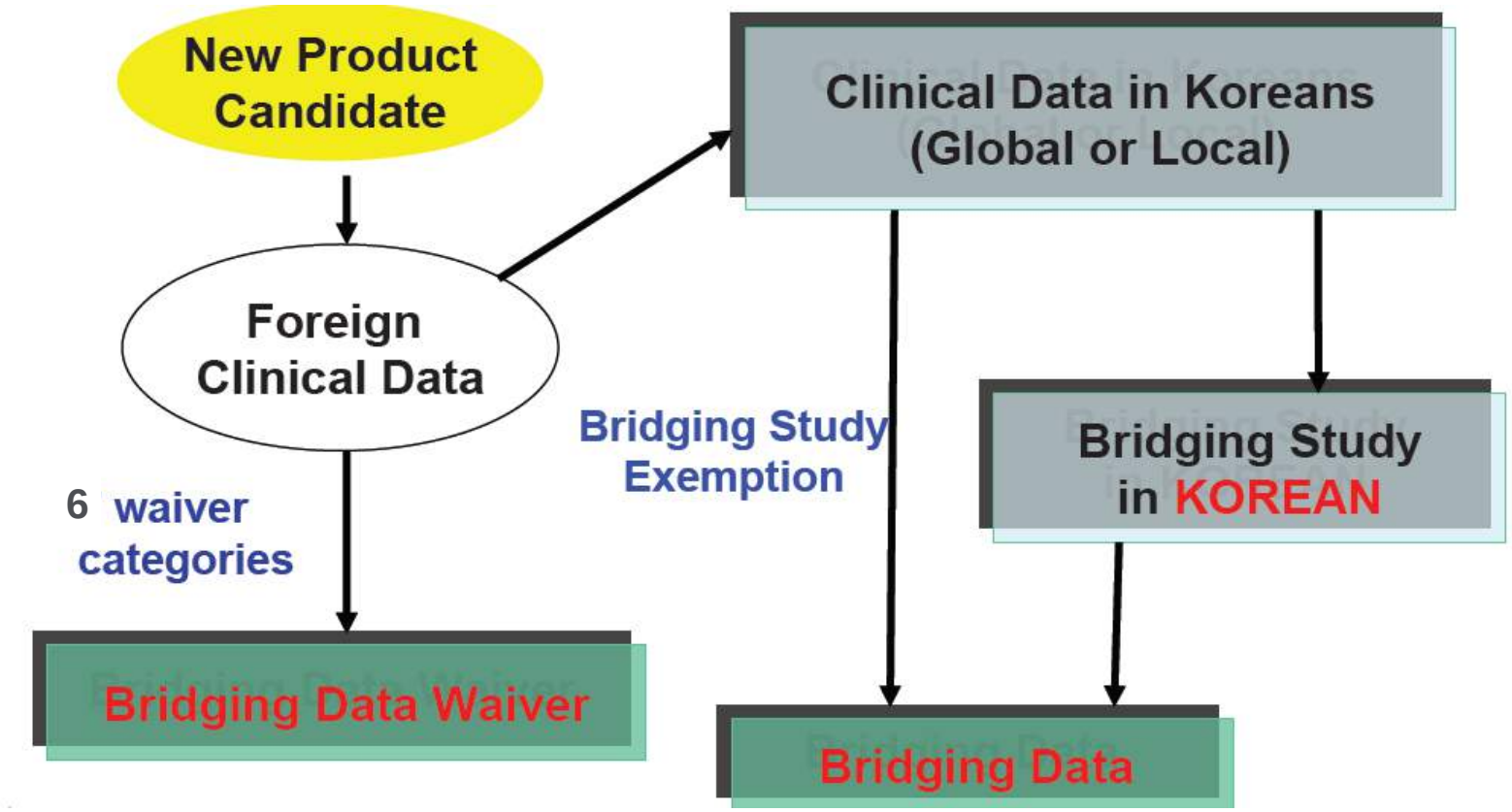
D.21 Introduction of test for viral markers when this introduction will have significant impact on the viral risk assessment.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II

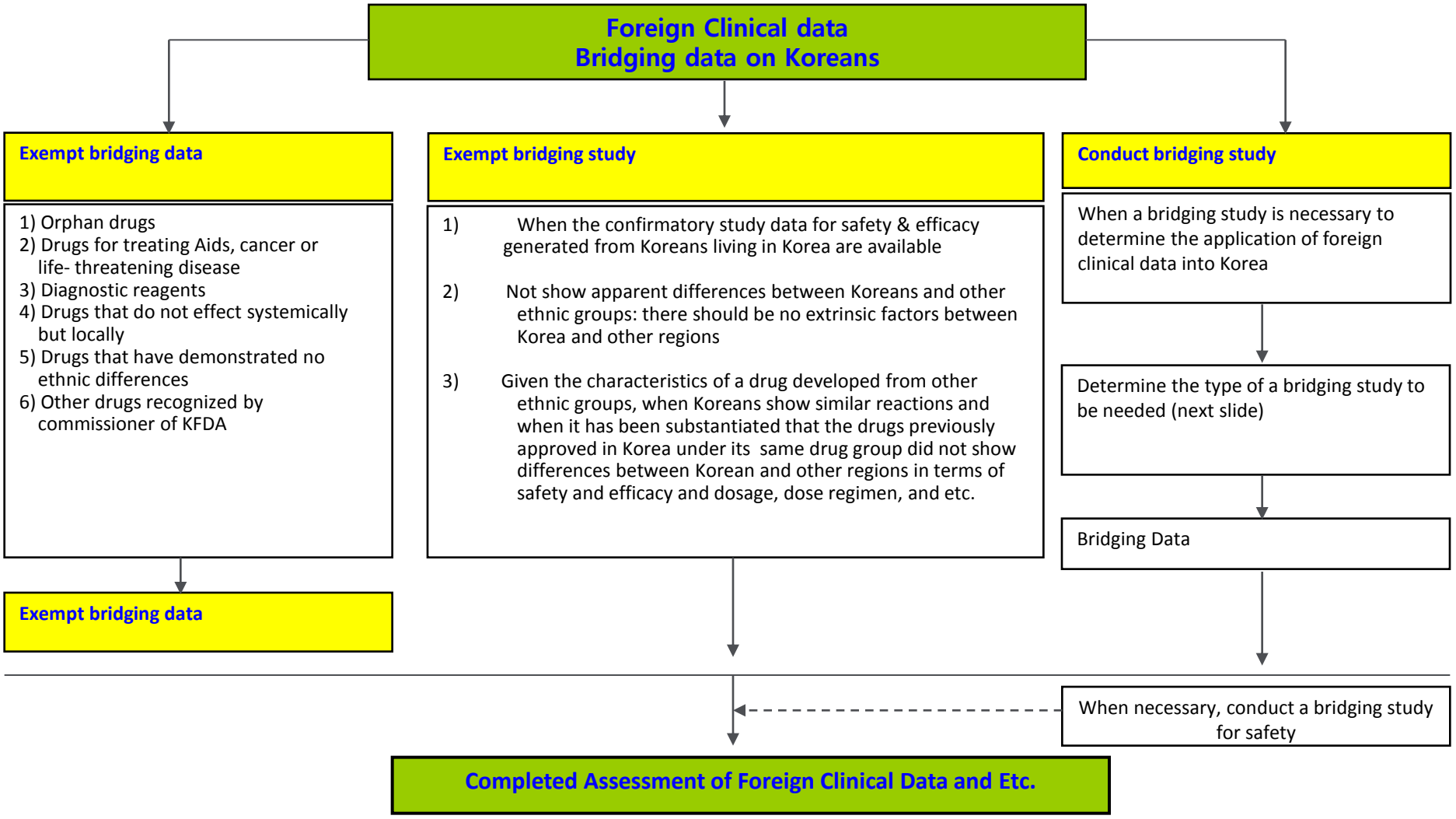
D.22 Change in the plasma pool preparation (e.g. manufacturing method, pool size, storage of plasma pool samples)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
		1	**IB**

Documentation

1. Updated relevant sections of the PMF dossier.

D.23 Change in the steps that would be taken if it is found retrospectively that donation(s) should have been excluded from processing ('look-back' procedure).	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II


New Product Candidate
Clinical Data in Koreans (Global or Local)
Foreign Clinical Data
Bridging Study Exemption
Bridging Study in KOREAN
6 waiver categories
Bridging Data Waiver
Bridging Data


Foreign Clinical data
Bridging data on Koreans
Exempt bridging data
1) Orphan drugs
2) Drugs for treating Aids, cancer or life- threatening disease
3) Diagnostic reagents
4) Drugs that do not effect systemically but locally
5) Drugs that have demonstrated no ethnic differences
6) Other drugs recognized by commissioner of KFDA
Exempt bridging data
Exempt bridging study
1) When the confirmatory study data for safety & efficacy generated from Koreans living in Korea are available
2) Not show apparent differences between Koreans and other ethnic groups: there should be no extrinsic factors between Korea and other regions
3) Given the characteristics of a drug developed from other ethnic groups, when Koreans show similar reactions and when it has been substantiated that the drugs previously approved in Korea under its same drug group did not show differences between Korean and other regions in terms of safety and efficacy and dosage, dose regimen, and etc.
Conduct bridging study
When a bridging study is necessary to determine the application of foreign clinical data into Korea
Determine the type of a bridging study to be needed (next slide)
Bridging Data
When necessary, conduct a bridging study for safety
Completed Assessment of Foreign Clinical Data and Etc.

BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA

PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA
NOMOR 24 TAHUN 2017
TENTANG
KRITERIA DAN TATA LAKSANA REGISTRASI OBAT

DENGAN RAHMAT TUHAN YANG MAHA ESA

KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA,

Menimbang : a. bahwa untuk melindungi masyarakat dari peredaran obat yang tidak memenuhi persyaratan khasiat, keamanan, dan mutu perlu dilakukan registrasi obat sebelum diedarkan;

b. bahwa ketentuan kriteria dan tata laksana registrasi obat sebagaimana telah diatur dalam Peraturan Kepala Badan Pengawas Obat dan Makanan Nomor HK.03.1.23.10.11.08481 Tahun 2011 tentang Kriteria dan Tata Laksana Registrasi Obat sebagaimana telah beberapa kali diubah terakhir dengan Peraturan Kepala Badan Pengawas Obat dan Makanan Nomor 17 Tahun 2016 tentang Perubahan Kedua atas Peraturan Kepala Badan Pengawas Obat dan Makanan Nomor HK.03.1.23.10.11.08481 Tahun 2011 tentang Kriteria dan Tata Laksana Registrasi Obat perlu disesuaikan dengan perkembangan ilmu pengetahuan dan teknologi terkini;

c. bahwa berdasarkan pertimbangan sebagaimana dimaksud dalam huruf a dan huruf b, perlu menetapkan Peraturan Kepala Badan Pengawas Obat dan Makanan tentang Kriteria dan Tata Laksana Registrasi Obat;

Mengingat : 1. Ordonansi Obat Keras (*Sterkwerkende Geneesmiddelen Ordonnantie, Staatsblad 1949:419*);

2. Undang-Undang Nomor 5 Tahun 1997 tentang Psikotropika (Lembaran Negara Republik Indonesia Tahun 1997 Nomor 10, Tambahan Lembaran Negara Republik Indonesia Nomor 3671);
3. Undang-Undang Nomor 8 Tahun 1999 tentang Perlindungan Konsumen (Lembaran Negara Republik Indonesia Tahun 1999 Nomor 42, Tambahan Lembaran Negara Republik Indonesia Nomor 3821);
4. Undang-Undang Nomor 35 Tahun 2009 tentang Narkotika (Lembaran Negara Republik Indonesia Tahun 2009 Nomor 143, Tambahan Lembaran Negara Republik Indonesia Nomor 5062);
5. Undang-Undang Nomor 36 Tahun 2009 tentang Kesehatan (Lembaran Negara Republik Indonesia Tahun 2009 Nomor 144, Tambahan Lembaran Negara Republik Indonesia Nomor 5063);
6. Peraturan Presiden Nomor 80 Tahun 2017 tentang Badan Pengawas Obat dan Makanan (Lembaran Negara Republik Indonesia Tahun 2017 Nomor 180);
7. Peraturan Menteri Kesehatan Nomor 1010/MENKES/PER/XI/2008 tentang Registrasi Obat sebagaimana telah diubah dengan Peraturan Menteri Kesehatan Nomor 1120/MENKES/PER/XII/2008 tentang Perubahan atas Peraturan Menteri Kesehatan Nomor 1010/Menkes/Per/XI/2008 tentang Registrasi Obat;
8. Peraturan Menteri Kesehatan Nomor 1799/MENKES/PER/XII/2010 tentang Industri Farmasi sebagaimana telah diubah dengan Peraturan Menteri Kesehatan Nomor 16 Tahun 2013 tentang Perubahan atas Peraturan Menteri Kesehatan Nomor

1799/MENKES/PER/XII/2010 tentang Industri Farmasi (Berita Negara Republik Indonesia Tahun 2013 Nomor 442);

9. Peraturan Kepala Badan Pengawas Obat dan Makanan Nomor HK.03.01.23.12.11.10217 Tahun 2011 tentang Obat Wajib Uji Ekivalensi (Berita Negara Republik Indonesia Tahun 2012 Nomor 120);
10. Peraturan Kepala Badan Pengawas Obat dan Makanan Nomor HK.03.1.34.11.12.7542 Tahun 2012 tentang Pedoman Teknis Cara Distribusi Obat yang Baik (Berita Negara Republik Indonesia Tahun 2012 Nomor 1268);
11. Peraturan Kepala Badan Pengawas Obat dan Makanan Nomor HK.03.1.33.12.12.8195 Tahun 2012 tentang Penerapan Pedoman Cara Pembuatan Obat yang Baik (Berita Negara Republik Indonesia Tahun 2013 Nomor 122);
12. Keputusan Kepala Badan Pengawas Obat dan Makanan Nomor 02001/SK/KBPOM Tahun 2001 tentang Organisasi dan Tata Kerja Badan Pengawas Obat dan Makanan sebagaimana telah diubah dengan Keputusan Kepala Badan Pengawas Obat dan Makanan Nomor HK.00.05.21.4231 Tahun 2004 tentang Perubahan atas Keputusan Kepala Badan Pengawas Obat dan Makanan Nomor 02001/SK/KBPOM Tahun 2001 tentang Organisasi dan Tata Kerja Badan Pengawas Obat dan Makanan;

MEMUTUSKAN:

Menetapkan : PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN TENTANG KRITERIA DAN TATA LAKSANA REGISTRASI OBAT.

BAB I

KETENTUAN UMUM

Pasal 1

Dalam Peraturan Kepala Badan ini yang dimaksud dengan:

1. Registrasi Obat yang selanjutnya disebut Registrasi adalah prosedur pendaftaran dan evaluasi Obat untuk mendapatkan persetujuan.
2. Obat adalah obat jadi termasuk Produk Biologi, yang merupakan bahan atau paduan bahan digunakan untuk mempengaruhi atau menyelidiki sistem fisiologi atau keadaan patologi dalam rangka penetapan diagnosis, pencegahan, penyembuhan, pemulihan dan peningkatan kesehatan, dan kontrasepsi untuk manusia.
3. Produk Biologi adalah produk yang mengandung bahan biologi yang berasal dari manusia, hewan atau mikroorganisme yang dibuat dengan cara konvensional, antara lain ekstraksi, fraksinasi, reproduksi, kultivasi, atau melalui metode bioteknologi, antara lain fermentasi, rekayasa genetika, kloning, termasuk tetapi tidak terbatas pada enzim, antibodi monoklonal, hormon, sel punca, terapi gen, vaksin, produk darah, produk rekombinan DNA, dan imunosera.
4. Kontrasepsi adalah Obat atau alat yang mengandung Obat yang tujuan penggunaannya untuk mencegah terjadinya konsepsi.
5. Narkotika adalah Obat yang berasal dari tanaman atau bukan tanaman, baik sintetis maupun semisintetis, yang dapat menyebabkan penurunan atau perubahan kesadaran, hilangnya rasa, mengurangi sampai menghilangkan rasa nyeri dan dapat menimbulkan ketergantungan, yang dibedakan ke dalam golongan sebagaimana diatur dalam Undang-Undang tentang Narkotika.
6. Psikotropika adalah Obat baik alamiah maupun sintetis bukan Narkotika, yang berkhasiat psikoaktif melalui pengaruh selektif pada susunan saraf pusat yang

menyebabkan perubahan khas pada aktifitas mental dan perilaku.

7. Izin Edar adalah bentuk persetujuan Registrasi untuk dapat diedarkan di wilayah Indonesia.
8. Pemilik Izin Edar adalah Pendaftar yang telah mendapatkan Izin Edar untuk Obat yang diajukan Registrasi.
9. Label adalah informasi yang dicantumkan pada kemasan.
10. Ringkasan Karakteristik Produk/Brosur adalah informasi lengkap yang disetujui oleh Kepala Badan terkait deskripsi Obat, khasiat dan keamanan Obat dari data hasil uji klinik, dan informasi lain yang dianggap perlu serta berfungsi sebagai sumber informasi bagi petugas kesehatan dan menjadi acuan dalam penyusunan Informasi Produk untuk Pasien.
11. Informasi Produk adalah keterangan lengkap mengenai Obat yang disetujui oleh Kepala Badan, meliputi khasiat, keamanan, cara penggunaannya serta informasi lain yang dianggap perlu yang dicantumkan pada Ringkasan Karakteristik Produk/Brosur dan/atau Informasi Produk untuk Pasien.
12. Informasi Produk untuk Pasien adalah informasi untuk pasien yang disetujui oleh Kepala Badan terkait khasiat, keamanan dan cara penggunaan Obat serta informasi lain yang dianggap perlu dengan menggunakan bahasa Indonesia yang mudah dimengerti dan dipahami oleh pasien.
13. Pendaftar adalah Industri Farmasi yang telah mendapatkan izin Industri Farmasi sesuai dengan ketentuan peraturan perundang-undangan.
14. Industri Farmasi adalah badan usaha yang memiliki izin dari Menteri Kesehatan untuk melakukan kegiatan pembuatan Obat atau bahan Obat.
15. Industri Farmasi Dalam Negeri adalah Industri Farmasi yang berlokasi di wilayah Indonesia.
16. Registrasi Baru adalah Registrasi untuk Obat yang belum mendapatkan Izin Edar di Indonesia.

17. Registrasi Variasi adalah Registrasi perubahan pada aspek administratif, khasiat, keamanan, mutu, dan/atau Informasi Produk dan Label Obat yang telah memiliki Izin Edar di Indonesia.
18. Registrasi Variasi Major adalah Registrasi Variasi yang berpengaruh bermakna terhadap aspek khasiat, keamanan dan/atau mutu Obat.
19. Registrasi Variasi Minor adalah Registrasi Variasi yang tidak termasuk kategori Registrasi Variasi Major maupun Registrasi Variasi Notifikasi.
20. Registrasi Variasi Notifikasi adalah Registrasi Variasi yang berpengaruh minimal atau tidak berpengaruh sama sekali terhadap aspek khasiat, keamanan, dan/atau mutu Obat, serta tidak mengubah informasi pada Izin Edar.
21. Registrasi Ulang adalah Registrasi perpanjangan masa berlaku Izin Edar.
22. Produk Biosimilar adalah Produk Biologi dengan profil khasiat, keamanan, dan mutu yang similar/serupa dengan Produk Biologi yang telah disetujui.
23. Cara Pembuatan Obat yang Baik yang selanjutnya disingkat CPOB adalah cara pembuatan Obat yang bertujuan untuk memastikan agar mutu Obat yang dihasilkan sesuai dengan persyaratan dan tujuan penggunaan.
24. Zat Aktif adalah komponen Obat yang mempunyai efek farmakologis.
25. Eksipien adalah komponen Obat yang tidak mempunyai efek farmakologis.
26. Komposisi adalah susunan kualitatif dan kuantitatif Zat Aktif dalam Obat.
27. Formula adalah susunan kualitatif dan kuantitatif Zat Aktif dan Eksipien dalam Obat.
28. Obat Baru adalah Obat dengan Zat Aktif baru, bentuk sediaan baru, kekuatan baru atau kombinasi baru yang belum pernah disetujui di Indonesia.
29. Obat Generik Bermerek adalah Obat dengan nama dagang yang mengandung Zat Aktif dengan Komposisi, kekuatan,

bentuk sediaan, rute pemberian, indikasi dan posologi sama dengan Obat originator yang sudah disetujui di Indonesia.

30. Obat Generik adalah Obat dengan nama sesuai *International Nonproprietary Names Modified* yang ditetapkan Badan Kesehatan Dunia (*World Health Organization*) atau nama yang ditetapkan dalam program kesehatan nasional.
31. Obat Generik Pertama adalah Obat Generik yang pertama didaftarkan di Indonesia dengan Zat Aktif sama dengan Obat originator yang disetujui di Indonesia.
32. Obat Produksi Dalam Negeri adalah Obat yang dibuat atau dikemas primer oleh Industri Farmasi di Indonesia.
33. Pemberi Kontrak adalah Industri Farmasi yang melimpahkan pekerjaan pembuatan Obat berdasarkan kontrak.
34. Penerima Kontrak adalah Industri Farmasi yang menerima pekerjaan pembuatan Obat berdasarkan kontrak.
35. Obat Impor adalah Obat yang dibuat oleh industri farmasi di luar negeri dalam bentuk Produk Jadi atau Produk Ruahan dalam kemasan primer yang akan diedarkan di Indonesia.
36. Produk Jadi adalah produk yang telah melalui seluruh tahap proses pembuatan.
37. Produk Ruahan adalah bahan yang telah selesai diolah dan tinggal memerlukan kegiatan pengemasan untuk menjadi Obat.
38. Obat Kontrak adalah Obat yang pembuatannya dilimpahkan kepada Industri Farmasi lain.
39. Obat Lisensi adalah Obat yang dibuat oleh Industri Farmasi Dalam Negeri atas dasar Lisensi.
40. Lisensi adalah pelimpahan hak dan wewenang penggunaan hasil penelitian dan pengembangan yang menyangkut khasiat, keamanan, mutu dan alih teknologi dalam pembuatan, dan/atau penggunaan nama dagang serta penjualan suatu Obat.

41. Obat yang Dilindungi Paten adalah Obat yang mendapatkan perlindungan paten berdasarkan Undang-Undang Paten yang berlaku di Indonesia.
42. Obat Pengembangan Baru adalah Obat atau bahan Obat berupa molekul baru atau Formula baru, Produk Biologi/bioteknologi yang sedang dikembangkan dan dibuat oleh institusi riset atau Industri Farmasi di Indonesia dan/atau di luar negeri untuk digunakan dalam tahapan uji nonklinik dan/atau uji klinik di Indonesia dengan tujuan untuk mendapatkan Izin Edar di Indonesia.
43. *Orphan Drug* adalah Obat yang sangat dibutuhkan untuk pengobatan penyakit langka dan telah dibuktikan keamanan dan efektivitasnya.
44. Formulir adalah formulir registrasi.
45. Hari adalah hari kerja.
46. Kepala Badan adalah Kepala Badan Pengawas Obat dan Makanan.

BAB II
PERSYARATAN DAN KRITERIA

Bagian Kesatu
Persyaratan

Pasal 2

(1) Obat yang akan diedarkan di wilayah Indonesia wajib memiliki Izin Edar.
(2) Untuk memperoleh Izin Edar sebagaimana dimaksud pada ayat (1) harus dilakukan Registrasi.
(3) Registrasi sebagaimana dimaksud pada ayat (2) diajukan oleh Pendaftar kepada Kepala Badan.

Pasal 3

(1) Dikecualikan dari ketentuan sebagaimana dimaksud dalam Pasal 2 ayat (1) diperuntukan bagi pemasukan Obat untuk penggunaan khusus.

(2) Pemasukan Obat untuk penggunaan khusus sebagaimana dimaksud pada ayat (1) dilaksanakan sesuai dengan ketentuan peraturan perundang-undangan.

Bagian Kedua
Kriteria

Pasal 4

(1) Obat yang mendapat Izin Edar harus memenuhi kriteria berikut:
   a. khasiat yang meyakinkan dan keamanan yang memadai dibuktikan melalui uji nonklinik dan uji klinik atau bukti-bukti lain sesuai dengan status perkembangan ilmu pengetahuan;
   b. mutu yang memenuhi syarat sesuai dengan standar yang ditetapkan, termasuk proses produksi sesuai dengan CPOB dan dilengkapi dengan bukti yang sahih; dan
   c. Informasi Produk dan Label berisi informasi lengkap, objektif dan tidak menyesatkan yang dapat menjamin penggunaan Obat secara tepat, rasional dan aman.

(2) Selain harus memenuhi kriteria sebagaimana dimaksud pada ayat (1), Obat juga harus memenuhi kriteria sebagai berikut:
   a. khusus untuk Psikotropika baru, harus memiliki keunggulan dibandingkan dengan Obat yang telah disetujui beredar di Indonesia; dan
   b. khusus Obat program kesehatan nasional, harus sesuai dengan persyaratan yang ditetapkan oleh instansi pemerintah penyelenggara program kesehatan nasional.

BAB III

KATEGORI REGISTRASI

Pasal 5

(1) Registrasi terdiri atas:
   a. Registrasi Baru;
   b. Registrasi Variasi; dan
   c. Registrasi Ulang.

(2) Registrasi Baru sebagaimana dimaksud pada ayat (1) huruf a terdiri atas:
   a. kategori 1: Registrasi Obat Baru dan Produk Biologi, termasuk Produk Biosimilar.
   b. kategori 2: Registrasi Obat Generik dan Obat Generik Bermerek.
   c. kategori 3: Registrasi sediaan lain yang mengandung Obat dengan teknologi khusus, dapat berupa *transdermal patch*, *implant*, dan *beads*.

(3) Registrasi Variasi sebagaimana dimaksud pada ayat (1) huruf b terdiri atas:
   a. kategori 4: Registrasi Variasi Major.
   b. kategori 5: Registrasi Variasi Minor.
   c. kategori 6: Registrasi Variasi Notifikasi.

(4) Registrasi Ulang sebagaimana dimaksud pada ayat (1) huruf c masuk ke dalam kategori 7.

BAB IV

PERSYARATAN REGISTRASI

Bagian Kesatu

Nama Obat

Pasal 6

(1) Nama Obat yang diregistrasi dapat menggunakan:
   a. nama generik; atau
   b. nama dagang.

(2) Nama generik sebagaimana dimaksud pada ayat (1) huruf a sesuai dengan *International Nonproprietary Names Modified* yang ditetapkan Badan Kesehatan Dunia (*World Health Organization*) atau nama yang ditetapkan dalam program kesehatan nasional.

(3) Nama dagang sebagaimana dimaksud pada ayat (1) huruf b merupakan nama yang diberikan oleh Pendaftar sebagai identitas Obat.

(4) Pemberian nama dagang sebagaimana dimaksud pada ayat (1) huruf b berdasarkan kajian mandiri dan menjadi tanggung jawab Pendaftar.

(5) Kajian mandiri sebagaimana dimaksud pada ayat (4) mengacu pada Pedoman Umum Nama Obat sebagaimana tercantum dalam Lampiran I yang merupakan bagian tidak terpisahkan dari Peraturan Kepala Badan ini.

(6) Dalam hal kajian mandiri sebagaimana dimaksud pada ayat (5) tidak sesuai dengan Pedoman Umum Nama Obat sebagaimana pada Lampiran I, usulan nama Obat tersebut tidak dapat disetujui.

(7) Apabila di kemudian hari ada pihak lain yang lebih berhak atas nama Obat yang tercantum dalam Izin Edar sesuai dengan ketentuan peraturan perundang-undangan, Pendaftar harus mengganti nama Obat.

Bagian Kedua

Registrasi

Pasal 7

(1) Registrasi dilakukan oleh Pendaftar dengan menyerahkan dokumen registrasi.

(2) Obat yang diregistrasi berupa:

a. Obat Produksi Dalam Negeri; atau

b. Obat Impor.

Bagian Ketiga

Registrasi Obat Produksi Dalam Negeri

Pasal 8

(1) Pendaftar yang melakukan permohonan Registrasi Obat Produksi Dalam Negeri harus memenuhi persyaratan sebagai berikut:
   a. memiliki izin Industri Farmasi; dan
   b. memiliki sertifikat CPOB yang masih berlaku sesuai dengan jenis dan bentuk sediaan yang diregistrasi.

(2) Dikecualikan dari ketentuan sebagaimana dimaksud pada ayat (1) huruf a dan huruf b, untuk Registrasi Obat Produksi Dalam Negeri yang dilakukan oleh calon Industri Farmasi yang sedang melakukan pembangunan.

(3) Dikecualikan dari ketentuan sebagaimana dimaksud pada ayat (1) huruf b, untuk Registrasi Obat Produksi Dalam Negeri yang dilakukan oleh Industri Farmasi yang menambah fasilitas untuk bentuk sediaan baru atau Industri Farmasi yang melakukan perluasan fasilitas produksi.

(4) Persyaratan Registrasi Obat Produksi Dalam Negeri sebagaimana dimaksud pada ayat (2) dan ayat (3) berupa rekomendasi berdasarkan hasil inspeksi pemenuhan persyaratan CPOB.

(5) Dalam hal Registrasi dilakukan berdasarkan ketentuan sebagaimana dimaksud pada ayat (2) dan ayat (3), Izin Edar akan diterbitkan setelah Pendaftar memenuhi persyaratan sebagaimana dimaksud pada ayat (1).

Bagian Keempat

Registrasi Obat Kontrak Produksi Dalam Negeri

Pasal 9

(1) Registrasi Obat Kontrak produksi dalam negeri hanya dapat dilakukan oleh Pemberi Kontrak sebagai Pendaftar.

(2) Registrasi sebagaimana dimaksud pada ayat (1) harus memenuhi ketentuan sebagai berikut:
   a. memiliki izin Industri Farmasi;
   b. memiliki paling sedikit 1 (satu) fasilitas produksi yang telah memenuhi persyaratan CPOB; dan
   c. memiliki dokumen perjanjian kontrak.

(3) Industri Farmasi Pemberi Kontrak dan Industri Farmasi Penerima Kontrak bertanggung jawab terhadap aspek khasiat, keamanan, dan mutu Obat yang dikontrakkan, dengan penanggung jawab utama Industri Farmasi Pemberi Kontrak sebagai Pemilik Izin Edar.

(4) Industri Farmasi Penerima Kontrak harus memiliki sertifikat CPOB yang masih berlaku sesuai dengan bentuk sediaan Obat yang akan diproduksi.

(5) Industri Farmasi Penerima Kontrak tidak dapat mengalihkan pembuatan Obat yang dikontrakkan kepada pihak ketiga.

Pasal 10

(1) Pembuatan Obat Kontrak produksi dalam negeri berupa:
   a. seluruh tahapan pembuatan; atau
   b. sebagian tahapan pembuatan.

(2) Formula Obat Kontrak produksi dalam negeri sebagaimana dimaksud pada ayat (1) berupa:
   a. Formula dari Pemberi Kontrak; atau
   b. Formula dari Penerima Kontrak.

(3) Obat Kontrak produksi dalam negeri sebagaimana dimaksud pada ayat (1) dapat diproduksi pada lebih dari 1 (satu) tempat produksi dengan memberikan justifikasi.

(4) Obat Kontrak produksi dalam negeri sebagaimana dimaksud pada ayat (3) harus memiliki mutu yang sama, meliputi Formula dan spesifikasi produk.

Bagian Kelima

Registrasi Obat Impor

Pasal 11

(1) Obat Impor berupa:
   a. Obat Impor dalam bentuk Produk Ruahan; atau
   b. Obat Impor dalam bentuk Produk Jadi.

(2) Registrasi Obat Impor diutamakan untuk:
   a. Obat program kesehatan nasional;
   b. Obat penemuan baru; dan/atau
   c. Obat yang dibutuhkan tetapi tidak dapat diproduksi di dalam negeri.

Pasal 12

Obat program kesehatan nasional sebagaimana dimaksud dalam Pasal 11 ayat (2) huruf a ditetapkan oleh instansi pemerintah penyelenggara program kesehatan nasional.

Pasal 13

(1) Obat penemuan baru sebagaimana dimaksud dalam Pasal 11 ayat (2) huruf b terdiri atas:
   a. Obat yang masih dalam perlindungan paten; atau
   b. Obat originator.

(2) Obat originator sebagaimana dimaksud pada ayat (1) huruf b merupakan Obat yang pertama kali diberi Izin Edar di Indonesia berdasarkan data lengkap khasiat, keamanan, dan mutu.

Pasal 14

(1) Obat yang dibutuhkan tetapi tidak dapat diproduksi di dalam negeri sebagaimana dimaksud dalam Pasal 11 ayat (2) huruf c berupa:
   a. Obat yang memerlukan teknologi dan fasilitas produksi khusus yang belum dimiliki Industri Farmasi di Indonesia;
   b. Obat yang memerlukan teknologi dan fasilitas produksi khusus yang telah tersedia di Indonesia,

tetapi kapasitasnya tidak mencukupi untuk memenuhi kebutuhan dalam negeri;

c. Obat yang secara ekonomis tidak memungkinkan diproduksi di dalam negeri karena kebutuhannya dalam jumlah sedikit, dapat berupa Obat untuk penyakit langka (*Orphan Drug*) di Indonesia; atau

d. Obat yang diproduksi secara sentralistik di luar negeri oleh industri farmasi multinasional yang memiliki Industri Farmasi di Indonesia dengan menunjukkan perimbangan kegiatan ekspor dan impor.

(2) Registrasi Obat Impor sebagaimana dimaksud pada ayat (1) harus dilengkapi dengan justifikasi bahwa Obat yang bersangkutan tidak dapat diproduksi di Indonesia.

Pasal 15

(1) Registrasi Obat Impor hanya dapat dilakukan oleh Pendaftar yang mendapatkan persetujuan tertulis dari industri farmasi di luar negeri.

(2) Dikecualikan dari ketentuan mendapatkan persetujuan tertulis dari industri farmasi di luar negeri sebagaimana dimaksud pada ayat (1) untuk Pendaftar yang merupakan afiliasi dari perusahaan induk.

(3) Persetujuan tertulis sebagaimana dimaksud pada ayat (1) harus mencantumkan masa berlaku kerja sama.

(4) Industri farmasi di luar negeri sebagaimana dimaksud pada ayat (1) wajib memiliki izin Industri Farmasi dan memenuhi persyaratan CPOB yang dibuktikan dengan:

a. izin industri farmasi dari otoritas negara setempat;

b. sertifikat CPOB yang masih berlaku atau dokumen lain yang setara yang dikeluarkan oleh otoritas pengawas Obat setempat dan/atau otoritas pengawas Obat negara lain; dan

c. laporan hasil inspeksi terakhir dan perubahan terkait paling lama 2 (dua) tahun yang dikeluarkan oleh otoritas pengawas Obat setempat dan/atau otoritas pengawas Obat negara lain.

(5) Jika diperlukan, untuk memastikan pemenuhan persyaratan CPOB sebagaimana dimaksud pada ayat (4) dapat dilakukan pemeriksaan setempat pada fasilitas pembuatan Obat sesuai dengan ketentuan peraturan perundang-undangan.

(6) Dalam hal Obat Impor sebagaimana dimaksud pada ayat (1) yang sebagian atau seluruh tahapan pembuatannya dilakukan oleh lebih dari 1 (satu) Industri Farmasi, seluruh tahapan pembuatan dimaksud harus memenuhi persyaratan sebagaimana dimaksud pada ayat (4).

Pasal 16

(1) Registrasi Obat Impor sebagaimana dimaksud dalam Pasal 14 ayat (1) secara bertahap harus dilakukan alih teknologi untuk dapat diproduksi di dalam negeri.

(2) Alih teknologi sebagaimana dimaksud pada ayat (1) dapat berupa alih pengetahuan/kemampuan di bidang:
   a. pengembangan produk;
   b. teknik dan metode/proses produksi; dan/atau
   c. pengawasan mutu.

(3) Alih teknologi sebagaimana dimaksud pada ayat (1) dapat diberikan kepada perwakilan industri farmasi luar negeri di Indonesia atau Industri Farmasi lain di Indonesia berdasarkan kesepakatan antara pemilik dan penerima teknologi.

Bagian Keenam
Registrasi Narkotika

Pasal 17

(1) Registrasi Narkotika hanya dapat dilakukan oleh Pendaftar yang memiliki izin khusus untuk memproduksi Narkotika dari Menteri Kesehatan.

(2) Registrasi Narkotika sebagaimana dimaksud pada ayat (1) dilaksanakan sesuai dengan persyaratan dan tata laksana Registrasi sebagaimana diatur dalam Peraturan Kepala Badan ini.

Bagian Ketujuh

Registrasi Obat Lisensi

Pasal 18

(1) Registrasi Obat Lisensi dilakukan oleh Pendaftar yang telah mendapatkan penunjukan dari pemberi lisensi.

(2) Registrasi sebagaimana dimaksud pada ayat (1) harus memenuhi ketentuan:
   a. memiliki izin Industri Farmasi;
   b. memiliki sertifikat CPOB yang masih berlaku sesuai dengan jenis dan bentuk sediaan yang diregistrasi; dan
   c. memiliki dokumen perjanjian lisensi.

(3) Dokumen perjanjian lisensi sebagaimana dimaksud pada ayat (2) huruf c paling sedikit harus memuat:
   a. informasi hal-hal yang dilisensikan; dan
   b. masa berlaku lisensi.

(4) Pemberi lisensi sebagaimana dimaksud pada ayat (1) dapat berupa:
   a. Industri Farmasi di dalam negeri atau industri farmasi di luar negeri; atau
   b. badan riset pemilik Formula dan teknologi di dalam atau di luar negeri.

(5) Pemberi lisensi sebagaimana dimaksud pada ayat (4) harus memiliki bukti status sebagai Industri Farmasi atau badan riset.

Bagian Kedelapan

Registrasi Obat Khusus Ekspor

Pasal 19

(1) Registrasi Obat khusus ekspor dilakukan oleh Pendaftar.

(2) Obat khusus ekspor sebagaimana dimaksud pada ayat (1) terdiri atas:
   a. Obat Produksi Dalam Negeri yang ditujukan khusus ekspor; dan
   b. Obat Impor khusus ekspor.

(3) Pendaftar untuk Registrasi Obat Produksi Dalam Negeri yang ditujukan khusus ekspor sebagaimana dimaksud pada ayat (2) huruf a harus memenuhi persyaratan sebagai berikut:
   a. memiliki izin Industri Farmasi; dan
   b. memiliki sertifikat CPOB yang masih berlaku sesuai dengan jenis dan bentuk sediaan yang diregistrasi.

(4) Pendaftar untuk Registrasi Obat Impor khusus ekspor sebagaimana dimaksud pada ayat (2) huruf b harus memenuhi persyaratan sebagai berikut:
   a. memiliki izin Industri Farmasi;
   b. memiliki sertifikat CPOB yang masih berlaku sesuai dengan jenis dan bentuk sediaan yang diregistrasi; dan
   c. mendapatkan persetujuan tertulis dari industri farmasi di luar negeri.

(5) Obat khusus ekspor sebagaimana dimaksud pada ayat (2) dilarang diedarkan di wilayah Indonesia.

Bagian Kesembilan
Registrasi Obat yang Dilindungi Paten

Pasal 20

(1) Registrasi Obat dengan Zat Aktif yang dilindungi paten di Indonesia hanya dapat dilakukan oleh:
   a. Pendaftar pemilik hak paten; atau
   b. Pendaftar yang ditunjuk oleh pemilik hak paten.

(2) Hak paten sebagaimana dimaksud pada ayat (1) harus dibuktikan dengan sertifikat paten.

Pasal 21

(1) Registrasi Obat Generik Pertama dengan Zat Aktif yang masih dilindungi paten di Indonesia dapat diajukan oleh Pendaftar yang bukan pemilik hak paten sesuai dengan ketentuan peraturan perundang-undangan.

(2) Registrasi sebagaimana dimaksud pada ayat (1) dapat mulai diajukan 5 (lima) tahun sebelum berakhirnya perlindungan paten.

(3) Pendaftar Registrasi Obat Generik Pertama sebagaimana dimaksud pada ayat (1), harus menyerahkan dokumen sebagai berikut:

a. informasi tanggal berakhirnya masa perlindungan paten dari instansi yang berwenang; dan

b. data ekivalensi dan/atau data lain untuk menjamin kesetaraan khasiat, keamanan dan mutu.

(4) Izin Edar terhadap pengajuan Registrasi Obat Generik Pertama sebagaimana dimaksud pada ayat (1) diterbitkan setelah habis masa perlindungan paten.

Bagian Kesepuluh

Registrasi Obat Pengembangan Baru

Pasal 22

(1) Registrasi Obat dengan tahapan uji klinik yang dilakukan di Indonesia harus melalui penilaian Obat Pengembangan Baru.

(2) Penilaian Obat Pengembangan Baru sebagaimana dimaksud pada ayat (1) sesuai dengan ketentuan peraturan perundang-undangan.

Bagian Kesebelas

Registrasi Obat Generik

Pasal 23

(1) Registrasi Obat Generik diajukan oleh Pendaftar menggunakan nama generik sebagaimana dimaksud dalam Pasal 6 ayat (2).

(2) Seluruh tahapan pembuatan Obat Generik dilakukan di dalam negeri.

(3) Dikecualikan dari ketentuan sebagaimana dimaksud pada ayat (2) untuk Obat yang sebagian tahapan pembuatan belum dapat dilakukan di dalam negeri.

(4) Dalam hal Pendaftar sudah memiliki Obat Generik Bermerek dengan Zat Aktif yang sama, Obat Generik yang diregistrasi harus dibuat dengan Formula, sumber bahan baku, spesifikasi Obat, mutu, spesifikasi kemasan, proses produksi, dan menggunakan fasilitas produksi yang sama.

(5) Spesifikasi sebagaimana dimaksud pada ayat (4) meliputi:
a. ukuran;
b. bentuk;
c. warna;
d. aroma; dan
e. rasa.

(6) Label Obat Generik harus mencantumkan informasi sebagai berikut:
a. harga eceran tertinggi sesuai dengan ketentuan peraturan perundang-undangan; dan
b. logo generik berwarna hijau menggunakan format sebagai berikut:

(7) Logo generik sebagaimana dimaksud pada ayat (6) huruf b dicantumkan secara proporsional sesuai dengan ukuran kemasan.

(8) Dalam hal Pendaftar mengajukan Registrasi Obat Generik dengan lebih dari 1 (satu) kekuatan Zat Aktif, pada kemasan harus dicantumkan kekuatan Zat Aktif setelah bentuk sediaan dengan ukuran huruf sesuai dengan ukuran huruf nama generik.

Bagian Kedua Belas

Registrasi *Orphan Drug*

Pasal 24

Ketentuan lebih lanjut mengenai Registrasi *Orphan Drug* diatur secara khusus dengan Peraturan Kepala Badan.

BAB V

TATA LAKSANA REGISTRASI

Bagian Kesatu

Umum

Pasal 25

(1) Registrasi terdiri dari:
   a. tahap praregistrasi; dan
   b. tahap registrasi.
(2) Permohonan praregistrasi dan registrasi sebagaimana dimaksud pada ayat (1) diajukan oleh Pendaftar secara tertulis kepada Kepala Badan dengan melampirkan dokumen praregistrasi dan dokumen registrasi.
(3) Permohonan sebagaimana dimaksud pada ayat (2) diajukan dengan mengisi Formulir sesuai dengan contoh sebagaimana tercantum dalam Lampiran II yang merupakan bagian tidak terpisahkan dari Peraturan Kepala Badan ini.
(4) Petunjuk pengisian Formulir sebagaimana dimaksud pada ayat (3) tercantum dalam Lampiran III yang merupakan bagian tidak terpisahkan dari Peraturan Kepala Badan ini.
(5) Dokumen praregistrasi dan dokumen registrasi harus menggunakan bahasa Indonesia atau bahasa Inggris.
(6) Permohonan praregistrasi dan registrasi dapat diajukan secara elektronik sesuai dengan ketentuan yang berlaku.
(7) Dalam hal Registrasi secara elektronik belum dapat dilaksanakan atau sistem elektronik tidak berfungsi, Registrasi dilakukan secara manual.

Pasal 26

(1) Terhadap permohonan praregistrasi dan registrasi sebagaimana dimaksud dalam Pasal 25 ayat (1) dikenai biaya sebagai penerimaan negara bukan pajak sesuai dengan ketentuan peraturan perundang-undangan.
(2) Biaya sebagaimana dimaksud pada ayat (1) harus dibayarkan paling lama 10 (sepuluh) Hari terhitung sejak

tanggal Surat Perintah Bayar-Layanan Publik (SPB-LP) diterbitkan.

(3) Pendaftar wajib melakukan konfirmasi pembayaran SPB-LP dan menyerahkan dokumen praregistrasi atau dokumen registrasi paling lama 3 (tiga) Hari terhitung sejak tanggal pembayaran.

(4) Dalam hal Pendaftar tidak melakukan konfirmasi pembayaran SPB-LP dan menyerahkan dokumen praregistrasi atau dokumen registrasi sebagaimana dimaksud pada ayat (3), permohonan dinyatakan batal.

Paragraf Kesatu

Dokumen Registrasi

Pasal 27

(1) Dokumen registrasi sebagaimana dimaksud dalam Pasal 25 ayat (2) terdiri atas:

a. bagian I : dokumen administratif, Informasi Produk dan Label.
b. bagian II : dokumen mutu.
c. bagian III : dokumen nonklinik.
d. bagian IV : dokumen klinik.

(2) Dokumen registrasi sebagaimana dimaksud pada ayat (1) disusun sesuai dengan format *ASEAN Common Technical Dossier (ACTD)* dan mengacu pada tata cara penyusunan dokumen registrasi sebagaimana tercantum dalam Lampiran IV yang merupakan bagian tidak terpisahkan dari Peraturan Kepala Badan ini.

(3) Dokumen registrasi sebagaimana dimaksud pada ayat (1) sesuai dengan contoh sebagaimana tercantum dalam Lampiran V yang merupakan bagian tidak terpisahkan dari Peraturan Kepala Badan ini.

(4) Dokumen registrasi sebagaimana dimaksud pada ayat (1) merupakan dokumen rahasia yang dipergunakan hanya untuk keperluan evaluasi oleh yang berwenang.

Pasal 28

(1) Dokumen administratif sebagaimana dimaksud dalam Pasal 27 ayat (1) huruf a sesuai dengan contoh sebagaimana tercantum dalam Lampiran VI yang merupakan bagian tidak terpisahkan dari Peraturan Kepala Badan ini.

(2) Dokumen mutu sebagaimana dimaksud dalam Pasal 27 ayat (1) huruf b tercantum dalam Lampiran VII yang merupakan bagian tidak terpisahkan dari Peraturan Kepala Badan ini.

(3) Dokumen nonklinik sebagaimana dimaksud dalam Pasal 27 ayat (1) huruf c tercantum dalam Lampiran VIII yang merupakan bagian tidak terpisahkan dari Peraturan Kepala Badan ini.

(4) Dokumen klinik sebagaimana dimaksud dalam Pasal 27 ayat (1) huruf d tercantum dalam Lampiran IX yang merupakan bagian tidak terpisahkan dari Peraturan Kepala Badan ini.

Pasal 29

(1) Dokumen Informasi Produk sebagaimana dimaksud dalam Pasal 27 ayat (1) huruf a terdiri atas:
   a. Ringkasan Karakteristik Produk/Brosur; dan
   b. Informasi Produk untuk Pasien.

(2) Informasi Produk untuk Pasien sebagaimana dimaksud pada ayat (1) huruf b, untuk golongan Obat tanpa resep dokter harus disertakan pada kemasan terkecil, dapat berupa *catch cover*/amplop, blister, atau brosur yang melekat kuat pada kemasan terkecil, yang terbaca selama penggunaan Obat.

(3) Dokumen Informasi Produk sebagaimana dimaksud pada ayat (1) paling sedikit harus mencantumkan informasi sebagaimana tercantum dalam Lampiran X yang merupakan bagian tidak terpisahkan dari Peraturan Kepala Badan ini.

Pasal 30

(1) Dokumen Label sebagaimana dimaksud dalam Pasal 27 ayat (1) huruf a meliputi etiket, strip/blister, ampul/vial, *catch cover*/amplop, dan bungkus luar.

(2) Label sebagaimana dimaksud pada ayat (1) harus mencantumkan identitas yang mampu telusur untuk menjamin keabsahan produk.

(3) Ketentuan lebih lanjut mengenai identitas yang mampu telusur untuk menjamin keabsahan produk sebagaimana dimaksud pada ayat (2) diatur dengan Peraturan Kepala Badan.

(4) Informasi minimal yang harus dicantumkan pada Label sebagaimana dimaksud pada ayat (1) tercantum dalam Lampiran XI yang merupakan bagian tidak terpisahkan dari Peraturan Kepala Badan ini.

Pasal 31

(1) Informasi Produk untuk Pasien sebagaimana dimaksud dalam Pasal 29 ayat (1) huruf b harus menggunakan bahasa Indonesia, huruf Latin, dan angka Arab.

(2) Penggunaan bahasa selain bahasa Indonesia sebagaimana dimaksud pada ayat (1) dapat dilakukan sepanjang tidak ada padanannya dalam bahasa Indonesia.

(3) Selain menggunakan bahasa Indonesia sebagaimana dimaksud pada ayat (1), Informasi Produk untuk Pasien dapat ditambahkan bahasa Inggris sesuai dengan informasi yang disetujui.

(4) Dikecualikan dari ketentuan sebagaimana dimaksud pada ayat (1) untuk Obat khusus ekspor.

Paragraf Kedua

Tanggung Jawab Pendaftar

Pasal 32

(1) Pendaftar bertanggung jawab atas:

a. kelengkapan dokumen yang diserahkan;

b. kebenaran dan keabsahan informasi yang tercantum dalam dokumen registrasi; dan

c. perubahan data dan Informasi Produk yang sedang dalam proses Registrasi atau sudah memiliki Izin Edar.

(2) Tanggung jawab Pendaftar sebagaimana dimaksud pada ayat (1) harus dinyatakan secara tertulis dalam surat penyataan tercantum dalam Lampiran XII yang merupakan bagian tidak terpisahkan dari Peraturan Kepala Badan ini.

(3) Setiap perubahan data dan/atau Informasi Produk sebagaimana dimaksud pada ayat (1) huruf c harus mendapatkan persetujuan Kepala Badan.

Bagian Kedua

Praregistrasi

Pasal 33

Permohonan praregistrasi Obat dilakukan untuk penapisan Registrasi meliputi penentuan kategori Registrasi, penentuan jalur evaluasi, penentuan biaya evaluasi, dan penentuan dokumen registrasi.

Pasal 34

Dikecualikan dari ketentuan sebagaimana dimaksud dalam Pasal 33 untuk:

a. Registrasi Obat Generik kategori 2 produksi dalam negeri sebagaimana dimaksud dalam Pasal 5 ayat (2) huruf b;

b. Registrasi Variasi kategori 4 yang tidak memerlukan uji klinik sebagaimana dimaksud dalam Pasal 5 ayat (3) huruf a, kategori 5, dan kategori 6 sebagaimana dimaksud dalam Pasal 5 ayat (3) huruf b dan huruf c; dan

c. Registrasi Ulang kategori 7 sebagaimana dimaksud dalam Pasal 5 ayat (4).

Pasal 35

Permohonan sebagaimana dimaksud dalam Pasal 33 diajukan dengan:

a. mengisi Formulir sebagaimana tercantum dalam Lampiran II yang merupakan bagian tidak terpisahkan dari Peraturan Kepala Badan ini;
b. menyerahkan bukti pembayaran biaya praregistrasi; dan
c. melampirkan dokumen sebagaimana tercantum dalam Lampiran XIII yang merupakan bagian tidak terpisahkan dari Peraturan Kepala Badan ini.

Pasal 36

(1) Hasil Praregistrasi (HPR) diterbitkan dalam jangka waktu paling lama 40 (empat puluh) Hari terhitung sejak diterimanya permohonan sebagaimana dimaksud dalam Pasal 33.
(2) HPR sebagaimana dimaksud pada ayat (1) bersifat mengikat dan berlaku selama 1 (satu) tahun sejak tanggal diterbitkan.
(3) Dalam hal diperlukan tambahan data, permintaan tambahan data disampaikan secara tertulis kepada Pendaftar.
(4) Dalam hal Pendaftar diberikan surat permintaan tambahan data sebagaimana dimaksud pada ayat (3), perhitungan jangka waktu sebagaimana dimaksud pada ayat (1) dihentikan (*clock off*) sampai Pendaftar menyampaikan tambahan data yang diminta.
(5) Paling lama 20 (dua puluh) Hari terhitung sejak tanggal surat permintaan tambahan data, Pendaftar harus menyampaikan tambahan data.
(6) Perhitungan waktu evaluasi akan dilanjutkan (*clock on*) setelah Pendaftar menyerahkan tambahan data secara lengkap.
(7) Dalam hal Pendaftar tidak dapat menyampaikan tambahan data dalam jangka waktu 20 (dua puluh) Hari sebagaimana dimaksud pada ayat (5), Pendaftar dapat

mengajukan perpanjangan pemenuhan tambahan data 1 (satu) kali dengan dilengkapi justifikasi.

(8) Dalam hal Pendaftar tidak dapat menyampaikan tambahan data sebagaimana dimaksud pada ayat (7), praregistrasi dinyatakan batal dan biaya yang sudah dibayarkan tidak dapat ditarik kembali.

Bagian Ketiga

Jalur Evaluasi

Pasal 37

(1) Jalur evaluasi terdiri atas:

a. jalur 7 (tujuh) Hari meliputi Registrasi Obat khusus ekspor;

b. jalur 10 (sepuluh) Hari meliputi Registrasi Ulang;

c. jalur 40 (empat puluh) Hari meliputi Registrasi Variasi Minor;

d. jalur 100 (seratus) Hari meliputi:

1) Registrasi Baru Obat Baru dan Produk Biologi yang diindikasikan untuk terapi penyakit serius yang mengancam nyawa manusia *(life saving)*, dan/atau mudah menular kepada orang lain, dan/atau belum ada atau kurangnya pilihan terapi lain yang aman dan efektif;

2) Registrasi Baru Obat Baru dan Produk Biologi yang berdasarkan justifikasi diindikasikan untuk penyakit serius dan langka *(Orphan Drug)* di Indonesia;

3) Registrasi Baru Obat Baru, Produk Biologi, Obat Generik, dan Obat Generik Bermerek ditujukan untuk program kesehatan nasional yang dilengkapi dengan dokumen penunjang kebutuhan program atau hasil prakualifikasi Badan Kesehatan Dunia (*World Health Organization*);

4) Registrasi Baru Obat Baru dan Produk Biologi yang telah melalui proses Obat Pengembangan

Baru yang dikembangkan oleh institusi riset atau Industri Farmasi di Indonesia, dibuat oleh Industri Farmasi di Indonesia dan sekurangnya 1 (satu) uji klinik dilakukan di Indonesia;

5) Registrasi Baru Obat Generik yang memiliki Formula, sumber bahan baku, spesifikasi Obat, mutu, spesifikasi kemasan, proses produksi, dan menggunakan fasilitas produksi yang sama dengan Obat Generik Bermerek yang telah disetujui;

6) Registrasi Variasi Major indikasi baru/posologi baru untuk Obat yang ditujukan sebagaimana dimaksud pada angka 1) sampai dengan angka 4);

7) Registrasi Variasi Major terkait mutu dan Informasi Produk.

e. jalur 120 (seratus dua puluh) Hari meliputi Registrasi Baru Obat Baru dan Registrasi Variasi Major indikasi baru/posologi baru yang telah disetujui sekurangnya di 3 (tiga) negara dengan sistem evaluasi yang telah dikenal baik;

f. jalur 150 (seratus lima puluh) Hari meliputi Registrasi Baru Obat Generik dan Obat Generik Bermerek yang tidak termasuk dalam jalur evaluasi sebagaimana dimaksud pada huruf d;

g. jalur 300 (tiga ratus) Hari meliputi Registrasi Baru Obat Baru dan Produk Biologi serta Registrasi Variasi Major indikasi baru/posologi baru yang tidak termasuk dalam jalur evaluasi sebagaimana dimaksud pada huruf d dan huruf e.

(2) Kriteria penetapan jalur 120 (seratus dua puluh) Hari sebagaimana tercantum pada ayat (1) huruf e mengacu sebagaimana tercantum dalam Lampiran XIII yang merupakan bagian tidak terpisahkan dari Peraturan Kepala Badan ini.

Bagian Keempat

Registrasi Baru

Pasal 38

(1) Permohonan Registrasi Baru diajukan dengan mengisi Formulir sebagaimana contoh tercantum dalam Lampiran II dan melampirkan dokumen registrasi.

(2) Kelengkapan dokumen Registrasi Baru sebagaimana dimaksud pada ayat (1) mengacu sebagaimana tercantum dalam Lampiran XIV yang merupakan bagian tidak terpisahkan dari Peraturan Kepala Badan ini.

(3) Dikecualikan dari ketentuan sebagaimana dimaksud pada ayat (2), untuk Registrasi Obat khusus ekspor mengacu pada persyaratan sebagaimana tercantum dalam Lampiran XV yang merupakan bagian tidak terpisahkan dari Peraturan Kepala Badan ini.

Pasal 39

(1) Selain harus melengkapi dokumen Registrasi Baru sebagaimana dimaksud dalam Pasal 38 ayat (2), untuk Registrasi Baru kategori 1 sebagaimana dimaksud dalam Pasal 5 ayat (2) huruf a, Pendaftar juga harus menyerahkan rencana manajemen risiko.

(2) Ketentuan lebih lanjut mengenai penilaian rencana manajemen risiko sebagaimana dimaksud pada ayat (1) diatur dengan Peraturan Kepala Badan.

Bagian Kelima

Registrasi Variasi

Pasal 40

(1) Perubahan terhadap Obat yang telah mendapatkan Izin Edar dapat berupa perubahan aspek administratif, khasiat, keamanan, mutu, dan/atau Informasi Produk dan Label.

(2) Perubahan sebagaimana dimaksud pada ayat (1) harus dilaporkan kepada Kepala Badan melalui mekanisme Registrasi Variasi.

(3) Permohonan Registrasi Variasi sebagaimana dimaksud dalam Pasal 5 ayat (3) diajukan dengan mengisi Formulir sebagaimana contoh tercantum dalam Lampiran II dan melampirkan dokumen Registrasi Variasi sesuai dengan perubahan yang diajukan mengacu sebagaimana tercantum dalam Lampiran XVI yang merupakan bagian tidak terpisahkan dari Peraturan Kepala Badan ini.

Pasal 41

(1) Dikecualikan dari ketentuan sebagaimana dimaksud dalam Pasal 40 ayat (1) untuk Registrasi Variasi Notifikasi sebagaimana dimaksud dalam Pasal 5 ayat (3) huruf c, Pendaftar dapat melakukan perubahan dan melaporkan kepada Kepala Badan paling lambat 6 (enam) bulan sejak dilakukan perubahan.

(2) Jika perubahan yang dilaporkan tidak sesuai dengan jenis perubahan sebagaimana tercantum dalam Lampiran XVI huruf B angka 3, notifikasi tersebut ditolak dan Pendaftar harus melakukan Registrasi sesuai dengan kategori Registrasi Variasi yang ditetapkan.

(3) Implementasi perubahan sebagaimana dimaksud pada ayat (1) dilakukan melalui mekanisme pengendalian perubahan.

(4) Terhadap perubahan sebagaimana dimaksud pada ayat (1) dapat dilakukan verifikasi setempat dan Pendaftar harus dapat menunjukkan dokumentasi terkait perubahan yang diajukan.

(5) Jika hasil verifikasi tidak sesuai dengan jenis perubahan notifikasi yang dilaporkan, notifikasi tersebut ditolak dan Pendaftar dapat dikenai sanksi sesuai dengan ketentuan peraturan perundang-undangan.

Bagian Keenam

Registrasi Ulang

Pasal 42

(1) Registrasi Ulang diajukan paling cepat 12 (dua belas) bulan dan paling lambat 2 (dua) bulan sebelum berakhir masa berlaku Izin Edar.

(2) Dikecualikan dari ketentuan sebagaimana dimaksud pada ayat (1), permohonan Registrasi Ulang tanpa perubahan dapat diajukan paling lambat 1 (satu) bulan sebelum berakhir masa Izin Edar.

(3) Permohonan Registrasi Ulang sebagaimana dimaksud pada ayat (1) dan ayat (2) diajukan dengan mengisi Formulir sebagaimana contoh tercantum dalam Lampiran II dan melampirkan dokumen Registrasi Ulang sebagaimana tercantum dalam Lampiran XVII yang merupakan bagian tidak terpisahkan dari Peraturan Kepala Badan ini.

(4) Perpanjangan Izin Edar sebagai persetujuan atas permohonan Registrasi Ulang sebagaimana dimaksud pada ayat (1) dan ayat (2) berlaku sejak berakhir masa Izin Edar yang lama, sepanjang tidak terdapat:

a. perubahan Zat Aktif;
b. perubahan produsen Obat;
c. perubahan Pendaftar;
d. perubahan bentuk sediaan;
e. perubahan Formula;
f. perubahan jenis dan besar kemasan; dan/atau
g. pelanggaran terhadap ketentuan peraturan perundang-undangan.

(5) Dalam hal Registrasi Ulang terdapat perubahan sebagaimana dimaksud pada ayat (4) huruf a sampai dengan huruf f, Registrasi diproses sesuai dengan kategori Registrasi Variasi.

(6) Obat yang tidak diregistrasi ulang sampai dengan jangka waktu sebagaimana dimaksud pada ayat (1) dan ayat (2), dapat diajukan kembali sebagai Registrasi Baru dengan

mengikuti tata cara sebagaimana diatur dalam Pasal 25 sampai dengan Pasal 39.

Bagian Ketujuh

Contoh Obat dan Baku Pembanding

Pasal 43

Kepala Badan dapat mewajibkan kepada Pendaftar untuk menyerahkan contoh Obat, bahan Obat, dan baku pembanding sesuai dengan kebutuhan.

BAB VI

EVALUASI DAN PEMBERIAN KEPUTUSAN

Bagian Kesatu

Evaluasi

Pasal 44

(1) Terhadap pengajuan permohonan Registrasi yang telah dinyatakan memenuhi kelengkapan dokumen sebagaimana dimaksud dalam Pasal 27 ayat (1), dilakukan evaluasi.
(2) Evaluasi sebagaimana dimaksud pada ayat (1) merupakan penilaian terhadap aspek khasiat, keamanan, mutu, Informasi Produk, dan/atau Label sesuai dengan kriteria dan kategori Registrasi sebagaimana dimaksud dalam Pasal 4 dan Pasal 5.
(3) Evaluasi sebagaimana dimaksud pada ayat (1) dilaksanakan sesuai dengan jalur evaluasi sebagaimana dimaksud dalam Pasal 37.
(4) Perhitungan waktu evaluasi sebagaimana dimaksud pada ayat (2) sesuai dengan jalur evaluasi sebagaimana dimaksud dalam Pasal 37 dihitung sejak dokumen registrasi sebagaimana dimaksud dalam Pasal 27 ayat (1) diterima.

Pasal 45

(1) Evaluasi sebagaimana dimaksud dalam Pasal 44 dilakukan terhadap data khasiat dan keamanan berdasarkan pembuktian ilmiah dan pedoman penilaian khasiat keamanan oleh Tim Penilai Khasiat-Keamanan.

(2) Tim Penilai Obat Nasional (TPON) melakukan pembahasan terhadap hasil evaluasi sebagaimana dimaksud pada ayat (1) dan memberikan rekomendasi keputusan kepada Kepala Badan.

(3) Dalam hal diperlukan klarifikasi dan/atau penjelasan teknis secara rinci terhadap dokumen registrasi sebagaimana dimaksud dalam Pasal 27 ayat (1), TPON dapat meminta klarifikasi kepada Pendaftar melalui dengar pendapat.

(4) Untuk pelaksanaan dengar pendapat sebagaimana dimaksud pada ayat (3), Kepala Badan menyampaikan pemberitahuan secara tertulis kepada Pendaftar.

(5) Kepala Badan menyampaikan keputusan hasil evaluasi sebagaimana dimaksud pada ayat (2) secara tertulis kepada Pendaftar paling lama 30 (tiga puluh) Hari terhitung sejak pelaksanaan rapat berkala TPON.

Pasal 46

(1) Evaluasi data mutu dilakukan oleh Tim Penilai Mutu sesuai dengan kriteria sebagaimana dimaksud dalam Pasal 4 ayat (1) huruf b didasarkan pada kesahihan informasi dokumen dan data inspeksi CPOB terakhir.

(2) Informasi dalam dokumen mutu sebagaimana dimaksud pada ayat (1) harus menggunakan data sahih dan aktual, Formula sesuai dengan Formula yang akan dipasarkan, dan proses pembuatannya telah tervalidasi.

(3) Jika diperlukan, untuk memastikan kesahihan informasi dokumen sebagaimana dimaksud pada ayat (1) dilakukan pemeriksaan setempat di fasilitas pembuatan Obat (*in-situ*).

Pasal 47

(1) Evaluasi Informasi Produk dan Label dilakukan oleh Tim Penilai Informasi Produk dan Label untuk memastikan bahwa informasi yang tercantum pada Informasi Produk dan Label sesuai dengan kriteria sebagaimana dimaksud dalam Pasal 4 ayat (1) huruf c.

(2) Evaluasi Informasi Produk dan Label sebagaimana dimaksud pada ayat (1) mengacu pada:
   a. hasil evaluasi khasiat, keamanan, dan mutu sebagaimana dimaksud dalam Pasal 45 dan Pasal 46;
   b. Informasi Produk Obat Baru yang telah disetujui oleh Kepala Badan; atau
   c. standar informasi Obat yang ditetapkan oleh Kepala Badan.

Pasal 48

(1) Dalam hal diperlukan tambahan data, Kepala Badan menyampaikan permintaan tambahan data secara tertulis kepada Pendaftar.

(2) Pendaftar harus menyampaikan tambahan data sebagaimana dimaksud pada ayat (1) paling lama 100 (seratus) Hari terhitung sejak tanggal permintaan tambahan data.

(3) Dalam hal Pendaftar tidak dapat menyampaikan tambahan data dalam jangka waktu 100 (seratus) Hari sebagaimana dimaksud pada ayat (2), Pendaftar dapat mengajukan perpanjangan pemenuhan tambahan data 1 (satu) kali dengan dilengkapi justifikasi.

(4) Dalam hal diperlukan tambahan data sebagaimana dimaksud pada ayat (1), perhitungan waktu evaluasi dihentikan (*clock off*).

(5) Perhitungan waktu evaluasi akan dilanjutkan (*clock on*) setelah Pendaftar menyerahkan tambahan data secara lengkap.

(6) Dalam hal Pendaftar tidak dapat memenuhi ketentuan sebagaimana dimaksud pada ayat (2) dan ayat (3),

Registrasi dinyatakan batal dan biaya yang sudah dibayarkan tidak dapat ditarik kembali.

(7) Registrasi yang dinyatakan batal sebagaimana dimaksud pada ayat (6), dapat diajukan kembali dengan mengikuti tata cara sebagaimana diatur dalam Pasal 25 sampai dengan Pasal 43.

Bagian Kedua

Pemberian Keputusan

Pasal 49

(1) Keputusan Kepala Badan terhadap Registrasi diberikan dengan mempertimbangkan:
   a. hasil evaluasi dokumen registrasi dan/atau rekomendasi TPON/Tim Penilai Khasiat-Keamanan/Tim Penilai Mutu/Tim Penilai Informasi Produk dan Label; dan/atau
   b. hasil pemeriksaan setempat di fasilitas pembuatan Obat (*in-situ*).

(2) Keputusan sebagaimana dimaksud pada ayat (1) berupa:
   a. pemberian persetujuan; atau
   b. penolakan.

(3) Pemberian persetujuan sebagaimana dimaksud pada ayat (2) huruf a hanya diberikan kepada Pendaftar yang memenuhi persyaratan administrasi dan ketentuan sebagaimana dimaksud dalam Pasal 4.

(4) Penolakan sebagaimana dimaksud pada ayat (2) huruf b diberikan jika dokumen registrasi tidak memenuhi ketentuan sebagaimana dimaksud dalam Pasal 4.

Paragraf Kesatu

Persetujuan

Pasal 50

(1) Sebelum diterbitkan persetujuan sebagaimana dimaksud dalam Pasal 49 ayat (2) huruf a dapat diterbitkan surat pemberitahuan persetujuan (*approvable letter*).

(2) Dalam hal diterbitkan surat pemberitahuan persetujuan (*approvable letter)* sebagaimana dimaksud pada ayat (1), Pendaftar dapat:

a. melakukan pembuatan Obat skala komersial; atau

b. melaksanakan pemasukan Obat Impor.

(3) Dalam hal Pendaftar melaksanakan pemasukan Obat Impor sebagaimana dimaksud pada ayat (2) huruf b, persyaratan harus memiliki Izin Edar dapat menggunakan surat pemberitahuan persetujuan (*approvable letter)* untuk penerbitan surat keterangan impor atau surat persetujuan impor.

(4) Surat pemberitahuan persetujuan (*approvable letter)* sebagaimana dimaksud pada ayat (1) bukan dimaksudkan sebagai pengganti Izin Edar dan hanya dapat digunakan untuk 1 (satu) kali pemasukan.

(5) Surat pemberitahuan persetujuan (*approvable letter)* sebagaimana dimaksud pada ayat (1) berlaku dalam jangka waktu paling lama 2 (dua) tahun terhitung sejak tanggal surat pemberitahuan diterbitkan.

Pasal 51

(1) Persetujuan sebagaimana dimaksud dalam Pasal 49 ayat (2) huruf a diberitahukan secara tertulis kepada Pendaftar berupa:

a. Izin Edar;

b. persetujuan khusus ekspor; atau

c. persetujuan Registrasi Variasi.

(2) Izin Edar sebagaimana dimaksud pada ayat (1) huruf a diterbitkan apabila hasil pembuatan Obat skala komersial memenuhi persyaratan atau telah menyerahkan bukti pemasukan Obat Impor.

Pasal 52

(1) Persetujuan Registrasi Variasi sebagaimana dimaksud dalam Pasal 51 ayat (1) huruf c berupa:

a. Izin Edar baru; atau

b. surat persetujuan Registrasi Variasi yang merupakan adendum Izin Edar.

(2) Persetujuan Registrasi Variasi sebagaimana dimaksud pada ayat (1) wajib dilaksanakan paling lambat 6 (enam) bulan sejak tanggal persetujuan diterbitkan.

(3) Persetujuan lama masih dapat diproduksi paling lama 6 (enam) bulan setelah diterbitkannya persetujuan baru selama persetujuan baru belum dilaksanakan.

(4) Obat sesuai dengan persetujuan lama yang diproduksi sebelum pelaksanaan persetujuan Registrasi Variasi sebagaimana dimaksud pada ayat (3) dapat diedarkan sepanjang masih memenuhi persyaratan mutu.

(5) Pendaftar wajib melaporkan jumlah, nomor bets, dan tanggal kedaluwarsa bets terakhir yang diedarkan sebelum pelaksanaan Registrasi Variasi sebagaimana dimaksud pada ayat (3) kepada Kepala Badan.

(6) Dikecualikan dari ketentuan sebagaimana dimaksud pada ayat (2) sampai dengan ayat (4) untuk perubahan:
   a. Pendaftar; atau
   b. terkait pengetatan aspek keamanan sebagai tindak lanjut hasil pengawasan, dilaksanakan sesuai dengan ketentuan yang ditetapkan.

Paragraf Kedua

Penolakan

Pasal 53

(1) Kepala Badan menyampaikan penolakan sebagaimana dimaksud dalam Pasal 49 ayat (2) huruf b secara tertulis kepada Pendaftar.

(2) Dalam hal permohonan Registrasi ditolak, biaya Registrasi yang telah dibayarkan tidak dapat ditarik kembali.

(3) Registrasi yang ditolak sebagaimana dimaksud pada ayat (1), dapat diajukan kembali dengan mengikuti tata cara sebagaimana diatur dalam Pasal 25 sampai dengan Pasal 43.

Bagian Ketiga

Peninjauan Kembali

Pasal 54

(1) Dalam hal adanya keberatan terhadap keputusan penolakan sebagaimana dimaksud dalam Pasal 49 ayat (2) huruf b, Pendaftar dapat mengajukan permohonan peninjauan kembali secara tertulis kepada Kepala Badan.

(2) Peninjauan kembali sebagaimana dimaksud pada ayat (1) dapat diajukan dalam jangka waktu paling lama 6 (enam) bulan terhitung sejak tanggal surat penolakan dan hanya dapat dilakukan 1 (satu) kali.

Pasal 55

Dalam hal adanya keberatan terhadap hasil evaluasi khasiat dan keamanan sebagaimana dimaksud dalam Pasal 49 ayat (1) huruf a, Pendaftar dapat mengajukan permohonan peninjauan kembali secara tertulis kepada Kepala Badan paling lama 20 (dua puluh) Hari terhitung sejak tanggal surat pemberitahuan hasil evaluasi khasiat dan keamanan dan hanya dapat dilakukan 1 (satu) kali.

Pasal 56

(1) Permohonan peninjauan kembali sebagaimana dimaksud dalam Pasal 54 dan Pasal 55 dapat dilakukan melalui mekanisme dengar pendapat dan/atau menyerahkan dokumen berupa data baru dan/atau data yang sudah pernah diajukan dengan dilengkapi justifikasi.

(2) Pembahasan terhadap permohonan peninjauan kembali sebagaimana dimaksud dalam Pasal 54 dan Pasal 55 dilakukan paling lama 100 (seratus) Hari terhitung sejak dokumen diterima.

Bagian Keempat

Pengajuan Kembali Registrasi

Pasal 57

(1) Dalam hal Registrasi ditolak, Pendaftar dapat mengajukan permohonan Registrasi kembali dengan mengikuti tata cara sebagaimana diatur dalam Pasal 25 sampai dengan Pasal 43.

(2) Dalam hal Registrasi ditolak karena alasan tidak memenuhi kriteria khasiat dan keamanan, selain harus mengikuti ketentuan sebagaimana dimaksud pada ayat (1), pengajuan kembali Registrasi hanya dapat diajukan dengan data baru dan paling cepat 1 (satu) tahun setelah tanggal surat penolakan.

BAB VII

MASA BERLAKU IZIN EDAR

Pasal 58

(1) Izin Edar dan persetujuan khusus ekspor berlaku paling lama 5 (lima) tahun selama memenuhi ketentuan peraturan perundang-undangan.

(2) Dalam hal Izin Edar tidak diregistrasi ulang sebagaimana dimaksud dalam Pasal 42 ayat (1) dan ayat (2), Obat tidak dapat diproduksi dan/atau diedarkan, dan yang sudah beredar wajib dilakukan penarikan kembali.

(3) Dikecualikan dari ketentuan sebagaimana dimaksud pada ayat (1), untuk Registrasi Obat berdasarkan perjanjian/ penunjukan dengan masa kerja sama kurang dari 5 (lima) tahun, masa berlaku Izin Edar sesuai dengan masa berlaku kerja sama dalam dokumen perjanjian.

(4) Obat yang telah habis masa berlaku Izin Edarnya dapat diperpanjang selama memenuhi kriteria sebagaimana diatur dalam Pasal 42.

Pasal 59

Dalam hal perjanjian/penunjukan sebagaimana dimaksud dalam Pasal 58 ayat (3) dihentikan sebelum masa Izin Edar berakhir, Izin Edar Obat yang bersangkutan dinyatakan batal.

BAB VIII

PELAKSANAAN IZIN EDAR

Pasal 60

(1) Industri Farmasi yang telah mendapatkan Izin Edar wajib membuat dan mengirimkan laporan produksi atau laporan pemasukan Obat Impor kepada Kepala Badan.
(2) Laporan produksi atau laporan pemasukan Obat Impor sebagaimana dimaksud pada ayat (1) dilaksanakan sesuai dengan ketentuan peraturan perundang-undangan.
(3) Laporan produksi atau laporan pemasukan Obat Impor sebagaimana dimaksud pada ayat (1) tidak menghapuskan kewajiban bagi Industri Farmasi untuk menyampaikan laporan lain sesuai dengan ketentuan peraturan perundang-undangan.

Pasal 61

(1) Pemilik Izin Edar Obat wajib melakukan pemantauan khasiat, keamanan dan mutu Obat selama Obat diedarkan dan melaporkan hasilnya kepada Kepala Badan.
(2) Pemantauan khasiat, keamanan, dan mutu Obat selama Obat diedarkan sebagaimana dimaksud pada ayat (1) dilaksanakan sesuai dengan ketentuan peraturan perundang-undangan.

BAB IX

PENILAIAN KEMBALI

Pasal 62

(1) Terhadap Obat yang telah diberikan Izin Edar dapat dilakukan penilaian kembali.

(2) Penilaian kembali sebagaimana dimaksud pada ayat (1) dilakukan jika berdasarkan hasil pemantauan sebagaimana dimaksud dalam Pasal 61 ayat (2) terdapat data dan informasi terkini mengenai khasiat, keamanan, dan mutu Obat.

(3) Pelaksanaan penilaian kembali sebagaimana dimaksud pada ayat (1) mengacu sebagaimana tercantum dalam Lampiran XVIII yang merupakan bagian tidak terpisahkan dari Peraturan Kepala Badan ini.

(4) Keputusan terhadap hasil penilaian kembali sebagaimana dimaksud pada ayat (2) berupa:

a. perubahan Label;
b. perbaikan Komposisi/Formula;
c. pemberian batasan penggunaan;
d. perubahan penggolongan Obat;
e. penarikan Obat dari peredaran; dan/atau
f. pembekuan Izin Edar/pencabutan Izin Edar.

(5) Keputusan sebagaimana dimaksud pada ayat (4) disampaikan secara tertulis kepada Pemilik Izin Edar untuk ditindaklanjuti.

BAB X
SANKSI

Pasal 63

(1) Pelanggaran terhadap ketentuan dalam Peraturan Kepala Badan ini dapat dikenai sanksi administratif berupa:

a. peringatan tertulis;
b. pembatalan proses Registrasi;
c. pembekuan Izin Edar Obat;
d. pencabutan Izin Edar Obat; dan/atau
e. larangan untuk melakukan pendaftaran selama 2 (dua) tahun.

(2) Sanksi administratif sebagaimana dimaksud pada ayat (1) huruf b dan/atau huruf e dapat dikenai berdasarkan atau dalam hal:

a. tidak memenuhi ketentuan sebagaimana dimaksud dalam Pasal 4;

b. tidak memenuhi ketentuan sebagaimana dimaksud dalam Pasal 32 ayat (1) huruf b; dan/atau

c. data tidak sahih sebagaimana dimaksud dalam Pasal 46.

(3) Sanksi administratif sebagaimana dimaksud pada ayat (1) huruf c dan/atau huruf d dapat dikenai berdasarkan atau dalam hal:

a. tidak melaksanakan kewajiban sebagaimana dimaksud dalam Pasal 60 ayat (1) dan ayat (2);

b. izin Industri Farmasi Pemilik Izin Edar dicabut; dan/atau

c. Pemilik Izin Edar melakukan pelanggaran di bidang produksi, distribusi, promosi, dan/atau Label Obat.

BAB XI
KETENTUAN LAIN-LAIN

Pasal 64

(1) Untuk menjamin kestabilan Obat dalam bentuk sediaan oral padat, registrasi Obat dengan kemasan botol berisi paling banyak 100 (seratus) butir.

(2) Registrasi Obat dengan kemasan botol sebagaimana dimaksud pada ayat (1) hanya dapat dilakukan untuk Obat dengan Zat Aktif yang stabil.

Pasal 65

Jika Pendaftar melakukan Registrasi yang memiliki lebih dari 1 (satu) kekuatan Zat Aktif, maka harus memiliki perbedaan spesifikasi antara lain ukuran, bentuk, dan/atau warna.

BAB XII

KETENTUAN PERALIHAN

Pasal 66

Registrasi yang telah diajukan sebelum berlakunya Peraturan Kepala Badan ini, tetap diproses berdasarkan Peraturan Kepala Badan Pengawas Obat dan Makanan Nomor HK.03.1.23.10.11.08481 Tahun 2011 tentang Kriteria dan Tata Laksana Registrasi Obat sebagaimana telah beberapa kali diubah terakhir dengan Peraturan Kepala Badan Pengawas Obat dan Makanan Nomor 17 Tahun 2016 tentang Perubahan Kedua atas Peraturan Kepala Badan Pengawas Obat dan Makanan Nomor HK.03.1.23.10.11.08481 Tahun 2011 tentang Kriteria dan Tata Laksana Registrasi Obat.

BAB XIII

KETENTUAN PENUTUP

Pasal 67

Pada saat Peraturan Kepala Badan ini mulai berlaku:

1. Peraturan Kepala Badan Pengawas Obat dan Makanan Nomor HK.03.1.23.10.11.08481 Tahun 2011 tentang Kriteria dan Tata Laksana Registrasi Obat (Berita Negara Republik Indonesia Tahun 2011 Nomor 634);
2. Peraturan Kepala Badan Pengawas Obat dan Makanan Nomor 3 Tahun 2013 tentang Perubahan atas Peraturan Kepala Badan Pengawas Obat dan Makanan Nomor HK.03.1.23.10.11.08481 Tahun 2011 tentang Kriteria dan Tata Laksana Registrasi Obat (Berita Negara Republik Indonesia Tahun 2013 Nomor 540);
3. Peraturan Kepala Badan Pengawas Obat dan Makanan Nomor 17 Tahun 2016 tentang Perubahan Kedua atas Peraturan Kepala Badan Pengawas Obat dan Makanan Nomor HK.03.1.23.10.11.08481 Tahun 2011 tentang Kriteria dan Tata Laksana Registrasi Obat (Berita Negara Republik Indonesia Tahun 2016 Nomor 1140);

dicabut dan dinyatakan tidak berlaku lagi.

Pasal 68

Peraturan Kepala Badan ini mulai berlaku pada tanggal diundangkan.

Agar setiap orang mengetahuinya, memerintahkan pengundangan Peraturan Kepala Badan ini dengan penempatannya dalam Berita Negara Republik Indonesia.

Ditetapkan di Jakarta
pada tanggal 24 November 2017

KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA,

ttd.

PENNY K. LUKITO

Diundangkan di Jakarta
pada tanggal 24 November 2017

DIREKTUR JENDERAL
PERATURAN PERUNDANG-UNDANGAN
KEMENTERIAN HUKUM DAN HAK ASASI MANUSIA
REPUBLIK INDONESIA,

ttd.

WIDODO EKATJAHJANA

BERITA NEGARA REPUBLIK INDONESIA TAHUN 2017 NOMOR 1692

LAMPIRAN I
PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA
NOMOR 24 TAHUN 2017
TENTANG
KRITERIA DAN TATA LAKSANA REGISTRASI OBAT

PEDOMAN UMUM NAMA OBAT

Nama Obat harus memperhatikan ketentuan sebagai berikut:

1. Nama dagang harus objektif dan tidak menyesatkan.
2. Nama dagang yang sama hanya dapat digunakan oleh satu Industri Farmasi Pemilik Izin Edar untuk Obat dengan Zat Aktif, indikasi, dan golongan yang sama.
3. Nama dagang tidak boleh menggunakan seluruhnya atau potongan nama generik dari Zat Aktif yang tidak dikandung.
4. Nama dagang tidak boleh sama atau sangat mirip dalam hal bunyi atau penulisan dengan nama dagang Obat yang telah terdaftar dengan Zat Aktif yang berbeda.
5. Nama dagang golongan Obat tanpa resep dokter yang mengandung paling sedikit satu Zat Aktif yang sama dan/atau kelas terapi yang sama dapat menggunakan nama dagang yang sama sebagai nama payung.
6. Nama dagang tidak boleh menggunakan nama yang sama atau mirip dengan Obat yang sudah dibatalkan izin edarnya karena masalah keamanan, penyalahgunaan, dan pelanggaran lainnya.

KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA,

ttd.

PENNY K. LUKITO

LAMPIRAN II
PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA
NOMOR 24 TAHUN 2017
TENTANG
KRITERIA DAN TATA LAKSANA REGISTRASI OBAT

FORMULIR REGISTRASI

BADAN POM RI

BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA

FORMULIR REGISTRASI OBAT DAN PRODUK BIOLOGI

DOKUMEN RAHASIA

Diisi Oleh Badan POM

No. Pendaftaran

Tanggal Penerimaan *dd / mm / yyyy* Kode Evaluasi Subkode Evaluasi

A. URAIAN OBAT #)

Kategori registrasi

Jenis obat *) Baru Generik Produk Biologi

Jenis Produk *) Produk Tunggal Produk Kombinasi Produk *Combipack*

Golongan obat *) Keras Bebas Bebas Terbatas Narkotika Psikotropika

Nama Obat

Bentuk Sediaan Kekuatan Satuan ukuran

Kelas Terapi Kode ATC

Kemasan (Jenis dan Deskripsi)

Besar Kemasan

*) : Pilih salah satu

Bentuk Sediaan, Kekuatan, Kemasan lain

Bentuk Sediaan	Kekuatan	Jenis Kemasan	Besar Kemasan	NIE *)	Masa Berlaku NIE

*) : NIE : Nomor Izin Edar

B. KETERANGAN LENGKAP PENDAFTAR #)

Nama Pendaftar

Alamat Pendaftar Nama jalan dan nomor Kota Negara

Alamat Surat-menyurat Nama jalan dan nomor Kota Negara

Nomor telepon & fax *E-mail*

C. STATUS PRODUKSI #)

Status Produksi *) Produksi dalam negeri

Produksi sendiri

Produksi berdasarkan kontrak

Produksi berdasarkan lisensi

Impor ☐

Obat ditujukan hanya untuk ekspor *) Ya ☐ Tidak ☐

Nama Pemberi Lisensi

Alamat Pemberi Lisensi | Nama jalan dan nomor | Kota | Negara

Produsen

Nama	Alamat			SMF **)	CPOB	Fungsi/Peran
	Nama jalan dan nomor	Kota	Negara			

*) : Pilih salah satu **) : Tanda terima penyerahan

D. FORMULA #)

1. Zat Aktif

Satuan Dosis

CAS NO.	Nama	Jumlah	Satuan		Sumber hewan/manusia	Produsen	DMF**)	Negara Produsen

2. Eksipien

CAS NO.	Nama	Jumlah	Satuan		Sumber hewan/manusia	Fungsi	Produsen	Negara Produsen

3. Pelarut

CAS NO.	Nama	Jumlah	Satuan		Sumber hewan/manusia	Produsen	Negara Produsen

**) : Diisi bila DMF dipersyaratkan dan tersedia.

E. INFORMASI OBAT

Pemerian obat ##)

Spesifikasi dan Metode Analisis Obat ##) | Spesifikasi Obat | Metode Analisis Obat

Indikasi #)

Posologi #)

Rute Pemberian Obat #)

F. INFORMASI PRAREGISTRASI

Hasil Praregistrasi (HPR)*) Ada ☐ Tidak ☐

Tanggal Penerbitan HPR

Kategori Registrasi

Biaya Evaluasi Terbilang

Jalur Evaluasi *) 300 HK ☐ 150 HK ☐ 120 HK ☐ 100 HK ☐ 40 HK ☐ 10 HK ☐ 7 HK ☐

*) : Pilih salah satu

G. CARA PENYIMPANAN DAN BATAS KEDALUWARSA

Cara Penyimpanan	
Batas Kedaluwarsa	
Batas Kedaluwarsa setelah kemasan dibuka/rekonstitusi *)	

*) : Diisi untuk bentuk sediaan tertentu, misalnya tetes mata (setelah kemasan dibuka) atau serbuk liofilisasi untuk rekonstitusi (setelah obat di rekonstitusi)

H. STATUS REGISTRASI DI NEGARA LAIN *) ###)

Negara	Status Registrasi	Tanggal Persetujuan	Golongan Obat

*) : Diisi hanya untuk Obat Baru, Produk Biologi dan Obat Generik Impor

I. INFORMASI PATEN *) ###)

Judul Paten	Nomor Penerimaan Paten	Tanggal Penerimaan Paten

*) : Jika ada

J. RIWAYAT REGISTRASI ###)

Kategori registrasi	Tanggal Pengajuan	Tanggal Persetujuan	NIE	Masa Berlaku NIE

K. KETERANGAN SISTEM PENOMORAN BETS

L. INFORMASI HARGA

Kemasan	HNA *)	HET **)

*) : HNA : Harga Netto Apotek
**) : HET : Harga Eceran Tertinggi

M. KOMITMEN YANG HARUS DIPENUHI

N. DOKUMEN TEKNIS

Jenis Format Dokumen *) ACTD ☐ ICH CTD ☐

		Jumlah ordner/map	Jumlah Salinan
BAGIAN I	: Dokumen Administratif dan Informasi Produk		
BAGIAN II	: Dokumen Mutu		
BAGIAN III	: Dokumen Nonklinik		
BAGIAN IV	: Dokumen Klinik		

*) : Pilih salah satu

O. KETERANGAN PETUGAS REGISTRASI

Nama	
Jabatan	
Alamat	
Nomor telepon & fax	

Nomor telepon genggam	
E-mail	

Keterangan:

1. #) : Harus diisi pada saat pengajuan praregistrasi dan tidak dapat diperbaharui pada saat pengajuan Registrasi.

   ##) : Diisi pada saat pengajuan praregistrasi dan dapat diperbaharui pada saat pengajuan Registrasi.

2. Untuk Registrasi Variasi dan Registrasi Ulang yang diajukan bersamaan dengan perubahan tertentu, seluruh informasi yang tercantum dalam Formulir Registrasi harus diisi sesuai dengan yang telah disetujui, kecuali untuk bagian yang akan dilakukan perubahan maka informasi dapat diperbaharui.
3. Untuk Registrasi Ulang, seluruh informasi yang tercantum dalam Formulir Registrasi harus diisi sesuai dengan yang telah disetujui.

KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA,

ttd.

PENNY K. LUKITO

LAMPIRAN III
PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA
NOMOR 24 TAHUN 2017
TENTANG
KRITERIA DAN TATA LAKSANA REGISTRASI OBAT

PETUNJUK PENGISIAN FORMULIR REGISTRASI

A. URAIAN OBAT #)

1. Kategori Registrasi
   Diisi sesuai kategori Registrasi yang diajukan atau sesuai yang tercantum pada Hasil Praregistrasi (HPR).

2. Jenis Obat
   Diisi dengan tanda centang (√) pada salah satu pilihan sesuai jenis Obat yang didaftarkan, yaitu Obat Baru, Obat Generik (untuk Obat Generik dan Obat Generik Bermerek) atau Produk Biologi (untuk Produk Biologi dan Produk Biosimilar).

3. Jenis Produk
   Diisi dengan tanda centang (√) pada salah satu pilihan sesuai jenis produk, yaitu:
   a. Produk Tunggal, jika produk hanya terdiri dari Obat saja;
   b. Produk Kombinasi, jika produk terdiri dari Obat dan pelarut atau alat bantu penggunaan Obat (misalnya *syringe, aerosol, spray, implant*); atau
   c. Produk *Combipack*, jika produk terdiri dari dua atau tiga Obat yang dikemas dalam satu kemasan dengan tujuan untuk diberikan ke pasien secara bersamaan.

4. Golongan Obat
   Diisi dengan tanda centang (√) pada salah satu pilihan sesuai golongan Obat, yaitu Obat Keras, Obat Bebas, Obat Bebas Terbatas, Narkotika atau Psikotropika.

5. Nama Obat
   Diisi dengan nama Obat yang didaftarkan.

6. Bentuk sediaan, kekuatan dan satuan ukuran
   Bentuk sediaan dicantumkan terperinci dilengkapi dengan kekuatan sediaan dan satuan ukuran. Contoh: tablet salut gula 5 mg.

   6.1. Bentuk sediaan:
   Aerosol foam, aerosol metered dose, aerosol spray, oral spray, buscal spray, transdermal spray, topical spray, serbuk *spray,* eliksir, emulsi, enema, gas, gel, gel mata, granul *effervescent,* granula, *intra uterine device (IUD), implant,* kapsul, kapsul lunak, kapsul pelepasan lambat, kaplet, kaplet salut selaput, kaplet salut enterik, kaplet salut gula, kaplet pelepasan lambat, kaplet pelepasan cepat, kaplet kunyah, kaplet kunyah salut selaput, krim, krim lemak, larutan, larutan inhalasi, larutan injeksi, infus, obat kumur, ovula, pasta, pil, *patch, pessary,* salep, salep

mata, sampo, semprot hidung, serbuk *aerosol*, serbuk oral, serbuk inhaler, serbuk injeksi, serbuk injeksi liofilisasi, serbuk infus, serbuk obat luar/serbuk tabur, serbuk steril, serbuk *effervescent*, sirup, sirup kering, sirup kering pelepasan lambat, *subdermal implants*, supositoria, suspensi, suspensi injeksi, suspensi/cairan obat luar, cairan steril, cairan mata, cairan diagnostik, tablet, tablet *effervescent*, tablet hisap, tablet kunyah, tablet pelepasan cepat, tablet lepas lambat, tablet disintegrasi oral, tablet dispersibel, tablet cepat larut, tablet salut gula, tablet salut enterik, tablet salut selaput, tablet sublingual, tablet sublingual pelepasan lambat, tablet vaginal, tablet lapis, tablet lapis lepas lambat, *chewing gum*, tetes mata, tetes hidung, tetes telinga, tetes oral *(oral drops)*, tetes mata dan telinga, *transdermal*, *transdermal urethral*, *tulle*/plester obat, *vaginal cream, vaginal gel, vaginal douche, vaginal ring,* atau *vaginal tissue.*

6.2. Kekuatan sediaan:
Kekuatan sediaan dapat dinyatakan dengan bobot atau volume untuk:

6.2.1. tiap satu satuan bentuk sediaan untuk tablet, kapsul, pil, supositoria dan ovula.
6.2.2. tiap g atau % b/b untuk salep dan krim.
6.2.3. tiap mL atau tiap kemasan untuk larutan injeksi.
6.2.4. tiap kemasan dalam g atau mg untuk serbuk injeksi.
6.2.5. tiap 5 mL atau 15 mL untuk sirup, suspensi, emulsi, eliksir, obat kumur.
6.2.6. tiap mL atau % b/v untuk obat tetes.
6.2.7. tiap kemasan untuk serbuk pemakaian oral.
6.2.8. tiap g untuk serbuk pemakaian luar.
6.2.9. tiap dosis untuk *aerosol*/inhalasi/semprot dan sebagainya.
6.2.10. tiap satuan luas permukaan atau tiap satuan bobot untuk kasa atau plester.
6.2.11. tiap unit takaran/dosis bagi Produk Biologi.

6.3. Satuan ukuran:
Kadar Zat Aktif dan Eksipien dinyatakan dengan satuan ukuran:

6.3.1.	Kilogram	disingkat	kg
6.3.2.	Gram	disingkat	g
6.3.3.	Miligram	disingkat	mg
6.3.4.	Mikrogram	disingkat	mcg
6.3.5.	Liter	disingkat	L
6.3.6.	Mililiter	disingkat	mL
6.3.7.	Sentimeter	disingkat	cm
6.3.8.	Gram ekivalen	disingkat	grek
6.3.9.	Miligram ekivalen	disingkat	mgrek
6.3.10.	Unit internasional	disingkat	IU
6.3.11.	Micromole	disingkat	mcmol
6.3.12.	Mole	disingkat	mol
6.3.13.	Nanogram	disingkat	ng
6.3.14.	Sentimeter persegi	disingkat	cm^2
6.3.15.	*Colony forming units*	disingkat	CFU
6.3.16.	*Plaque forming units*	disingkat	PFU
6.3.17.	*Cell Culture Infectious Dose* 50%	disingkat	$CCID_{50}$

6.3.18. Jumlah antigen D	disingkat	D-Antigen Unit

7. Kelas Terapi dan Kode ATC
   Diisi sesuai *WHO Anatomical Therapeutic Chemical Code* yang diterbitkan oleh *WHO Collaborating Centre for Drug Statistics Methodology* (www.whocc.no/atc_ddd_index/).

8. Kemasan (Jenis dan Deskripsi)
   Pada kolom pertama dicantumkan jenis kemasan, misalnya blister, ampul, vial, botol, dan lain-lain.

   Pada kolom kedua dicantumkan deskripsi dan komposisi kemasan primer secara spesifik, termasuk jenis bahan, warna, ukuran dan sebagainya, misalnya:
   - Vial, kaca borosilikat coklat 20 mL tipe I dengan penutup karet.
   - Blister, PVC/PE dengan alu foil.

9. Besar Kemasan
   Dicantumkan jumlah sistem kemasan dalam kemasan sekunder dan jumlah bentuk sediaan per sistem kemasan, misalnya :
   - Dus, 1 blister @ 10 tablet.
   - Dus, 1 vial @ 5 mL.

   Dicantumkan pula pelarut dan/atau alat bantu penggunaan Obat yang disertakan dalam kemasan.

10. Bentuk sediaan, kekuatan, dan kemasan lain
    Diisi untuk bentuk sediaan, kekuatan, jenis kemasan, dan besar kemasan lain yang terdaftar dan/atau yang sedang didaftarkan. Nomor Izin Edar terakhir dicantumkan untuk Obat yang telah terdaftar disertai dengan masa berlaku Izin Edar.

B. KETERANGAN LENGKAP PENDAFTAR #)

1. Nama Pendaftar
   Diisi dengan nama Industri Farmasi Pendaftar sesuai dengan yang tercantum dalam surat izin Industri Farmasi.

2. Alamat Pendaftar
   Diisi dengan alamat Industri Farmasi Pendaftar sesuai dengan yang tercantum dalam surat izin Industri Farmasi lengkap dengan nama jalan, nomor, kota, dan negara.

3. Alamat Surat Menyurat
   Diisi dengan alamat surat-menyurat Industri Farmasi Pendaftar lengkap dengan nama jalan, nomor, kota, negara, nomor telepon dan fax, serta *e-mail* Pendaftar.

C. STATUS PRODUKSI #)

1. Status Produksi
   Diisi dengan tanda centang (√) pada salah satu pilihan sesuai status produksi Obat yang didaftarkan, yaitu produksi dalam negeri dan impor. Jika produksi dalam negeri, centang (√) pada salah satu

pilihan, yaitu produksi sendiri, produksi berdasarkan kontrak, atau produksi berdasarkan lisensi.

2. Obat ditujukan hanya untuk ekspor
   Diisi dengan tanda centang (√) pada salah satu pilihan, yaitu "Ya" jika Obat ditujukan hanya untuk ekspor dan "Tidak" jika Obat tidak hanya ditujukan untuk diekspor.

3. Nama Pemberi Lisensi
   Diisi dengan nama Industri Farmasi pemberi lisensi.

4. Alamat Pemberi Lisensi
   Diisi dengan alamat Industri Farmasi pemberi lisensi lengkap dengan nama jalan, nomor, kota, dan negara.

5. Produsen
   Diisi dengan keterangan lengkap produsen yaitu Industri Farmasi yang terlibat dalam proses produksi misalnya pembuatan Zat Aktif (khusus Produk Biologi), Obat setengah jadi/granulasi/bentuk sediaan setengah jadi (*bulk*) atau Obat jadi dan/atau pelarut dan/atau alat bantu penggunaan Obat, pengemasan primer dan/atau sekunder, penanggung jawab untuk pelulusan bets atau lainnya.

   5.1. Nama
   Diisi dengan nama Industri Farmasi pembuat Obat.

   5.2. Alamat
   Diisi dengan alamat lengkap dengan nama jalan, nomor, kota, dan negara.

   5.3. *SMF (Site Master File)* ##)
   Diisi dengan tanda centang (√) bila SMF dipersyaratkan dan tersedia.

   5.4. CPOB
   Diisi dengan tanggal berakhirnya masa berlaku sertifikat CPOB sesuai dengan bentuk sediaan produk yang didaftarkan.

   5.5. Fungsi/Peran
   Diisi dengan jenis pelaksanaan kegiatan (tahapan pembuatan) yang dikerjakan oleh produsen, misalnya pembuatan Zat Aktif (khusus Produk Biologi), Obat setengah jadi/granulasi/bentuk sediaan setengah jadi *(bulk)* atau Obat jadi dan/atau pelarut dan/atau alat bantu penggunaan Obat, pengemasan primer dan/atau sekunder, penanggung jawab untuk pelulusan bets atau lainnya.

D. FORMULA #)

1. Zat Aktif

   1.1 Satuan dosis
   Diisi dengan takaran dan satuan ukuran, misalnya "tiap 5 mL sirup mengandung:" atau "tiap tablet mengandung:". Untuk Zat Aktif dalam bentuk garam/ester harus dituliskan kesetaraan terhadap basenya jika zat yang aktif dalam bentuk base.

1.2 CAS No.
Diisi sesuai Zat Aktif yang digunakan.

1.3 Nama

1.3.1 Zat Aktif dituliskan sesuai *International Nonproprietary Names Modified (INNM).*

Bila nama belum tercantum dalam INNM, dituliskan sesuai *United States Adopted Names (USAN)* atau *British Approved Name Modified (BANM).*

1.3.2 Zat Aktif dalam bentuk ester atau garam dituliskan bentuk ester atau garamnya.

1.3.3 Zat Aktif berupa garam anorganik yang mengandung air kristal harus dituliskan nama kimianya secara tepat termasuk air kristal yang dikandungnya.
Contoh: Amoxicillin trihydrate.

1.3.4 Sesepora logam *(trace element)* dituliskan nama kimia garamnya yang tepat termasuk air kristal yang dikandungnya, di samping logamnya.

1.4 Jumlah
Diisi sesuai jumlah Zat Aktif yang digunakan per satuan dosis.

1.5 Satuan
Diisi sesuai satuan Zat Aktif yang digunakan (lihat tata cara penulisan satuan ukuran pada bagian A.6.3).

1.6 Sumber hewan/manusia
Pada kolom pertama dicantumkan "Ya" jika Zat Aktif bersumber dari hewan/manusia dan "Tidak" jika Zat Aktif tidak bersumber dari hewan/manusia.

Pada kolom kedua dicantumkan jenis hewan atau manusia sebagai sumber Zat Aktif.
Contoh: Ya; *bovine.*
Ya; human/manusia.

1.7 Produsen
Diisi dengan nama produsen Zat Aktif disertai alamat lengkap dengan nama jalan, nomor, dan kota.

1.8 *DMF (Drug Master File)*[##)]
Diisi dengan tanda centang (√) bila DMF dipersyaratkan dan tersedia.

1.9 Negara Produsen
Diisi dengan negara produsen Zat Aktif.

2. Eksipien

2.1 CAS No.
Diisi sesuai Eksipien yang digunakan.

2.2 Nama
Eksipien dan Eksipien dalam kombinasi dituliskan sesuai nama *International Nonproprietary Names* (INN) dan *International Nonproprietary Names Modified* (INNM).

Eksipien yang digunakan harus sesuai dengan ketentuan tentang bahan tambahan yang berlaku.

Zat warna dituliskan dengan nama sederhana yang umum/*common name*, harus dituliskan nomor indeks warnanya (*CI number*) dan mencantumkan kelarutan dalam air (*Dye*) atau dalam minyak (*Lake*). Contoh: Brilliant Blue FCF C142090 (*Dye*).

Zat warna yang digunakan harus sesuai dengan ketentuan tentang bahan tambahan yang berlaku.

2.3 Jumlah
Diisi sesuai jumlah Eksipien yang digunakan per satuan dosis.

2.4 Satuan
Diisi sesuai satuan Eksipien yang digunakan (lihat tata cara penulisan satuan ukuran pada item A.6.3).

2.5 Sumber hewan/manusia
Pada kolom pertama dicantumkan "Ya" jika Eksipien bersumber dari hewan/manusia dan "Tidak" jika Eksipien tidak bersumber dari hewan/manusia.

Pada kolom kedua dicantumkan jenis hewan atau manusia sebagai sumber Eksipien.
Contoh: Ya; *bovine.*
Ya; human/manusia.

2.6 Fungsi
Diisi sesuai fungsi/kegunaan Eksipien yang digunakan.

2.7 Produsen
Diisi dengan nama produsen Eksipien disertai alamat lengkap dengan nama jalan, nomor, dan kota.

2.8 Negara Produsen
Diisi dengan negara produsen Eksipien.

3. Pelarut

3.1. CAS No.
Diisi sesuai pelarut yang digunakan.

3.2. Nama
Pelarut dituliskan sesuai dengan nama yang tercantum dalam Farmakope Indonesia. Bila zat tersebut tidak terdapat dalam Farmakope Indonesia dituliskan nama sesuai dengan judul dalam *Merck Index*. Bila zat tersebut tidak terdapat dalam *Merck Index*, dituliskan nama kimianya sesuai dengan nomenklatur dari *IUPAC (International Union of Pure and Applied Chemistry)* atau *IUB (International Union of Biochemistry)*.

3.3. Jumlah
Diisi sesuai jumlah pelarut yang digunakan per satuan dosis.

3.4. Satuan
Diisi sesuai satuan pelarut yang digunakan (lihat tata cara penulisan satuan ukuran pada bagian A.6.3).

3.5. Sumber hewan/manusia
Pada kolom pertama dicantumkan "Ya" jika pelarut bersumber dari hewan/manusia dan "Tidak" jika pelarut tidak bersumber dari hewan/manusia.

Pada kolom kedua dicantumkan jenis hewan atau manusia sebagai sumber pelarut.
Contoh: Ya; *bovine.*
Ya; human/manusia.

3.6. Produsen
Diisi dengan nama produsen pelarut disertai alamat lengkap dengan nama jalan, nomor, dan kota.

3.7. Negara Produsen
Diisi dengan negara produsen pelarut.

E. INFORMASI OBAT

1. Pemerian Obat ##)
Dijelaskan bentuk, warna, ukuran, berat, dan tanda-tanda khusus yang terdapat pada Obat tersebut sesuai spesifikasi Obat.

2. Spesifikasi dan Metode Analisis Obat ##)
Spesifikasi Obat dinyatakan dengan menguraikan pemerian (termasuk tanda pengenal pada tablet, kapsul, dan lain-lain), bobot/volume obat, tetapan fisika dan kimia, batas kadar atau potensi dan persyaratan-persyaratan lainnya (sterilitas, pirogenitas, dan lain-lain).

Metode analisis Obat bila mengikuti salah satu Farmakope cukup dituliskan Farmakope yang digunakan yang dilengkapi dengan nomor edisi dan nomor halamannya. Bila tidak mengikuti salah satu Farmakope, dapat dituliskan *in-house.* Metode analisis yang perlu diterangkan meliputi metode identifikasi, penetapan kadar atau potensi dan metode analisis khusus (sterilitas, pirogenitas, dan sebagainya).

3. Indikasi #)
Dicantumkan indikasi yang diajukan atau yang telah disetujui secara lengkap. Merupakan indikasi pemakaian Obat dalam terapi, dicantumkan jenis-jenis penyakit yang diindikasikan.

4. Posologi #)
Dicantumkan posologi yang diajukan atau yang telah disetujui secara lengkap. Disebutkan cara penggunaan, jumlah, frekuensi, dan lama pemakaian. Cara penggunaan harus disebutkan dengan jelas, misalnya injeksi intravena, intramuskular atau yang lain. Jumlah pemakaian harus dinyatakan dalam takaran yang lazim dan batas-batas untuk orang dewasa maupun anak. Frekuensi pemakaian ialah jumlah pemberian dalam satu hari atau tiap berapa jam Obat itu diberikan.

Lama pemakaian diuraikan dengan menyebutkan berapa lama Obat itu harus/boleh diberikan, berapa lama pemakaian harus dihentikan sebelum dipakai kembali atau berapa lama Obat itu minimal harus digunakan.

5. Rute pemberian Obat #)
   Dijelaskan cara pemberian Obat misalnya peroral, parenteral misalnya injeksi intravena, topikal, dan lain-lain.

F. INFORMASI PRAREGISTRASI

1. Hasil Praregistrasi (HPR)
   Diisi dengan tanda centang (√) pada salah satu pilihan sesuai ada/tidaknya HPR.

2. Tanggal Penerbitan HPR
   Diisi dengan tanggal penerbitan HPR.

3. Kategori Registrasi
   Pada kolom pertama dicantumkan kategori Registrasi sesuai yang diajukan atau sesuai yang tercantum pada HPR.

   Pada kolom kedua dicantumkan informasi jenis kategori Registrasi secara rinci.

   Contoh: - Obat Baru dengan Zat Aktif baru.

   - Obat Generik yang memerlukan uji klinik.

4. Biaya Evaluasi
   Diisi dengan angka nominal dan terbilang sesuai kategori yang diajukan atau sesuai yang tercantum pada HPR atau sesuai ketentuan yang berlaku (jika tidak melalui proses praregistrasi).

5. Jalur Evaluasi
   Diisi dengan tanda centang (√) pada salah satu pilihan jalur evaluasi sesuai kategori Registrasi yang diajukan, atau sesuai yang tercantum pada HPR, yaitu 300 HK, 150 HK, 120 HK, 100 HK, 40 HK, 10 HK, atau 7 HK.

G. CARA PENYIMPANAN DAN BATAS KEDALUWARSA

1. Cara Penyimpanan
   Dicantumkan cara penyimpanan yang diajukan atau yang telah disetujui dilengkapi dengan suhu dan kelembaban.

2. Batas Kedaluwarsa
   Dicantumkan batas kedaluwarsa yang diajukan atau yang telah disetujui.

3. Batas Kedaluwarsa Setelah Kemasan Dibuka/Direkonstitusi
   Dicantumkan batas kedaluwarsa untuk bentuk sediaan tertentu, misalnya tetes mata (setelah kemasan dibuka) atau serbuk liofilisasi untuk rekonstitusi (setelah Obat direkonstitusi).

H. STATUS REGISTRASI DI NEGARA LAIN ##)

Diisi hanya untuk Obat Baru, Produk Biologi, dan Obat Generik impor.

1. Negara
   Diisi dengan nama negara lain tempat Obat tersebut diregistrasi.

2. Status Registrasi
   Diisi dengan status Registrasi di negara lain.

3. Tanggal Persetujuan
   Diisi dengan tanggal persetujuan di negara lain jika Obat telah disetujui di negara tersebut.

4. Golongan Obat
   Diisi dengan golongan Obat di negara lain.

I. INFORMASI PATEN ##)

Diisi jika ada.

1. Judul Paten
   Diisi dengan judul paten yang dikeluarkan oleh institusi terkait di Indonesia.

2. Nomor Penerimaan Paten
   Diisi dengan nomor penerimaan paten yang dikeluarkan oleh institusi terkait di Indonesia.

3. Tanggal Penerimaan Paten
   Diisi dengan tanggal penerimaan paten yang dikeluarkan oleh institusi terkait di Indonesia.

J. RIWAYAT REGISTRASI ##)

Diisi untuk Registrasi Variasi dan penambahan indikasi/posologi. Seluruh Registrasi yang pernah disetujui dan yang sedang dalam proses evaluasi (bila ada) harus dicantumkan.

1. Kategori Registrasi
   Diisi dengan kategori Registrasi yang pernah disetujui dan yang sedang dalam proses evaluasi (bila ada).

2. Tanggal Pengajuan
   Diisi dengan tanggal pengajuan Registrasi yang sedang dalam proses evaluasi (bila ada).

3. Tanggal Persetujuan
   Diisi dengan tanggal persetujuan untuk Obat yang disetujui sebelumnya.

4. NIE
   Diisi dengan NIE (Nomor Izin Edar) Obat yang disetujui sebelumnya.

5. Masa Berlaku NIE
   Diisi dengan masa berlaku NIE untuk Obat yang disetujui sebelumnya.

K. KETERANGAN SISTEM PENOMORAN BETS

Diisi dengan kode yang terdiri dari huruf Latin atau angka Arab atau gabungan keduanya yang merupakan tanda pengenal suatu bets, untuk penelusuran kembali riwayat lengkap pembuatan bets tersebut, termasuk tahap-tahap produksi, pengawasan, dan distribusi.

L. INFORMASI HARGA

1. Kemasan
   Diisi sesuai besar kemasan yang akan didaftarkan.

2. HNA
   Diisi dengan Harga Netto Apotek (HNA) tiap satuan kemasan hingga kemasan terkecil yang akan diberlakukan di seluruh Indonesia.

3. HET
   Diisi dengan Harga Eceran Tertinggi (HET) tiap satuan kemasan hingga kemasan terkecil yang akan diberlakukan di seluruh Indonesia.

M. KOMITMEN YANG HARUS DIPENUHI

Diisi dengan komitmen yang harus dipenuhi apabila ada persyaratan yang belum dapat diserahkan.

N. DOKUMEN TEKNIS

1. Jenis Format Dokumen
   Diisi dengan tanda centang (√) pada salah satu pilihan sesuai jenis format dokumen yang digunakan untuk Registrasi, yaitu format ACTD atau format ICH CTD.

2. Bagian I (Dokumen Administratif dan Informasi Produk)
   Diisi sesuai jumlah ordner/map dan jumlah salinan untuk Bagian I (Dokumen Administratif dan Informasi Produk).

3. Bagian II (Dokumen Mutu)
   Diisi sesuai jumlah ordner/map dan jumlah salinan untuk Bagian II (Dokumen Mutu).

4. Bagian III (Dokumen Nonklinik)
   Diisi sesuai jumlah ordner/map dan jumlah salinan untuk Bagian III (Dokumen Nonklinik).

5. Bagian IV (Dokumen Klinik)
   Diisi sesuai jumlah ordner/map dan jumlah salinan untuk Bagian IV (Dokumen Klinik).

O. KETERANGAN PETUGAS REGISTRASI ##)

Diisi dengan data diri petugas Registrasi.

1. Nama
   Diisi dengan nama lengkap petugas Registrasi Industri Farmasi Pendaftar.

2. Jabatan
   Diisi dengan jabatan petugas Registrasi di Industri Farmasi Pendaftar.

3. Alamat
   Diisi dengan alamat petugas Registrasi yang dapat dihubungi.

4. Nomor telepon dan fax
   Diisi dengan nomor telepon dan fax petugas Registrasi yang dapat dihubungi.

5. Nomor telepon genggam
   Diisi dengan nomor telepon genggam petugas Registrasi yang dapat dihubungi.

6. *E-mail*
   Diisi dengan alamat *e-mail* aktif petugas Registrasi.

Keterangan:

#) : Harus diisi pada saat pengajuan praregistrasi dan tidak dapat diperbaharui pada saat pengajuan Registrasi.
##) : Diisi pada saat pengajuan praregistrasi dan dapat diperbaharui pada saat pengajuan Registrasi.

Untuk Registrasi Variasi atau Registrasi Ulang yang diajukan bersamaan dengan perubahan tertentu, seluruh informasi yang tercantum dalam Formulir Registrasi harus diisi sesuai dengan yang telah disetujui, kecuali untuk bagian yang akan dilakukan perubahan maka informasi dapat diperbaharui.

Untuk Registrasi Ulang tanpa perubahan, seluruh informasi yang tercantum dalam Formulir Registrasi harus diisi sesuai dengan yang telah disetujui.

KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA,

ttd.

PENNY K. LUKITO

LAMPIRAN IV
PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA
NOMOR 24 TAHUN 2017
TENTANG
KRITERIA DAN TATA LAKSANA REGISTRASI OBAT

TATA CARA PENYUSUNAN DOKUMEN REGISTRASI

Dokumen registrasi terdiri dari empat bagian sebagai berikut:

1. Bagian I : Dokumen Administratif dan Informasi Produk terdiri dari:
   A. Daftar Isi Keseluruhan
   B. Dokumen Administratif
   C. Informasi Produk dan Label

2. Bagian II : Dokumen Mutu terdiri dari:
   A. Ringkasan Dokumen Mutu (RDM)
   B. Dokumen Mutu
   C. Daftar Pustaka

3. Bagian III : Dokumen Nonklinik terdiri dari:
   A. Tinjauan Studi Nonklinik
   B. Ringkasan dan Matriks Studi Nonklinik
   C. Laporan Studi Nonklinik (jika perlu)
   D. Daftar Pustaka

4. Bagian IV : Dokumen Klinik terdiri dari:
   A. Tinjauan Studi Klinik
   B. Ringkasan Studi Klinik
   C. Matriks Studi Klinik
   D. Laporan Studi Klinik
   E. Daftar Pustaka

Dokumen registrasi dapat berupa *hardcopy* atau *softcopy*.

I. Dokumen Registrasi *Hardcopy*

Setiap bagian pada dokumen registrasi harus dilengkapi daftar isi yang menunjukkan letak masing-masing dokumen dan diberi kertas pembatas antarbagian dan antardokumen. Pembatas antarbagian diberi judul sesuai nama bagian (contoh: Bagian IV.A. Tinjauan Studi Klinik) atau judul dokumen sesuai dengan format dokumen registrasi.

Setiap bagian dokumen registrasi harus dibundel dalam ordner/map terpisah atau beberapa bagian dokumen registrasi dapat digabungkan dalam ordner dengan kertas pembatas di antara setiap dokumen tersebut. Penggunaan ordner/map disesuaikan dengan banyaknya dokumen registrasi.

A. Jumlah salinan dokumen registrasi

	Obat Baru & Produk Biologi	Obat Generik	Variasi	Registrasi Ulang
Bagian I – Dokumen Administratif dan Informasi Produk				
- Sertifikat dan dokumen administratif lain	1 rangkap	1 rangkap	1 rangkap	1 rangkap
- Formulir Registrasi	3 rangkap	3 rangkap	3 rangkap	3 rangkap
- Label	1 rangkap*)	1 rangkap*)	1 rangkap*)	3 rangkap
- Informasi Produk	1 rangkap*)	1 rangkap*)	1 rangkap*)	4 rangkap
Bagian II – Dokumen Mutu	1 rangkap	1 rangkap	1 rangkap (jika perlu)	1 rangkap
Bagian III – Dokumen Nonklinik	1 rangkap	-	1 rangkap (jika perlu)	-
Bagian IV – Dokumen Klinik	1 rangkap (kecuali Tinjauan Studi Klinik dan Matriks Laporan Studi Klinik 2 rangkap)	1 rangkap (jika perlu)	1 rangkap (jika perlu)	1 rangkap (jika perlu)

*) Jika dokumen telah sesuai dengan hasil evaluasi, Pendaftar harus menyerahkan sebanyak 4 (empat) rangkap.

B. Ukuran kertas

Apabila dokumen registrasi dalam bentuk *hardcopy* harus menggunakan kertas ukuran standar Internasional (A4: 8.27 x 11,69 inci). Untuk kasus tertentu penggunaan kertas yang lebih besar dari ukuran standar diperbolehkan antara lain denah, diagram sintesis, Formula bets atau alur pembuatan Obat. Halaman kertas ini harus dilipat dan dapat dilihat tanpa membuka penutup ordner dan dapat dilipat kembali tanpa menimbulkan kerusakan pada saat penyimpanan.

C. Huruf

Ukuran huruf untuk narasi dan tabel harus menggunakan jenis dan ukuran yang cukup besar dan dapat terbaca dengan mudah, bahkan setelah digandakan atau ditampilkan secara elektronik.

Contoh: untuk narasi menggunakan huruf *Times New Roman* dengan ukuran 12. Untuk tabel, alur, dan diagram dapat menggunakan huruf ukuran 9 – 10.

D. Warna ordner atau map

Untuk dokumen *hardcopy* mengikuti ketentuan sebagai berikut:

Jenis Registrasi	Warna
Registrasi Baru, Variasi, dan Ulang Obat Baru	Biru
Registrasi Baru, Variasi, dan Ulang Produk Biologi	Abu-abu
Registrasi Baru Obat Generik	Hitam
Registrasi Variasi dan Ulang Obat Generik	Hijau
Registrasi Ulang Tanpa Perubahan	Kuning
Registrasi Obat Khusus Ekspor	Merah
Registrasi Variasi Notifikasi	Putih Transparan

E. Penomoran ordner/map

Setiap ordner/map harus diberikan nomor yang berbeda berdasarkan urutannya.

F. Identifikasi ordner/map

Pada bagian tengah sampul depan untuk setiap ordner/map harus dituliskan informasi sebagai berikut:

- Nama Obat.
- Bentuk Sediaan.
- Komposisi.
- Jenis dan Besar Kemasan.
- Nama Pendaftar.
- Nama Produsen.

Pada bagian depan dan samping ordner harus dituliskan nomor ordner, kecuali map hanya dicantumkan pada bagian depan dalam format berikut: x dari y dimana x adalah nomor ordner spesifik dan y adalah jumlah ordner total untuk bagian terkait. Contoh: ordner ke-6 untuk Bagian Keamanan dengan total 50 ordner untuk semua bagian dituliskan 6 dari 50 pada sudut kanan bawah.

G. Identifikasi dokumen

Pada setiap dokumen harus dicantumkan informasi berikut:

- Nama atau kode dokumen harus dicantumkan pada sudut kanan atas kertas pembatas.
- Sistem penomoran subbagian harus dicantumkan pada sudut kanan bawah, contoh:
  Bagian x, Ord. X, Subbagian x.x

Dimana:

Bagian x	: Bagian dokumen
Ord. X.	: Nomor ordner
Subbagian x.x	: Nomor subbagian

Sebagai contoh: Pada bagian Mutu, subbagian Kontrol terhadap Zat Aktif harus ditulis Bagian II, Ord. 2, Subbagian B.S4 pada bagian sudut kanan bawah.

H. Penomoran halaman

Semua dokumen harus mempunyai nomor halaman. Penomorannya berdasarkan subbagian atau anak subbagian dokumen, bukan berdasarkan ordner atau bagian. Semua dokumen registrasi tidak boleh diberikan nomor secara berurutan berdasarkan halaman. Satu set penomoran halaman hanya untuk setiap subbagian.

Jika terdapat dokumen yang disisipkan dalam dokumen, seperti protokol dalam laporan studi, dokumen sisipan tersebut dimasukkan sebagai Lampiran. Setiap lampiran harus dipisahkan dengan kertas pembatas yang dinamai dengan benar.

Pada sudut kanan bawah setiap halaman, harus dituliskan sistem penomoran halaman dalam format berikut:

Bag. x, Ord. X, SubBag. x.x, Hal. xx

Dimana:

Bag. x	: bagian dari dokumen (Bagian)
Ord. X	: nomor ordner spesifik
SubBag. x.x	: nomor subbagian atau anak subbagian dari bagian terkait (subbagian)
Hal. xx	: halaman dari subbagian terkait

Contoh, dokumen spesifikasi Zat Aktif dari bagian mutu dituliskan: Bag. II, Ord.2, SubBag. B.S4.1, Hal. 7 pada sudut kanan bawah.

I. Penomoran halaman untuk dokumen tambahan data

Tambahan data tidak boleh mengubah urutan penomoran halaman. Jika jumlah halaman tambahan data melebihi nomor halaman yang ada, dapat ditambahkan dengan huruf a – z sebagai anak nomor halaman.

Contoh: halaman 6a, 6b, 6c ... dst

J. Dokumen dengan format ICH CTD

Dokumen dengan format ICH CTD dapat diserahkan sesuai dengan ketentuan ICH CTD yang berlaku, namun dokumen Bagian I harus disesuaikan dengan ketentuan dalam Peraturan ini.

II. Dokumen Registrasi *Softcopy*

Untuk dokumen registrasi *softcopy* dapat merujuk Petunjuk Teknis Registrasi Aplikasi Elektronik Obat.

III. Tambahan Data

Selain untuk Registrasi Baru, pedoman penyusunan dokumen registrasi dapat juga untuk penyusunan dokumen tambahan data. Surat-menyurat umum harus dimasukkan pada Bagian I.

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LAMPIRAN V
PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
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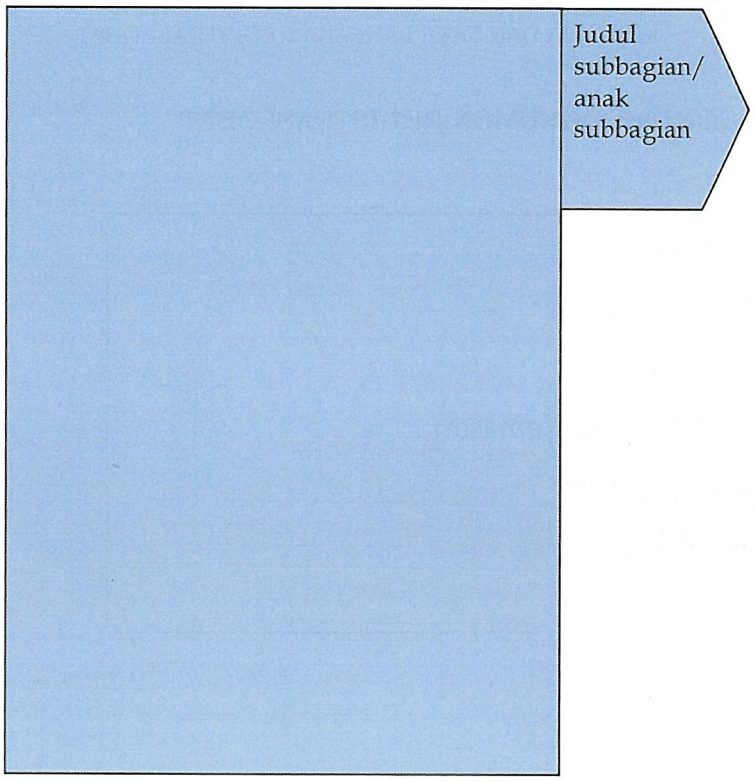
CONTOH DOKUMEN REGISTRASI OBAT

Nama Obat	:
Bentuk Sediaan	:
Komposisi	:
Jenis dan Besar Kemasan	:
Nama Pendaftar	:
Nama Produsen	:

CONTOH KERTAS PEMBATAS



Nama Obat	:
Bentuk Sediaan	:
Komposisi	:
Jenis dan Besar Kemasan	:
Nama Pendaftar	:
Nama Produsen	:

BAGIAN I :
DOKUMEN ADMINISTRATIF

Ordner.... dari ....

DAFTAR ISI KESELURUHAN

		Ord, Subbag, Hal.
	P6 Baku Pembanding	x, B.P6, xx
	P7 Spesifikasi dan Metode Pengujian Kemasan	x, B.P7, xx
	P8 Stabilitas	x, B.P8, xx
	P9 Bukti Ekivalensi (bila perlu)	x, B.P9, xx
Subbagian C	Daftar Pustaka	x, C, xx
BAGIAN III	DOKUMEN NONKLINIK	
Subbagian A	Tinjauan Studi Nonklinik	x, A, xx
Subbagian B	Ringkasan dan Matriks Studi Nonklinik	x, B, xx
Subbagian C	Laporan Studi Nonklinik	x, C, xx
Subbagian D	Daftar Pustaka	x, D, xx
BAGIAN IV	DOKUMEN KLINIK	
Subbagian A	Tinjauan Studi Klinik	x, A, xx
Subbagian B	Ringkasan Studi Klinik	x, B, xx
Subbagian C	Matriks Studi Klinik	x, C, xx
Subbagian D	Laporan Studi Klinik	x, D, xx
Subbagian E	Daftar Pustaka	x, E, xx

Nama Obat	:
Bentuk Sediaan	:
Komposisi	:
Jenis dan Besar Kemasan	:
Nama Pendaftar	:
Nama Produsen	:

BAGIAN II :
DOKUMEN MUTU

Ordner.... dari ....

Nama Obat	:
Bentuk Sediaan	:
Komposisi	:
Jenis dan Besar Kemasan	:
Nama Pendaftar	:
Nama Produsen	:

BAGIAN III :
DOKUMEN NONKLINIK

Ordner.... dari ....

Nama Obat	:
Bentuk Sediaan	:
Komposisi	:
Jenis dan Besar Kemasan	:
Nama Pendaftar	:
Nama Produsen	:

BAGIAN IV :
DOKUMEN KLINIK

Ordner.... dari ....

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DOKUMEN ADMINISTRATIF

1. Surat Pengantar.
2. Formulir Registrasi.
3. Pernyataan Pendaftar.
4. Sertifikat dan Dokumen Administratif Lain.
   - 4.1. Obat Produksi Dalam Negeri.
     - 4.1.1. Izin Industri Farmasi.
     - 4.1.2. Sertifikat CPOB yang masih berlaku untuk bentuk sediaan yang didaftarkan.
     - 4.1.3. Sertifikat CPOB produsen Zat Aktif.
     - 4.1.4. Data inspeksi CPOB terakhir dan perubahan terkait paling lama dua tahun yang dikeluarkan oleh Badan Pengawas Obat dan Makanan.
   - 4.2. Obat Lisensi.
     - 4.2.1. Izin Industri Farmasi atau dokumen penunjang dengan bukti yang cukup untuk badan/institusi riset sebagai pemberi lisensi.
     - 4.2.2. Izin Industri Farmasi sebagai penerima lisensi.
     - 4.2.3. Sertifikat CPOB Industri Farmasi penerima lisensi yang masih berlaku untuk bentuk sediaan yang didaftarkan.
     - 4.2.4. Sertifikat CPOB produsen Zat Aktif.
     - 4.2.5. Perjanjian lisensi.
   - 4.3. Obat Kontrak Produksi Dalam Negeri.
     - 4.3.1. Izin Industri Farmasi Pendaftar atau Pemberi Kontrak.
     - 4.3.2. Izin Industri Farmasi sebagai Penerima Kontrak.
     - 4.3.3. Sertifikat CPOB Industri Farmasi Pendaftar atau Pemberi Kontrak yang masih berlaku.
     - 4.3.4. Sertifikat CPOB Industri Farmasi Penerima Kontrak yang masih berlaku sesuai bentuk sediaan Obat yang dikontrakkan.
     - 4.3.5. Sertifikat CPOB produsen Zat Aktif.
     - 4.3.6. Perjanjian kontrak.
   - 4.4. Obat Khusus Ekspor.
     - 4.4.1. Izin Industri Farmasi.
     - 4.4.2. Sertifikat CPOB Pendaftar.

4.4.3. Sertifikat CPOB atau dokumen lain yang setara dari produsen sesuai bentuk sediaan yang didaftarkan (untuk Obat Impor khusus ekspor).

4.4.4. Sertifikat CPOB produsen Zat Aktif.

4.5. Obat Impor.

4.5.1. Izin Industri Farmasi produsen dan Pendaftar.

4.5.2. Surat penunjukkan dari industri farmasi atau pemilik produk di luar negeri dikecualikan untuk Pendaftar yang merupakan afiliasi dari perusahaan induk.

4.5.3. *Certificate of Pharmaceutical Product (CPP)* atau dokumen lain yang setara dari negara produsen dan/atau negara dimana diterbitkan sertifikat pelulusan bets (jika perlu).

4.5.4. Sertifikat CPOB yang masih berlaku dari produsen untuk bentuk sediaan yang didaftarkan atau dokumen lain yang setara (termasuk sertifikat CPOB produsen Zat Aktif untuk Produk Biologi).

4.5.5. Data inspeksi CPOB terakhir dan perubahan terkait paling lama dua tahun yang dikeluarkan oleh otoritas pengawas Obat setempat dan/atau otoritas pengawas Obat negara lain.

4.5.6. Sertifikat CPOB produsen Zat Aktif.

4.5.7. Justifikasi impor.

4.5.8. Bukti perimbangan kegiatan ekspor dan impor (jika perlu).

5. Hasil Praregistrasi.

6. Kuitansi/Bukti Pembayaran.

7. Dokumen Lain.

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DOKUMEN MUTU

Format dalam panduan ini berlaku untuk Registrasi Baru dan Registrasi Variasi yang mencakup Obat Baru, Produk Biologi dan Obat Generik. Dokumen mutu pada panduan ini hanya menunjukkan struktur dan tempat dimana informasi harus dicantumkan. Jenis dan ruang lingkup data penunjang mengacu pada pedoman/ketentuan yang berlaku secara nasional maupun internasional seperti Farmakope, Pedoman ICH, dan lain-lain. Persyaratan untuk Obat dengan Zat Aktif baru dan Produk Biologi dapat mengacu pada Pedoman ICH atau pedoman lain terkait.

Dokumen mutu terdiri dari:

1. Subbagian A : Ringkasan Dokumen Mutu (*Quality Overall Summary/ QOS*)
2. Subbagian B : Dokumen Mutu (*Body of Data*)

SUBBAGIAN A: RINGKASAN DOKUMEN MUTU

Ringkasan dokumen mutu (RDM) adalah ringkasan sesuai ruang lingkup dan format pada dokumen mutu lengkap (*body of data*). Informasi, data atau justifikasi yang tercantum dalam RDM harus konsisten dengan dokumen mutu lengkap yang diserahkan.

RDM harus mencantumkan ringkasan informasi yang sesuai dari setiap subbagian dokumen mutu lengkap. RDM juga harus mencakup penjelasan mengenai parameter utama kritis dari mutu Obat dan justifikasi bila terdapat penyimpangan prosedur terhadap pedoman yang berlaku. RDM harus memuat penjelasan yang terintegrasi terkait hubungan antara informasi yang tercantum dalam dokumen mutu dengan informasi penunjang dari bagian lain. Sebagai contoh yaitu hubungan antara data zat pengotor dalam Zat Aktif dengan hasil dari studi toksikologi.

Secara umum, informasi yang tercantum dalam RDM tidak melebihi empat puluh halaman (tidak termasuk tabel dan gambar). Untuk Produk Biologi atau Obat yang diproduksi dengan menggunakan proses yang lebih kompleks, informasi yang tercantum dalam RDM dapat lebih banyak namun tidak melebihi dari delapan puluh halaman (tidak termasuk tabel dan gambar).

Susunan dan informasi yang tercantum dalam RDM adalah sebagai berikut:

S ZAT AKTIF

S1 Informasi Umum
Ringkasan informasi dari S1 subbagian B.

S2 Proses Produksi dan Sumber Zat Aktif
Ringkasan informasi dari S2 subbagian B, termasuk :
- Nama dan alamat produsen.
- Ringkasan proses pembuatan dan kontrol proses. Untuk Produk Biologi harus mencakup informasi mulai dari bank sel, termasuk

kultur sel, pemanenan, pemurnian dan reaksi modifikasi, pengisian, kondisi penyimpanan dan pengiriman.

- Kontrol terhadap semua bahan (termasuk bahan awal, pelarut, reagen, katalisator) yang digunakan dalam pembuatan Zat Aktif, termasuk bahan yang berasal dari Produk Biologi.
- Kontrol terhadap tahap kritis dan zat antara, termasuk data stabilitas yang menunjang kondisi penyimpanan Produk Biologi.
- Validasi proses dan/atau studi dan evaluasi untuk proses sterilisasi dan aseptik.
- Deskripsi dan riwayat pengembangan proses pembuatan seperti yang dijelaskan dalam S2.2.

S3 Karakterisasi

Zat Aktif baru:

Konfirmasi struktur antara lain berdasarkan rute sintesis dan analisis spektrum, seperti dijelaskan dalam S3.1.

Produk Biologi:

Deskripsi struktur primer, sekunder dan tingkat yang lebih tinggi, dan informasi aktivitas biologik, kemurnian, dan imunokimia (jika perlu), seperti dijelaskan dalam S3.2.

Zat Aktif baru dan Produk Biologi:

Ringkasan kemurnian yang dimonitor atau diuji selama atau setelah pembuatan Zat Aktif, seperti dijelaskan dalam S3.2.

Obat Generik:

Sesuai persyaratan kompendial atau informasi yang setara dari produsen.

S4 Spesifikasi dan Metode Pengujian Zat Aktif

Uraian singkat tentang justifikasi penetapan spesifikasi, metode analisis, dan validasinya.

Spesifikasi yang diuraikan pada butir S4.1 subbagian B harus dicantumkan, demikian juga, bila ada tabel ringkasan dari hasil analisis bets yang dicantumkan pada butir S4.4.

Obat Generik:

Mengikuti persyaratan Farmakope atau informasi yang setara dari produsen.

S5 Baku Pembanding

Informasi dari butir S5 subbagian B (dalam bentuk tabel, bila sesuai) harus dicantumkan.

Obat Generik:

Baku pembanding yang digunakan sesuai Farmakope atau informasi yang setara dari produsen.

S6 Spesifikasi dan Pengujian kemasan

Uraian singkat dan pembahasan pada butir S6 subbagian B harus dicantumkan.

S7 Stabilitas

Bagian ini harus mencakup ringkasan studi yang dilakukan (kondisi pengujian, bets, metode analisis) dan diskusi singkat dari hasil studi dan kesimpulan, kondisi penyimpanan yang diajukan, periode uji ulang atau masa edar/*shelf life* bila relevan.

Protokol uji stabilitas pascapemasaran dan komitmen untuk memonitor stabilitas seperti yang tercantum pada butir P8 subbagian B perlu dicantumkan.

Rangkuman hasil uji stabilitas dalam bentuk tabel dengan gambaran grafis bilamana diperlukan.

Obat Generik:

Justifikasi penetapan tanggal pengujian ulang atau masa edar dapat mengacu pada literatur.

P OBAT JADI

P1 Pemerian dan Formula

Informasi butir P1 subbagian B dan komposisi harus dicantumkan di bagian ini.

P2 Pengembangan Produk

Pembahasan tentang informasi dan data dari butir P2 subbagian B, termasuk informasi dari studi pengembangan, komponen Obat, Obat, pengembangan proses pembuatan, sistem pengemasan, atribut mikrobiologik, spesifikasi dan sistem pengujian kemasan, dan kompatibilitas harus dicantumkan.

Obat Generik:

Justifikasi dapat menggunakan data literatur.

P3 Proses Pembuatan

Informasi dari butir P3 subbagian B, mencakup:

- Informasi produsen untuk setiap tahap pembuatan.
- Nama dan jumlah Zat Aktif dan Eksipien.
- Uraian singkat proses pembuatan dan kontrol tahap kritis serta produk antara yang ditujukan untuk menghasilkan produksi rutin yang konsisten dan produk yang bermutu.
- Uraian singkat hasil validasi proses seperti yang diuraikan pada butir P3.4 subbagian B.

P4 Spesifikasi dan Metode Pengujian Eksipien

Ringkasan mutu Eksipien seperti yang diuraikan pada butir P4 subbagian B perlu dicantumkan.

Obat Generik:

Sesuai persyaratan Farmakope atau informasi yang setara dari produsen.

P5 Spesifikasi dan Metode Pengujian Obat

Ringkasan tentang justifikasi penetapan spesifikasi, prosedur analisis, dan validasinya serta karakterisasi zat pengotor harus dicantumkan.

Spesifikasi yang tercantum pada butir P5.1 subbagian B dan ringkasan hasil analisis bets yang tercantum pada butir P5.4 subbagian B harus dicantumkan.

Obat Generik:

Karakterisasi zat pengotor dan spesifikasi Obat sesuai persyaratan Farmakope atau informasi yang setara dari produsen.

P6 Baku Pembanding

Informasi dari butir P6 subbagian B (bila sesuai dapat berbentuk tabel), perlu dicantumkan.

Obat Generik:

Sesuai persyaratan Farmakope atau informasi yang setara dari produsen.

P7 Spesifikasi dan Pengujian Kemasan

Uraian singkat informasi yang tercantum pada butir P7 subbagian B dan diskusi harus dicantumkan.

P8 Stabilitas

Ringkasan studi yang dilakukan (kondisi pengujian, bets yang diamati, dan metode analisis), uraian singkat hasil studi stabilitas serta analisis data dan kesimpulannya, harus dicantumkan.

Kesimpulan mengenai kondisi penyimpanan dan masa edar (*shelf life*) serta kondisi penyimpanan setelah kemasan dibuka (bila perlu) harus dicantumkan.

Ringkasan hasil studi stabilitas dalam bentuk tabel dan/atau grafik dari butir P8 subbagian B bila ada, perlu dicantumkan.

Protokol uji stabilitas pascapersetujuan Registrasi dan komitmen stabilitas untuk memonitor stabilitas seperti yang tercantum pada butir P8 subbagian B harus dicantumkan.

P9 Data Ekivalensi

Uraian singkat uji disolusi (*in vitro*) dan uji bioekivalensi (*in vivo*), jika dipersyaratkan.

SUBBAGIAN B: DOKUMEN MUTU

S ZAT AKTIF

S1 Informasi Umum

S1.1 Tata Nama

- *International Nonproprietary Name Modified (INNM).*
- Nama Farmakope bila relevan.
- Nomor registrasi dari *Chemical Abstract Service (CAS).*
- Kode laboratorium (jika ada).
- Nama kimia.

S1.2 Rumus Kimia

Zat Aktif baru:

Rumus bangun, termasuk stereokimia relatif dan absolut, rumus molekul dan bobot molekul relatif, harus dicantumkan.

Produk Biologi:
Urutan skematis asam amino yang menunjukkan tempat glikosilasi atau modifikasi *posttranslational* yang lain dan bobot molekul relatif, perlu dicantumkan jika ada.

Obat Generik:
Sesuai persyaratan Farmakope atau informasi lain yang setara dari produsen.

S1.3 Sifat-sifat umum

Sifat-sifat fisikokimia atau sifat-sifat lain yang relevan dari Zat Aktif termasuk aktifitas biologik untuk Produk Biologi harus dicantumkan.

Pustaka: Pedoman ICH, Obat baru: Q6A; Produk Biologi: Q6B.

S2 Proses Produksi dan Sumber Zat Aktif

S2.1 Produsen

Nama dan alamat lengkap termasuk kota dan negara produsen Zat Aktif perlu dicantumkan.

S2.2 Uraian dan Kontrol Proses Pembuatan

Uraian proses pembuatan Zat Aktif yang mencakup informasi proses pembuatan dan kontrol terhadap proses pembuatan perlu dicantumkan.

Zat Aktif baru:

- Skema alur proses sintesa yang meliputi rumus molekul, berat dan hasil sintesa, rumus kimia dari bahan awal; senyawa antara; reagensia dan Zat Aktif yang menggambarkan stereokimia, yang dapat mengidentifikasi kondisi operasional dan pelarut yang digunakan, perlu dicantumkan.
- Narasi uraian tahapan proses pembuatan dengan mencantumkan jumlah bahan baku, pelarut, katalisator, dan reagensia termasuk kontrol terhadap proses, peralatan dan kondisi operasional seperti suhu, tekanan, pH, waktu, dan lain-lain.
- Proses alternatif harus diuraikan secara detail sama seperti pada proses primer. Tahapan pemrosesan kembali harus diidentifikasi dan diberikan justifikasinya.

Produk Biologi:

Informasi proses pembuatan dimulai dari bank sel termasuk pengkulturan sel, pemanenan, reaksi modifikasi dan pemurnian, kondisi pengisian dan pengemasan, penyimpanan dan transportasi, termasuk diagram alur prosesnya.

Pustaka: Pedoman ICH Q5A, Q5B dan Q6B.

S2.3 Kontrol terhadap bahan

Bahan-bahan yang digunakan pada pembuatan Zat Aktif (seperti bahan baku, bahan awal, pelarut, reagensia, katalisator) harus dicantumkan sesuai urutan penggunaan dalam tahapan proses. Perlu juga dicantumkan informasi mutu dan pemeriksaannya.

Informasi yang menunjukkan bahwa bahan-bahan tersebut (termasuk bahan dari sumber biologi, seperti komponen media, antibodi monoklonal, enzim) memenuhi standar untuk tujuan penggunaannya (termasuk penghilangan atau kontrol terhadap bahan *adventitious*), perlu dicantumkan jika relevan. Untuk bahan dari sumber biologi harus mencantumkan informasi sumber, produsen, dan karakterisasi.

Pustaka: Pedoman ICH, Obat Baru: Q6A; Produk Biologi: Q6B.

Produk Biologi:

- Kontrol sumber dan bahan awal, ringkasan informasi keamanan dari virus yang digunakan perlu dicantumkan.
- Sumber, riwayat, dan pembuatan substrat sel.
- Informasi sumber substrat sel dan analisis konstruksi ekspresi yang digunakan untuk modifikasi sel secara genetik dan inkorporasinya ke dalam klon sel awal untuk membuat *Master Cell Bank* harus dicantumkan sesuai Q5B dan Q5D.
- *Cell banking system*, karakterisasi, dan pengujian.

  Informasi pada *cell banking system*; pengawasan mutu dan stabilitas *cell line* selama produksi dan penyimpanan (termasuk prosedur yang digunakan untuk pembuatan *Master* dan *Working Cell Bank)* harus dicantumkan sesuai Q5B dan Q5D.

Pustaka: Pedoman ICH Q5A, Q5B, Q5C, dan Q5D.

S2.4 Kontrol terhadap Tahapan Kritis dan Senyawa Antara

Tahapan kritis: pengujian dan kriteria penerimaan dengan justifikasinya, termasuk data percobaan, yang dilakukan pada tahapan kritis proses pembuatan untuk meyakinkan bahwa proses tersebut terkontrol.

Senyawa antara: spesifikasi dan metode analisis (jika ada), untuk senyawa antara *(intermediates)* yang diperoleh selama proses.

Pustaka: Pedoman ICH Q6A, Q6B,

Tambahan untuk Produk Biologi: data stabilitas yang menunjang kondisi penyimpanan.

Pustaka: Pedoman ICH Q6A, Q6B, Produk Biologi: Data stabilitas pendukung kondisi penyimpanan.

Pustaka: Pedoman ICH Q5C.

S2.5 Validasi proses dan/atau Evaluasi

Studi validasi proses dan/atau evaluasi untuk proses aseptik dan sterilisasi perlu dicantumkan.

Produk Biologi:

Informasi validasi dan evaluasi validasi yang memadai untuk membuktikan bahwa proses pembuatan (termasuk tahapan pemrosesan kembali) sesuai dengan tujuan dan untuk pemilihan kontrol proses kritis yang tepat (parameter operasional dan selama proses pembuatan/*in-process test*) dan batasannya untuk tahapan pembuatan kritis (contohnya, kultur sel, pemanenan, pemurnian dan modifikasi).

Informasi harus meliputi uraian rencana studi serta hasil analisis dan kesimpulan studi. Validasi metode analisis dan penentuan kadar harus dibandingkan, sebagai bagian dari justifikasi pemilihan kontrol proses kritis dan batasannya.

Studi penghilangan atau inaktivasi kontaminan virus pada proses pembuatan, harus diserahkan.

Pustaka: Pedoman ICH Q5A, Q5D, dan Q6B.

S2.6 Pengembangan proses pembuatan

Zat Aktif baru:

Uraian dan diskusi dari perubahan yang bermakna pada proses pembuatan dan lokasi produksi untuk Zat Aktif yang digunakan pada bets uji nonklinik, bets uji klinik, bets pilot, dan jika ada, bets skala produksi.

Pustaka: Pedoman ICH Q3A.

Produk Biologi:

Riwayat pengembangan proses pembuatan, seperti yang dijelaskan pada butir S2.2. Uraian perubahan yang dilakukan untuk pembuatan bets Zat Aktif yang digunakan sebagai pendukung Registrasi (contohnya, uji nonklinik dan klinik), termasuk perubahan proses atau peralatan yang kritis. Alasan perubahan harus dijelaskan termasuk informasi yang relevan pada pembuatan bets Zat Aktif selama pengembangan, seperti nomor bets, ukuran bets produksi dan penggunaan (contohnya stabilitas, bahan pembanding nonklinik) yang terkait dengan perubahan.

Perubahan yang bermakna harus dinilai dengan mengevaluasi potensinya terhadap dampak mutu Zat Aktif (dan/atau senyawa antara, jika ada). Untuk perubahan proses pembuatan yang bermakna, harus ada data dari uji analisis terbanding Zat Aktif yang terkait. Pembahasan harus meliputi justifikasi pemilihan uji dan evaluasi hasil uji.

Uji klinik dan nonklinik dalam modul lain dapat disertakan untuk melengkapi evaluasi pengaruh perubahan proses pembuatan pada Zat Aktif dan Obat yang terkait.

Pustaka: Pedoman ICH Q6B.

S3 Karakterisasi

S3.1 Elusidasi dari struktur dan Karakterisasi

Zat Aktif baru:

Konfirmasi struktur antara lain berdasarkan rute sintesis dan analisis spektrum. Informasi mengenai potensi terjadinya isomerisme, identifikasi stereokimiawi, atau potensi untuk pembentukan *polimorf* harus dicantumkan.

Pustaka: Pedoman ICH Q6A.

Produk Biologi:

Uraian detil mengenai struktur primer, sekunder dan tingkat yang lebih tinggi, serta informasi aktivitas biologik, kemurnian dan sifat imunokimia (jika relevan).

Pustaka: Pedoman ICH Q6B.

Obat Generik, Variasi Major, Variasi Minor:

Persyaratan Farmakope atau informasi lain yang setara dari produsen.

S3.2 Bahan Pengotor

Informasi bahan pengotor perlu dicantumkan.

Pustaka: Pedoman ICH Q3A, Q3C, Q5C, Q6A dan Q6B.

Obat Generik:

Persyaratan Farmakope atau informasi lain yang setara dari produsen.

S4 Spesifikasi dan Metode Pengujian Zat Aktif

S4.1 Spesifikasi

Informasi rinci spesifikasi, pengujian, dan kriteria penerimaan Zat Aktif perlu dicantumkan.

Pustaka: Pedoman ICH, Obat Baru: Q6A.

Produk Biologi:

Sumber, termasuk spesies hewan, tipe mikroorganisme, dan lain-lain harus disebutkan.

Pustaka: Pedoman ICH Q6B.

Obat Generik, Variasi Major, Variasi Minor:

Spesifikasi Zat Aktif sesuai Farmakope. Spesifikasi Zat Aktif yang tidak mengacu Farmakope harus disebutkan apakah berdasarkan *Certificate of Analysis (CoA)* dari produsen atau berdasarkan pengujian oleh Pendaftar.

S4.2 Prosedur analisis

Prosedur analisis yang digunakan untuk pengujian Zat Aktif harus rinci agar dapat digunakan oleh laboratorium lain untuk pengujian ulang.

Pustaka: Pedoman ICH, Obat Baru: Q2A; Produk Biologi: Q6B.

Obat Generik, Variasi Major, Variasi Minor:

Persyaratan sesuai Farmakope atau informasi lain yang setara dari produsen.

S4.3 Validasi Prosedur Analisis

Informasi validasi analisis termasuk data percobaan metode analisis yang digunakan untuk pengujian Zat Aktif perlu dicantumkan.

Parameter validasi yang harus diperhatikan adalah selektifitas, presisi (keberulangan presisi antara dan reprodusibilitas), akurasi, linearitas, rentang, limit kuantitasi, limit deteksi, *robustness*, dan uji kesesuaian sistem.

Pustaka: Pedoman ICH, Obat Baru: Q2A dan Q2B; Produk Biologi: Q6B.

Obat Generik, Variasi Major, Variasi Minor:

Dipersyaratkan hanya untuk metode non-Farmakope.

Referensi: *ASEAN Guideline for Validation of Analytical Procedure.*

S4.4 Analisis Bets

Uraian analisis bets dan hasil analisis perlu dicantumkan.
Pustaka: Pedoman ICH, Obat Baru: Q3A, Q3C dan Q6A; Produk Biologi: Q6B.

S4.5 Justifikasi spesifikasi

Justifikasi penetapan spesifikasi Zat Aktif perlu dicantumkan.

Pustaka: Pedoman ICH, Obat Baru: Q6A; Produk Biologi: Q6B.

S5 Baku Pembanding

Informasi mutu baku pembanding atau bahan baku yang digunakan untuk pengujian Zat Aktif, perlu dicantumkan.
Pustaka: Pedoman ICH, Obat Baru: Q6A; Produk Biologi: Q6B.

Obat Generik, Variasi Major, Variasi Minor:

Persyaratan sesuai Farmakope atau informasi lain yang setara dari produsen.

S6 Spesifikasi dan pengujian kemasan

Obat Baru dan Produk Biologi:

Agar dicantumkan uraian sistem pengemasan, termasuk identitas komponen kemasan primer dan spesifikasinya. Spesifikasi masing-masing komponen tersebut harus mencakup uraian dan identifikasi (ukuran kritis dan gambar bila sesuai). Untuk metode non-Farmakope disertai validasi yang sesuai.

Untuk komponen kemasan sekunder nonfungsional (yang tidak kontak langsung dengan produk) cukup dicantumkan uraian singkat, sedangkan untuk komponen kemasan sekunder fungsional perlu ada informasi tambahan untuk komponen tersebut.

Hal-hal yang perlu dipertimbangkan dalam pemilihan kemasan seperti bahan kemasan, kemampuan melindungi Zat Aktif terhadap kelembaban dan cahaya, kompatibilitas antara bahan kemasan dan Zat Aktif termasuk interaksi Zat Aktif dengan kemasan, *leaching* dan/atau keamanan komponen kemasan.

S7 Stabilitas

Ringkasan Stabilitas dan Kesimpulan

Perlu diberikan ringkasan studi yang dilakukan, protokol dan hasil studi. Ringkasan harus mencakup hasil studi, contohnya hasil *forced degradation* dan *stress condition*, termasuk kesimpulan kondisi penyimpanan dan tanggal uji ulang atau *shelf life*.

Pustaka: Pedoman ICH Q1A (R2), Q1B, dan Q5C.

Protokol Stabilitas Pascapemasaran dan Komitmen Stabilitas

Protokol uji stabilitas pascapemasaran dan komitmen untuk melakukan uji stabilitas.

Pustaka: Pedoman ICH Q1A (R2) dan Q5C.

Data Stabilitas

Hasil uji stabilitas (contohnya, hasil studi *forced degradation* dan *stress conditions*) yang dituangkan dalam bentuk tabel, grafik, atau narasi, dengan menyertakan informasi prosedur analisis yang digunakan serta validasi dari prosedur tersebut sesuai format yang ditentukan.

Pustaka: Pedoman ICH Q1A (R2), Q1B, Q2A, Q2B, dan Q5C.

Obat Generik, Variasi Major, Variasi Minor:

Data stabilitas dari produsen atau informasi lain yang setara.

P OBAT

P1 Pemerian dan Formula

Uraian dan komposisi Obat harus dicantumkan, seperti:

- Bentuk sediaan;
- Komposisi lengkap, jumlah tiap bahan baku dalam satu bets produksi (termasuk *overage*, bila ada), fungsi tiap bahan baku dan acuan mutu yang digunakan (contohnya monografi Farmakope atau spesifikasi dari produsen);
- Penjelasan pelarut yang digunakan untuk rekonstitusi; dan
- Tipe kemasan yang digunakan untuk Obat dan pelarut rekonstitusi, jika diperlukan.

Pustaka: Pedoman ICH, Obat Baru: Q6A; Produk Biologi: Q6B.

P2 Pengembangan Produk

P2.1 Informasi Studi Pengembangan

Obat dengan Zat Aktif baru dan Produk Biologi:

Bagian Pengembangan Farmasetika memberikan informasi dan data hasil studi pengembangan yang dilakukan untuk

memastikan bahwa bentuk sediaan, formulasi, proses pembuatan, sistem kemasan, atribut mikrobiologi dan cara pemberian sesuai dengan tujuan penggunaan Obat yang didaftarkan. Studi tersebut berbeda dari pengujian rutin yang dilakukan sesuai spesifikasi Obat. Bagian ini juga harus mengidentifikasi dan menggambarkan formulasi dan atribut proses (parameter klinik) yang dapat mempengaruhi reprodusibilitas bets, kinerja/khasiat produk, dan mutu Obat. Data pendukung dan hasil studi yang spesifik atau informasi dari literatur yang terpublikasi dapat disertakan sebagai lampiran. Tambahan data pendukung dapat digunakan sebagai acuan yang relevan untuk bagian nonklinik.

Pustaka: Pedoman ICH, Obat Baru: Q6A; Produk Biologi: Q6B.

P2.2 Komponen Obat

P2.2.1 Zat Aktif

Obat dengan Zat Aktif baru dan Produk Biologi:

Kompatibiltas Zat Aktif Obat dengan Eksipien harus dijelaskan. Sebagai tambahan, karakteristik fisikokimia (contohnya kadar air, kelarutan, distribusi ukuran partikel, *polimorf* atau bentuk padat) dari Zat Aktif yang dapat mempengaruhi mutu Obat harus dijelaskan pada bagian ini. Hal yang sama juga untuk sediaan kombinasi.

Kompatibilitas Zat Aktif Obat dengan Eksipien dan karakteristik fisikokimia Zat Aktif yang dapat mempengaruhi mutu Obat seperti kadar air, kelarutan, distribusi ukuran partikel, *polimorf* atau bentuk padat harus dijelaskan pada bagian ini. Hal yang sama juga untuk sediaan kombinasi.

<u>Obat Generik, Variasi Major, Variasi Minor:</u>

Informasi sesuai data literatur.

P2.2.2 Eksipien

Pemilihan Eksipien seperti yang tercantum pada butir P1, konsentrasi dan karakteristik yang mempengaruhi tampilan Obat, harus dijelaskan sesuai dengan fungsinya masing-masing.

<u>Obat Generik, Variasi Major, Variasi Minor:</u>

Informasi sesuai data literatur.

P2.3 Obat

P2.3.1 Pengembangan Formula

Ringkasan informasi pengembangan Formula Obat harus mempertimbangkan cara pemberian Obat sesuai dengan tujuan penggunaannya. Perbedaan antara formulasi klinik dan formulasi (contohnya Komposisi) seperti disebutkan pada butir P1 dan P2 harus dijelaskan. Hasil studi ekivalensi terbanding

(jika diperlukan) *in vitro* (contohnya uji disolusi) dan *in vivo* (contohnya bioekivalensi) harus dijelaskan.

P2.3.2 *Overages*

Overages dalam formulasi yang dicantumkan pada butir P1 harus dijelaskan.

P2.3.3 Sifat Fisikokimia dan Biologi

Perlu dicantumkan semua parameter Obat yang relevan seperti pH, kekuatan ikatan ion, disolusi, redispersi, rekonstitusi, distribusi ukuran partikel, agregasi, *polimorfism*, sifat alir, aktivitas biologi atau potensi dan aktivitas imunologi.

P2.4 Pengembangan Proses Pembuatan

Pemilihan dan optimasi proses pembuatan yang tercantum dalam butir P3.2 terutama pada tahap kritis harus dijelaskan. Metode sterilisasi harus dijelaskan dan diberikan justifikasinya jika diperlukan.

Perbedaan antara proses pembuatan bets Obat yang digunakan untuk uji klinik pivotal dan proses yang disebutkan pada butir P3.2 yang dapat mempengaruhi khasiat Obat perlu dicantumkan.

Obat Generik: mengacu kepada P3.2.

P2.5 Sistem Kemasan

Kesesuaian sistem kemasan yang digunakan untuk penyimpanan, transportasi (pengiriman) dan penggunaan Obat harus dijelaskan. Penjelasan menyangkut hal-hal seperti pemilihan bahan kemasan, perlindungan terhadap pengaruh kelembaban dan cahaya, kompatibilitas antara bahan kemasan dan Obat termasuk interaksi Obat dengan kemasan, *leaching*, keamanan bentuk kemasan dan ketepatan dosis pemberian dari alat yang digunakan sebagai bagian Obat jadi.

P2.6 Atribut Mikrobiologi

Atribut mikrobiologi dari sediaan perlu dicantumkan termasuk alasan untuk tidak melakukan uji batas mikroba pada sediaan nonsteril, pemilihan dan uji efektifitas pengawet dalam Obat yang mengandung bahan pengawet, jika perlu.

Untuk sediaan steril, integritas sistem kemasan dalam pencegahan kontaminasi miroba harus dicantumkan.

P2.7 Kompatibilitas

Kompatibilitas Obat dengan pelarut untuk rekonstitusi atau kompatibilitas Obat dengan kemasan/alat kesehatan yang digunakan, yang ditunjukkan dengan terjadinya endapan dalam larutan, interaksi Obat dengan kemasan injeksi, dan informasi stabilitas Obat dicantumkan untuk menunjang informasi pada Label.

Obat Generik, Variasi Major, Variasi Minor:

Data literatur dapat digunakan.

P3 Prosedur Pembuatan

P3.1 Produsen Obat

Harus mencantumkan nama, alamat, dan informasi penanggung jawab dari setiap fasilitas produksi, termasuk Pemberi Kontrak atau fasilitas produksi lain yang terlibat dalam proses pembuatan dan pengujian.

P3.2 Formula Bets

Formula harus mencantumkan nama dan jumlah/kuantitas Zat Aktif Obat dan Eksipien yang digunakan termasuk bahan yang hilang selama proses pembuatan.

- Kuantitas bahan (g, kg, Liter, dan lain-lain).
- *Overage*: data penunjang dan justifikasi *overage* harus disertakan.
- Jumlah per bets dan total unit dosis harus disebutkan.
- Uraian semua tahapan pembuatan Obat.

Pustaka: Pedoman ICH, Produk Biologi: Q6B.

P3.3 Proses Pembuatan dan Kontrol Proses

Diagram alur proses pembuatan Obat harus dicantumkan dengan menggambarkan setiap tahapan proses pembuatan dan menunjukkan pada tahap mana bahan-bahan tersebut digunakan. Pengawasan dilakukan pada tahap kritis pada produk antara dan Produk Jadi.

- Uraian lengkap proses pembuatan harus mencakup secara rinci semua hal penting pada tiap tahap proses pembuatan.
- Untuk sediaan steril, uraian mencakup persiapan dan sterilisasi komponen (contohnya, wadah, tutup, dan lain-lain).

P3.4 Kontrol terhadap Tahapan Kritis dan Produk Antara

Tahapan kritis: Pengujian dan kriteria penerimaan (dengan justifikasi termasuk data percobaan) yang dilakukan pada tahapan kritis proses pembuatan untuk memastikan bahwa proses tersebut terkontrol.

Produk Antara: Informasi mutu dan kontrol produk antara selama proses pembuatan Obat.

Pustaka: Pedoman ICH Q2A, Q2B, Q6A dan Q6B.

P3.5 Validasi Proses dan/atau Laporan

Uraian, dokumentasi, dan hasil studi validasi dari tahapan kritis atau penentuan kadar kritis yang dilakukan pada proses pembuatan harus diserahkan (Contohnya, validasi proses sterilisasi atau proses aseptik atau pengisian).

Pustaka: Pedoman ICH, Obat Baru: Q6A; Produk Biologi: Q6B.

Obat Generik, Variasi Major, Variasi Minor:

ASEAN Guideline on process validation

P4 Spesifikasi dan Metode Pengujian Eksipien

P4.1 Spesifikasi

Spesifikasi Eksipien.

Pustaka: Pedoman ICH, Obat Baru: Q6A; Produk Biologi: Q6B.

Obat Generik, Variasi Major, Variasi Minor:

Sesuai persyaratan Farmakope atau informasi lain yang setara dari produsen.

P4.2 Prosedur Analisis

Prosedur analisis yang digunakan untuk pengujian Eksipien dicantumkan jika diperlukan.

Pustaka: Pedoman ICH, Obat Baru: Q2A; Produk Biologi: Q6B.

Obat Generik, Variasi Major, Variasi Minor:

Sesuai persyaratan Farmakope atau informasi lain yang setara dari produsen.

P4.3 Eksipien bersumber dari hewan dan/atau manusia

Untuk Eksipien bersumber dari hewan dan/atau manusia, harus ada informasi *adventitious agents* (contohnya, sumber, spesifikasi, uraian uji yang dilakukan, data keamanan virus).

Pustaka: Pedoman ICH, Obat Baru: Q5A, Q5D; Produk Biologi: Q6B.

Obat Generik, Variasi Major, Variasi Minor:

Sesuai persyaratan Farmakope atau informasi lain yang setara dari produsen.

P4.4 Eksipien Baru

Informasi rinci mengenai pembuatan, karakterisasi dan kontrol, yang dapat digunakan untuk mendukung data keamanan nonklinik atau klinik.

P5 Spesifikasi dan Metode Pengujian Obat

P5.1 Spesifikasi

Spesifikasi Obat harus dicantumkan.

Pustaka: Pedoman ICH, Obat Baru: Q6A; Produk Biologi: Q6B.

P5.2 Prosedur Analisis

Prosedur analisis yang digunakan untuk pengujian Obat harus dicantumkan.

Pustaka: Pedoman ICH, Obat Baru: Q2A ; Produk Biologi: Q6B.

P5.3 Laporan Validasi Metode Analisis

Informasi validasi analisis termasuk data percobaan untuk metode analisis yang digunakan untuk pengujian Obat perlu dicantumkan.

Pustaka: Pedoman ICH, Obat Baru: Q2A dan Q2B; Produk Biologi: Q6B.

Obat Generik, Variasi Major, Variasi Minor:

Dipersyaratkan untuk metode non-Farmakope. Untuk metode yang sudah tercantum dalam Farmakope dipersyaratkan verifikasi metode analisis yang digunakan.

Referensi: *ASEAN Guideline for validation of analytical procedure.*

P5.4 Analisis Bets

Uraian bets dan hasil analisis bets perlu dicantumkan.

Produk Biologi:

Uraian (termasuk besar bets, asal dan penggunaan) dan hasil uji semua bets yang relevan (contohnya nonklinik, pilot untuk uji klinik, *scale-up*, dan jika ada bets skala produksi) yang digunakan untuk menetapkan spesifikasi dan mengevaluasi konsistensi pada proses pembuatan perlu dicantumkan.

Pustaka: Pedoman ICH, Obat baru: Q3A, Q3C, dan Q6A; Produk Biologi: Q6B; Obat Generik: mengacu kepada P3.4, P3.2.

Obat Generik dan Variasi Major:

Ringkasan tabel analisis bets dengan grafik yang sesuai ketentuan perlu dicantumkan.

P5.5 Karakterisasi Zat Pengotor

Bila informasi karakterisasi zat pengotor tidak/belum dicantumkan pada butir S3.2. Bahan Pengotor, maka perlu dicantumkan pada bagian ini.

Pustaka: Pedoman ICH, Obat baru: Q3B dan Q6A; Produk Biologi: Q6B.

Obat Generik, Variasi Major, Variasi Minor:

Persyaratan sesuai Farmakope atau informasi lain yang setara dari produsen.

P5.6 Justifikasi Spesifikasi

Justifikasi penetapan spesifikasi Obat perlu diberikan.

Pustaka: Pedoman ICH, Obat Baru: Q3B dan Q6A; Produk Biologi: Q6B.

Obat Generik, Variasi Major, Variasi Minor:

Persyaratan sesuai Farmakope atau informasi lain yang setara dari produsen.

P6 Baku Pembanding

Informasi mutu baku pembanding yang digunakan untuk pengujian Obat harus diberikan.

Pustaka: Pedoman ICH, Obat Baru: Q6A; Produk Biologi: Q6B.

Obat Generik, Variasi Major, Variasi Minor:

Sesuai persyaratan Farmakope atau informasi lain yang setara dari produsen.

P7 Spesifikasi dan Metode Pengujian Kemasan

Uraian sistem kemasan, termasuk identitas bahan komponen dan spesifikasi dari kemasan primer dan sekunder perlu dicantumkan. Spesifikasi tersebut harus mencakup uraian dan identifikasi (dimensi dan gambar yang sesuai).

Uraian singkat mengenai komponen kemasan sekunder nonfungsional dicantumkan (contohnya, alat yang tidak memberikan proteksi tambahan atau alat bantu pemberian Obat).

Untuk komponen kemasan sekunder fungsional harus ada informasi tambahan secara rinci.

Informasi yang dicantumkan harus sesuai pada P2.

P8 Stabilitas

Diperlukan bukti untuk menunjukkan bahwa produk bersifat stabil, memenuhi spesifikasi Produk Jadi selama *shelf life* yang diajukan, dimana tidak terjadi dekomposisi Obat dalam jumlah yang bermakna selama periode ini, serta menunjukkan tidak ada perubahan potensi dan efektivitas pengawet.

Ringkasan Stabilitas dan Kesimpulan

Obat dengan Zat Aktif baru dan Produk Biologi:

Semua kriteria yang mengikuti Pedoman ICH dapat diterima kecuali kondisi penyimpanan jangka panjang harus pada kondisi 30^{0}C, 75% RH. Harus dipertimbangkan kemampuan sistem pengemasan untuk memberikan perlindungan terhadap kelembaban.

Pustaka: Pedoman ICH Q1A (R2), Q1B, Q2A, Q2B dan Q5C.

Obat Generik, Variasi Major, Variasi Minor:

ASEAN Guideline on Stability Study of Drug Product.

Protokol Stabilitas Pascapemasaran dan Komitmen Uji Stabilitas

Protokol stabilitas pascapemasaran dan komitmen pelaksanaan uji stabilitas perlu diberikan.

Pustaka: Pedoman ICH, Obat Baru, Produk Biologi: Q1A (R2) dan Q5C.

Obat Generik:

ASEAN *Guideline on Stability Study of Drug Product.*

Data Stabilitas

Hasil uji stabilitas harus disajikan dalam format sesuai ketentuan (contohnya, tabel, grafik, narasi) termasuk informasi metode analisis yang digunakan untuk menghasilkan data dan validasi dari metode tersebut.

Pustaka:

- *ASEAN Guideline on Stability Study of Drug Product.*
- *ASEAN Guideline on Validation of Analytical Procedure.*

P9 Bukti Ekivalensi

Persyaratan untuk Obat Generik dan Variasi Major:

Jenis studi yang dilakukan, protokol yang digunakan dan hasil studi harus disajikan dalam laporan studi. Jenis studi yang dilakukan harus mengacu pada Pedoman Uji Bioekivalensi Badan POM dan *Guideline for Bioavailability and Bioequivalence Studies* atau *WHO Manual for Drug Regulatory Authority.*

Pustaka:

- Pedoman Uji Bioekivalensi Badan POM.
- *WHO, Regulatory Support Series No 5 ,"Bioequivalence Studies in Humans".*
- *ASEAN Guideline on Bioequivalence Study.*

SUBBAGIAN C: DAFTAR PUSTAKA

Daftar pustaka harus disertakan.

KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA,

ttd.

PENNY K. LUKITO

LAMPIRAN VIII
PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA
NOMOR 24 TAHUN 2017
TENTANG
KRITERIA DAN TATA LAKSANA REGISTRASI OBAT

DOKUMEN NONKLINIK

Dokumen nonklinik terdiri dari Tinjauan Studi Nonklinik *(Nonclinical Overview)*, Ringkasan dan Matriks Studi Nonklinik *(Nonclinical Written and Tabulated Summaries)*, dan Laporan Lengkap Studi Nonklinik *(Nonclinical Study Reports)*.

Tujuan utama Ringkasan dan Matriks Studi Nonklinik adalah untuk memberikan sinopsis yang faktual dan komprehensif dari data studi nonklinik. Pada saat pengajuan Registrasi (misalnya Zat Aktif baru) dokumen studi nonklinik yang harus diserahkan berupa tinjauan, ringkasan dan matriks studi nonklinik, sedangkan laporan lengkap studi nonklinik hanya jika dipersyaratkan. Dokumen studi nonklinik tidak dipersyaratkan untuk Obat Generik. Dokumen nonklinik untuk Produk Biosimilar mengacu pada Pedoman Umum Penilaian Produk Biosimilar.

SUBBAGIAN A: TINJAUAN STUDI NONKLINIK

Tinjauan Studi Nonklinik harus memberikan analisis informasi yang terintegrasi. Tinjauan studi nonklinik tidak melebihi tiga puluh halaman.

1. Aspek Umum

   Tinjauan Studi Nonklinik harus mencantumkan penilaian kritis dan terintegrasi dari evaluasi farmakologi, farmakokinetik dan toksikologi Obat. Pedoman yang relevan mengenai pelaksanaan studi perlu dipertimbangkan (jika ada), dan diberikan justifikasi bila terdapat penyimpangan prosedur terhadap pedoman yang berlaku.

   Dalam Tinjauan Studi Nonklinik harus mencantumkan pembahasan mengenai strategi pengujian studi nonklinik. Harus ada pernyataan bahwa studi nonklinik yang diserahkan sesuai dengan Cara Berlaboratorium yang Baik (*Good Laboratory Practice/ GLP*). Bila perlu, hubungan antara temuan nonklinik dan karakteristik mutu Obat, hasil uji klinik, atau efek yang terkait dengan produk yang berhubungan harus ditunjukkan.

   Evaluasi kemurnian dan hasil metabolisme yang ada pada Zat Aktif Obat dan produk Obat harus dicantumkan sesuai dengan apa yang diketahui mengenai efek farmakologik dan toksikologiknya. Evaluasi ini harus merupakan bagian dari justifikasi untuk batas kemurnian Zat Aktif Obat dan produk Obat yang diusulkan serta disesuaikan dengan dokumen mutu. Harus ada penjelasan mengenai pengaruh perbedaan struktur kimia/molekul, bentuk kiral dan profil kemurnian antara senyawa yang digunakan pada studi nonklinik dan produk Obat yang akan dipasarkan. Untuk Produk Biologi, perbandingan bahan yang digunakan pada studi nonklinik dan klinik serta yang diajukan untuk dipasarkan harus dievaluasi. Jika suatu Obat menggunakan Eksipien baru, evaluasi informasi mengenai keamanan Eksipien tersebut harus diberikan.

Perlu dipertimbangkan sifat-sifat produk terkait dan literatur ilmiah yang relevan. Informasi mutu bets dari Zat Aktif Obat yang digunakan dalam studi ini harus dijelaskan. Jika literatur ilmiah terpublikasi digunakan sebagai pengganti studi yang dilakukan oleh Pendaftar, sebaiknya ditunjang dengan justifikasi terhadap desain studi dan perbedaan dari pedoman.

Rujukan dalam Tinjauan Studi Nonklinik pada matriks studi dengan format berikut (Tabel X.X, Nomor laporan/studi).

2. Isi dan Struktur Format

Tinjauan Studi Nonklinik harus ditampilkan sesuai dengan urutan sebagai berikut:

Tinjauan Studi Nonklinik

1. Tinjauan strategi studi nonklinik.
2. Farmakologi.
3. Farmakokinetik.
4. Toksikologi.
5. Tinjauan Menyeluruh dan Kesimpulan.
6. Daftar Literatur.

Studi-studi yang dilakukan untuk menetapkan efek farmakodinamik, cara kerja, dan potensi efek samping Obat harus dievaluasi, serta mempertimbangan kemaknaan hasilnya.

Evaluasi data farmakokinetik, toksikokinetik dan metabolisme harus mencakup metode analisis yang digunakan, model farmakokinetik, dan sumber parameter-parameter yang relevan. Pertimbangan silang dengan studi-studi farmakologi atau toksikologi mungkin diperlukan (misalnya dampak dari kondisi penyakit, perubahan pada fisiologi, antibodi, dan pertimbangan data toksikokinetik). Bila terdapat inkonsistensi data harus dijelaskan. Perbandingan antarspesies dalam metabolisme dan paparan sistemik pada hewan dan manusia (AUC, C_{max}, dan parameter lainnya) perlu dijelaskan. Keterbatasan serta kegunaan studi nonklinik untuk memprediksi potensi efek samping Obat pada manusia harus menjadi perhatian.

Mula kerja, keparahan, dan durasi efek toksik, serta keterkaitannya dengan dosis dan derajat reversibilitas (atau ireversibilitas), serta perbedaan terkait dengan spesies atau jenis kelamin harus dievaluasi dan tanda-tanda penting harus dijelaskan terutama mengenai:

- Farmakodinamik.
- Tanda-tanda toksik.
- Penyebab kematian.
- Temuan patologis.
- Aktivitas genotoksik - struktur kimia senyawa Zat Aktif, cara kerja, dan hubungannya dengan senyawa-senyawa genotoksik yang telah dikenal.
- Potensi karsinogenik terkait dengan struktur kimia dari senyawa Zat Aktif, hubungannya dengan karsinogen yang telah dikenal, potensi genotoksiknya, dan data paparan.
- Risiko karsinogenik pada manusia – Jika ada data epidemiologik, maka data tersebut harus dipertimbangkan.
- Fertilitas, perkembangan embriofetal, toksisitas pra dan pascalahir.

- Studi pada hewan muda.
- Akibat dari penggunaan sebelum dan selama masa kehamilan, selama menyusui dan selama perkembangan anak.
- Toleransi lokal.
- Studi toksisitas lain dan/atau studi untuk memperjelas masalah khusus.

Evaluasi studi toksikologi harus disusun secara logis sehingga semua data yang relevan menjelaskan suatu efek dan/atau fenomena tertentu.

Ekstrapolasi data dari hewan ke manusia harus mempertimbangkan:

- Spesies hewan yang digunakan.
- Jumlah hewan yang digunakan.
- Rute pemberian Obat.
- Dosis yang digunakan.
- Durasi perlakuan atau durasi studi.
- Dosis *No Observed Adverse Effect Levels (NOAEL)* dan dosis toksik pada hewan, dan kaitannya dengan dosis maksimum yang direkomendasikan pada manusia. Tabel atau gambar yang menjelaskan informasi ini sebaiknya dicantumkan.
- Efek Zat Aktif yang diamati pada studi nonklinik, dan kaitannya dengan yang diharapkan pada manusia.

Jika digunakan alternatif hewan uji, maka harus dijelaskan validitas ilmiahnya.

Tinjauan Menyeluruh dan Kesimpulan harus menggambarkan dengan jelas sifat-sifat Obat, seperti yang ditunjukkan dalam studi nonklinik, dan menjadi kesimpulan yang masuk akal yang dapat mendukung keamanan produk yang akan digunakan secara klinis. Dengan mempertimbangkan hasil farmakologi, farmakokinetik, dan toksikologi, implikasi temuan nonklinik untuk keamanan penggunaan Obat pada manusia harus dijelaskan (seperti yang dijelaskan dalam Informasi Produk).

SUBBAGIAN B: RINGKASAN DAN MATRIKS STUDI NONKLINIK

1. Ringkasan Studi Nonklinik

1.1 Pendahuluan

Pedoman ini bertujuan untuk membantu menyiapkan ringkasan farmakologi, farmakokinetik, dan toksikologi nonklinik dalam format yang sesuai.

Urutan dan isi dari bagian Ringkasan Studi Nonklinik diuraikan dibawah ini. Penyusun dokumen yang baik fokus pada pemenuhan persyaratan regulator. Bila diperlukan Pendaftar dapat memodifikasi format untuk memudahkan memahami dan mengevaluasi hasil.

Jika diperlukan, efek terkait usia dan jenis kelamin harus dijelaskan. Temuan terkait dengan stereoisomer dan/atau metabolit harus dicantumkan. Pencantuman unit yang konsisten pada ringkasan nonklinik akan membantu proses evaluasi. Pencantuman tabel untuk mengkonversi unit mungkin juga dibutuhkan.

Pada bagian Pembahasan dan Kesimpulan, informasi antarstudi dan antarspesies harus terintegrasi, serta paparan pada hewan uji harus

terkait dengan paparan pada manusia yang mendapatkan dosis maksimal yang akan digunakan.

1.2 Uraian Umum

Urutan Uraian Informasi di dalam setiap bagian.

Jika ada, studi *in vitro* harus mendahului studi *in vivo*. Jika beberapa studi serupa diringkas di dalam bagian Farmakokinetik dan Toksikologi, studi tersebut harus diurutkan berdasarkan spesies, cara pemberian, dan kemudian lama pemberian (dimulai dengan waktu yang paling pendek).

Urutan spesies adalah sebagai berikut:

- Mencit.
- Tikus.
- Hamster.
- Hewan pengerat lainnya.
- Kelinci.
- Anjing.
- Primata selain manusia.
- Mamalia lainnya.
- Selain mamalia.

Rute pemberian Obat diurutkan sebagai berikut:

- Cara pemberian untuk penggunaan pada manusia.
- Oral.
- Intravena.
- Intramuskuler.
- Intraperitoneal.
- Subkutan.
- Inhalasi.
- Topikal.
- Lainnya.

Penggunaan Tabel dan Gambar

Meskipun Ringkasan Studi Nonklinik sebagian besar terdiri dari narasi, beberapa informasi lebih efektif dengan menggunakan tabel atau gambar. Tabel dan gambar dapat disisipkan di antara narasi atau dikelompokkan pada akhir setiap Ringkasan Studi Nonklinik.

Di dalam narasi, sitasi kepustakaan untuk ringkasan matriks studi harus dicantumkan dalam format sebagai berikut (Tabel X.X. nama/laporan/studi)

Panjang Ringkasan Studi Nonklinik

Meskipun tidak ada batasan formal untuk panjang Ringkasan Studi Nonklinik, tetapi direkomendasikan tidak lebih dari 100 – 150 halaman.

Urutan Ringkasan dan Matriks Studi

Direkomendasiakan urutan sebagai berikut:

- Pendahuluan.
- Ringkasan farmakologi.
- Matriks studi farmakologi.
- Ringkasan farmakokinetik.

- Matriks studi farmakokinetik.
- Ringkasan toksikologi.
- Matriks studi toksikologi.

2. Isi Ringkasan dan Matriks Studi Nonklinik

2.1 Pendahuluan

Tujuan dari bagian ini adalah memberikan informasi kepada penilai tentang Obat dan penggunaan klinis yang diusulkan. Informasi tersebut harus mencakup:

- Informasi singkat mengenai struktur Obat (sebaiknya, diagram struktur juga dicantumkan) dan sifat-sifat farmakologinya.
- Informasi mengenai indikasi klinis, dosis, dan lama penggunaan yang diajukan untuk Obat tersebut.

2.2 Farmakologi

2.2.1 Ringkasan

Dalam ringkasan farmakologi, data harus disajikan dengan urutan sebagai berikut:

- Ringkasan singkat.
- Farmakodinamik primer.
- Farmakodinamik sekunder.
- Farmakologi keamanan.
- Farmakodinamik interaksi Obat.
- Pembahasan dan kesimpulan.
- Tabel dan gambar (dapat dicantumkan di sini atau di dalam narasi).

2.2.1.1 Ringkasan singkat

Informasi penting dari studi farmakologi harus diringkas menjadi dua sampai tiga halaman. Bagian ini sebaiknya dimulai dengan gambaran singkat data farmakologi yang harus diperhatian seperti inklusi dan/atau eksklusi data tertentu (misalnya tidak adanya model hewan uji).

2.2.1.2 Farmakodinamik primer

Studi farmakodinamik primer harus diringkas dan dievaluasi. Jika memungkinkan, akan sangat berguna untuk menghubungkan farmakologi Obat tersebut dengan data yang ada (misalnya selektivitas, keamanan, potensi) pada Obat lain dalam kelasnya.

2.2.1.3 Farmakodinamik sekunder

Jika ada, studi farmakodinamik sekunder harus diringkas berdasarkan sistem organ dan dievaluasi pada bagian ini.

2.2.1.4 Farmakologi keamanan

Studi farmakologi keamanan diringkas dan dievaluasi pada bagian ini. Pada beberapa kasus, studi farmakodinamik sekunder dapat memberikan kontribusi pada evaluasi keamanan Obat bila studi

tersebut memprediksi atau menilai potensi efek samping Obat pada manusia. Dalam kasus demikian, studi farmakodinamik sekunder ini harus dipertimbangkan bersama-sama dengan studi farmakologi keamanan.

2.2.1.5 Farmakodinamik interaksi Obat

Apabila studi telah dilakukan, maka studi farmakodinamik interaksi Obat harus diringkas.

2.2.1.6 Pembahasan dan Kesimpulan

Bagian ini untuk membahas evaluasi farmakologik dan untuk mempertimbangkan kemaknaan hasilnya.

2.2.1.7 Tabel dan Gambar

Tabel dan gambar dapat disisipkan di antara ringkasan narasi atau dikelompokkan pada akhir setiap ringkasan.

2.2.2 Matriks Studi Farmakologi (lihat Daftar Matriks Studi)

2.3. Farmakokinetik

2.3.1 Ringkasan

Urutan Ringkasan Farmakokinetik sebagai berikut:

- Ringkasan singkat.
- Metode analisis.
- Absorpsi.
- Distribusi.
- Metabolisme.
- Ekskresi.
- Farmakokinetik interaksi Obat.
- Studi farmakokinetik lainnya.
- Pembahasan dan kesimpulan.
- Tabel dan grafik (dapat dicantumkan di sini atau di dalam narasi).

2.3.1.1. Ringkasan Singkat

Temuan penting dari studi farmakokinetik harus diringkas dengan singkat dalam dua atau tiga halaman. Bagian ini sebaiknya diawali dengan gambaran mengenai cakupan evaluasi farmakokinetik, dengan penekanan, misalnya, apakah spesies dan *strain* yang diteliti sama dengan yang digunakan untuk evaluasi farmakologi dan toksikologi, serta apakah formulasi yang digunakan sama atau identik.

2.3.1.2. Metode Analisis

Bagian ini harus berisi ringkasan singkat mengenai metode analisis untuk sampel biologis, termasuk deteksi dan batas kuantifikasi suatu prosedur analisis. Jika memungkinkan, data validasi untuk metode analisis dan stabilitas sampel biologis dibahas

pada bagian ini. Dampak potensial dari metode analisis yang berbeda pada interpretasi hasil harus dibahas pada bagian yang relevan berikut ini.

2.3.1.3. Absorpsi

Data berikut harus diringkas pada bagian ini:

- Absorpsi (tingkat dan kecepatan absorpsi, studi *in vivo* dan *in situ*).
- Parameter kinetik, bioekivalensi dan/atau bioavailabilitas (studi farmakokinetik serum/ plasma/darah).

2.3.1.4 Distribusi

Data berikut harus diringkas pada bagian ini:

- Studi distribusi jaringan.
- Ikatan protein dan distribusi dalam sel darah.
- Studi transfer ke dalam plasenta.

2.3.1.5 Metabolisme (Perbandingan Antarspesies)

Data berikut harus diringkas pada bagian ini:

- Struktur kimia dan jumlah metabolit dalam sampel biologis.
- Kemungkinan jalur metabolisme.
- Metabolisme presistemik (efek lintas awal saluran cerna/hati).
- Metabolisme *in vitro* termasuk studi P450.
- Induksi dan inhibisi enzim.

2.3.1.6 Ekskresi

Data berikut harus diringkas pada bagian ini:

- Rute dan jumlah ekskresi.
- Eksresi dalam air susu.

2.3.1.7 Farmakokinetik Interaksi Obat

Apabila studi telah dilakukan, maka studi farmakokinetik interaksi Obat nonklinik (*in vitro* dan/atau *in vivo*) harus diringkas dengan singkat dalam bagian ini.

2.3.1.8 Studi Farmakokinetik Lain

Apabila studi telah dilakukan pada model penyakit nonklinik (misalnya hewan dengan gangguan ginjal), maka harus diringkas pada bagian ini.

2.3.1.9 Pembahasan dan Kesimpulan

Bagian ini adalah untuk membahas evaluasi farmakokinetik dan mempertimbangkan kemaknaan hasilnya.

2.3.1.10 Tabel dan Grafik

Narasi tabel dan grafik dapat dimasukkan pada butir-butir yang sesuai diseluruh ringkasan narasi. Sebagai

alternatif, tabel dan grafik dimasukkan pada akhir ringkasan.

2.3.2 Ringkasan Matriks Studi Farmakokinetik dalam Format Matriks (lihat Daftar Matriks Studi)

2.4. Toksikologi

2.4.1 Ringkasan

Urutan Ringkasan Toksikologi harus sebagai berikut:

- Ringkasan singkat.
- Toksisitas dosis-tunggal.
- Toksisitas dosis-berulang.
- Genotoksisitas.
- Karsinogenisitas.
- Toksisitas reproduksi dan pengembangan.
- Studi pada hewan muda.
- Toleransi lokal.
- Studi toksisitas lainnya.
- Pembahasan dan Kesimpulan.
- Tabel dan Grafik (dapat dicantumkan di sini atau di dalam narasi).

2.4.1.1. Ringkasan Singkat

Temuan-temuan penting dari studi toksikologi harus diringkas secara singkat dalam beberapa halaman (umumnya tidak lebih dari enam halaman). Pada bagian ini, banyaknya evaluasi toksikologi dapat ditunjukkan dengan menggunakan tabel berisi daftar studi-studi toksikologi yang utama (hasilnya tidak harus disajikan seperti dalam tabel ini), misalnya:

Program Toksikologi

Tipe dan lama studi	Cara pemberian	Spesies	Senyawa yang diberikan*
Toksisitas dosis-tunggal	po dan iv	Tikus dan mencit	Senyawa Obat induk
Toksisitas dosis tunggal	po dan iv	Tikus dan mencit	Metabolit X
Toksisitas dosis-berulang			
1 bulan	po	Tikus dan anjing	Senyawa Obat induk
6 bulan	po	Tikus	Senyawa Obat induk
9 bulan	po	Anjing	Senyawa Obat induk
dll			

* Kolom ini harus dicantumkan hanya jika metabolitnya yang diteliti.

Ruang lingkup evaluasi toksikologi harus digambarkan dalam hubungannya dengan kegunaan klinis yang diajukan. Komentar terhadap status GLP dari studi harus dicantumkan.

2.4.1.2. Toksisitas Dosis-Tunggal

Data dosis-tunggal sebaiknya diringkas berdasarkan spesies dan cara pemberian. Dalam beberapa kasus, penyajian data dalam bentuk tabel akan membantu.

2.4.1.3. Toksisitas Dosis-Berulang (termasuk evaluasi toksikokinetik pendukung)

Studi harus diringkas berdasarkan spesies, cara pemberian, dan lama pemberian, dengan memberikan rincian singkat tentang metodologi dan penekanan terhadap temuan-temuan penting (misalnya sifat dan keparahan toksisitas organ target, hubungan antara dosis (paparan) dan/atau respon, dan NOAEL). Studi selain studi pivotal, dapat diringkas dengan tidak terlalu detail (studi pivotal merupakan studi GLP definitif yang sesuai dengan pedoman ICH M3).

2.4.1.4. Genotoksisitas

Studi harus diringkas dengan urutan sebagai berikut:

- Sistem sel nonmamalia *in vitro.*
- Sistem sel mamalia *in vitro.*
- Sistem mamalia *in vivo* (termasuk evaluasi toksikokinetik penunjang).
- Sistem lainnya.

2.4.1.5. Karsinogenisitas (termasuk evaluasi toksikokinetik penunjang)

Harus dijelaskan mengapa studi dipilih dan apa dasar pemilihan dosis yang tinggi. Setiap studi harus diringkas dengan urutan sebagai berikut:

- Studi jangka panjang (berdasarkan spesies), termasuk studi penentuan rentang dosis yang tidak sesuai apabila dimasukkan pada bagian toksisitas atau farmakokinetik dosis berulang.
- Studi jangka pendek atau menengah (termasuk studi penentuan rentang dosis yang tidak sesuai apabila dimasukkan dalam bagian toksisitas atau farmakokinetik dosis berulang).
- Studi-studi lainnya.

2.4.1.6. Toksisitas Reproduksi dan Pengembangan (termasuk dosis penentuan rentang dosis dan evaluasi toksikokinetik pendukung)

Studi harus diringkas dengan memberikan penjelasan singkat perihal metodologi dan penekanan terhadap temuan-temuan penting dengan urutan sebagai berikut:

- Fertilitas dan perkembangan embrionik awal.
- Perkembangan embrio-janin.
- Perkembangan Pranatal dan Pascalahir.
- Studi dimana keturunan (hewan muda) diberi Obat dan/atau dievaluasi lebih lanjut jika studi tersebut telah dilakukan.

Apabila digunakan desain studi yang dimodifikasi maka subjudul juga harus dimodifikasi.

2.4.1.7. Toleransi Lokal

Apabila studi toleransi lokal telah dilakukan, maka harus diringkas berdasarkan spesies, cara pemberian, dan lama pemberian, dengan memberikan penjelasan singkat mengenai metodologi dan penekanan terhadap temuan-temuan penting.

2.4.1.8. Studi Toksisitas Lainnya (Jika ada)

Apabila studi toksisitas lain telah dilakukan, maka harus diringkas. Apabila sesuai, rasionalisasi dilakukannya studi harus diberikan.

- Antigenisitas.
- Imunotoksisitas.
- Studi mekanistik (jika tidak dicantumkan di bagian lain).
- Ketergantungan.
- Studi terhadap metabolit.
- Studi terhadap pengotor.
- Studi lainnya.

2.4.1.9. Pembahasan dan Kesimpulan

Bagian ini adalah untuk membahas penilaian toksikologik dan kemaknaan hasilnya. Disarankan penggunaan tabel atau gambar untuk meringkas informasi ini.

2.4.1.10. Tabel dan Gambar

Narasi tabel dan gambar dapat dimasukkan pada butir-butir yang sesuai di seluruh ringkasan narasi. Sebagai alternatif, tabel dan gambar dapat dimasukkan pada akhir ringkasan.

2.4.2. Ringkasan Matriks Studi Toksikologi (lihat Daftar Matriks Studi)

3. Ringkasan Matriks Studi Nonklinik

Disarankan agar tabel ringkasan untuk informasi nonklinik dalam *Common Technical Document (CTD)* dibuat dalam format sesuai pedoman ini. Pendaftar dapat memodifikasi format, jika diperlukan, agar penyajian informasi sebaik mungkin dan dapat membantu pemahaman terhadap evaluasi hasil.

Pedoman ini tidak dimaksudkan untuk menunjukkan studi apa yang dipersyaratkan, tetapi hanya sebagai saran bagaimana mentabulasi hasil studi yang telah dilakukan. Jika perlu, Pendaftar dapat menambah atau menghapus beberapa bagian dari format. Satu format matriks studi dapat berisi hasil dari beberapa studi. Sebagai alternatif, dapat juga menyebutkan data dari satu studi dalam beberapa format matriks studi.

Format yang diajukan untuk tabel dalam Ringkasan matriks studi nonklinik diberikan dalam Daftar matriks studi. Daftar matriks studi berisi format baku (*template)* untuk digunakan dalam membuat tabel. Format

baku berisi catatan yang dicetak miring untuk memberi petunjuk pada pembuatannya (informasi yang dicetak miring harus dihapus ketika tabel dibuat). Akan tetapi, tetap menjadi tanggung jawab Pendaftar untuk memutuskan cara penyajian data yang terbaik untuk setiap produk. Harus diingat bahwa tinjauan ringkasan matriks studi bersama dengan ringkasan merupakan tinjauan utama dari informasi nonklinik. Penyajian data dengan menggunakan format baku dan contoh yang diberikan, harus tetap memastikan ketersediaan informasi yang cukup bagi penilai dan harus memberikan tinjauan singkat dari informasi terkait.

Apabila studi pada hewan muda telah dilakukan, maka harus dibuat matriks menggunakan format baku yang sesuai dengan jenis studi tersebut.

Pembuatan tabel untuk Ringkasan Matriks Studi Nonklinik harus mengikuti urutan Ringkasan Studi Nonklinik.

SUBBAGIAN C : LAPORAN STUDI NONKLINIK

Laporan lengkap studi nonklinik tidak dipersyaratkan kecuali jika dianggap perlu[1]. Pedoman ini menyajikan format yang telah disepakati untuk pengaturan laporan nonklinik dalam Dokumen Registrasi Bagian III untuk pendaftaran yang akan diserahkan kepada Badan POM. Pedoman ini tidak bertujuan untuk menunjukkan studi apa yang dipersyaratkan, tetapi hanya menunjukkan format yang sesuai untuk data nonklinik yang telah diperoleh.

Penempatan yang sesuai untuk setiap data individual hewan uji adalah di dalam laporan studi atau sebagai lampiran dari laporan studi.

1. Daftar Isi Laporan Studi Nonklinik

Daftar isi sebaiknya mencantumkan daftar semua Laporan Studi Nonklinik dan mencantumkan lokasi setiap laporan studi dalam Dokumen Registrasi bagian III. Daftar isi Laporan Studi Nonklinik harus mencantumkan semua item numerik yang ada dalam Dokumen Registrasi bagian III untuk mengidentifikasi semua komponen penting dari pendaftaran Obat (misalnya 2.3.5.1 Fertilitas dan perkembangan embrionik awal) dan dilanjutkan sampai ringkasan laporan studi. Jadi setiap laporan studi harus diidentifikasi dalam daftar isi.

Ilustrasi Bagian dari Daftar Isi Laporan Studi Nonklinik

1.1. Toksisitas Dosis-Berulang

Studi aa-aaa : 30 hari studi toksisitas dosis berulang dengan Obat X pada tikus.

Studi bb-bbb : 6 bulan studi toksisitas dosis berulang dengan Obat X pada tikus.

Studi cc-ccc : 30 hari studi toksisitas dosis berulang dengan Obat X pada anjing.

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[1] Di negara-negara anggota ASEAN lainnya, laporan studi nonklinik mungkin tidak dibutuhkan untuk pendaftaran Zat Aktif baru (NCE), produk bioteknologi, atau variasi major lainnya jika produk originator sudah didaftarkan dan disetujui untuk dipasarkan di negara-negara acuan.

Studi dd-ddd : 6 bulan studi toksisitas dosis berulang dengan Obat X pada anjing.

1.2. Genotoksisitas

1.2.1. *In vitro*
Studi ee-eee : Uji Ames dengan Obat X; dst.

2. Laporan Studi

Laporan studi harus disajikan dengan urutan berikut:

2.1 Farmakologi

2.1.1 Farmakodinamik primer.
2.1.2 Farmakodinamik sekunder.
2.1.3 Farmakologi keamanan.
2.1.4 Farmakodinamik interaksi Obat.

2.2 Farmakokinetik

2.2.1 Laporan metode analisis dan validasi (bila laporan terpisah).
2.2.2 Absorpsi.
2.2.3 Distribusi.
2.2.4 Metabolisme (perbandingan antarspesies).
2.2.5 Ekskresi.
2.2.6 Farmakokinetik interaksi Obat.
2.2.7 Studi farmakokinetik lain.

2.3 Toksikologi

2.3.1 Toksisitas dosis tunggal (berdasarkan spesies, cara pemberian).
2.3.2 Toksisitas dosis berulang (berdasarkan spesies, cara pemberian, lama pemberian, termasuk evaluasi toksikokinetik penunjang).
2.3.3 Genotoksisitas
2.3.3.1 *In vitro.*
2.3.3.2 *In vivo* (termasuk evaluasi toksikokinetik penunjang).
2.3.4 Karsinogenisitas (termasuk evaluasi toksikokinetik penunjang)
2.3.4.1 Studi jangka panjang (berdasarkan spesies, termasuk studi penentuan rentang dosis yang tidak dapat dimasukkan dalam toksisitas atau farmakokinetik dosis berulang).
2.3.4.2 Studi jangka pendek atau jangka menengah (termasuk studi penentuan rentang dosis yang tidak dapat dimasukkan dalam toksisitas atau farmakokinetik dosis berulang).
2.3.4.3 Studi lain.
2.3.5 Toksisitas reproduksi dan pengembangan (termasuk studi penentuan rentang dosis dan evaluasi toksikokinetik penunjang. Bila digunakan desain studi yang dimodifikasi, subjudul berikut juga harus dimodifikasi)
2.3.5.1 Fertilitas dan perkembangan embrionik awal.
2.3.5.2 Perkembangan embrio-janin.
2.3.5.3 Perkembangan pranatal dan pascalahir, termasuk fungsi maternal.
2.3.5.4 Studi dimana keturunan (hewan muda) diberi Obat dan/atau dievaluasi lebih lanjut.

2.3.6 Toleransi Lokal
2.3.7 Studi Toksisitas Lain (bila ada)
2.3.7.1 Antigenisitas.
2.3.7.2 Imunotoksisitas.
2.3.7.3 Studi mekanistik (bila tidak termasuk dicantumkan di tempat lain).
2.3.7.4 Ketergantungan.
2.3.7.5 Metabolit.
2.3.7.6 Pengotor.
2.3.7.7 Studi lain.

SUBBAGIAN D: DAFTAR PUSTAKA

Daftar pustaka yang digunakan, ditetapkan sesuai dengan Deklarasi Vancouver, 1979 "*Uniform Requirements for Manuscripts Submitted to Biomedical Journals*", atau sistem yang digunakan dalam "*Chemical Abstracts*". Salinan pustaka penting yang disebutkan dalam tinjauan nonklinik harus dicantumkan di bagian ini. Semua pustaka yang belum diberikan harus tersedia jika diminta.

MATRIKS: FORMAT BAKU MATRIKS RINGKASAN STUDI NONKLINIK

2.2.2 Farmakologi
2.2.2.1 Farmakologi: tinjauan
2.2.2.2 Farmakodinamik primer*
2.2.2.3 Farmakodinamik sekunder*
2.2.2.4 Farmakologi keamanan
2.2.2.5 Farmakodinamik interaksi obat*

2.3.2 Farmakokinetik
2.3.2.1 Farmakokinetik: tinjauan
2.3.2.2 Metode analisis dan laporan validasi*
2.3.2.3 Farmakokinetik: absorpsi setelah dosis tunggal
2.3.2.4 Farmakokinetik: absorpsi setelah dosis berulang
2.3.2.5 Farmakokinetik: distribusi organ
2.3.2.6 Farmakokinetik: ikatan protein plasma
2.3.2.7 Farmakokinetik: studi pada hewan hamil atau menyusui
2.3.2.8 Farmakokinetik: studi distribusi lainnya
2.3.2.9 Farmakokinetik: metabolisme *in vivo*
2.3.2.10 Farmakokinetik: metabolisme *in vitro*
2.3.2.11 Farmakokinetik: jalur metabolik yang mungkin
2.3.2.12 Farmakokinetik: induksi/hambatan enzim yang pemetabolisme obat
2.3.2.13 Farmakokinetik: ekskresi
2.3.2.14 Farmakokinetik: ekskresi melalui empedu
2.3.2.15 Farmakokinetik: interaksi obat
2.3.2.16 Farmakokinetik: lain-lain

2.4.2 Toksikologi
2.4.2.1 Toksikologi:tinjauan
2.4.2.2 Toksikokinetik: tinjauan studi toksikokinetik
2.4.2.3 Toksikokinetik: tinjauan data toksikokinetik
2.4.2.4 Toksikologi: zat aktif
2.4.2.5 Toksisitas dosis tunggal
2.4.2.6 Toksisitas dosis berulang: studi nonpivotal
2.4.2.7 Toksisitas dosis berulang: studi pivotal
2.4.2.8 Genotoksisitas: *in vitro*
2.4.2.9 Genotoksisitas: *in vivo*
2.4.2.10 Karsinogenisitas
2.4.2.11 Toksisitas reproduksi dan pengembangan: studi nonpivotal
2.4.2.12 Toksisitas reproduksi dan pengembangan: fertilitas dan pengembangan embrionik awal sampai implantasi (pivotal)
2.4.2.13 Toksisitas reproduksi dan pengembangan: efek pada pengembangan embriofetal (pivotal)
2.4.2.14 Toksisitas reproduksi dan pengembangan: efek pada pengembangan pra dan pascalahir, termasuk fungsi maternal (pivotal)
2.4.2.15 Studi pada hewan muda[a]
2.4.2.16 Toleransi lokal
2.4.2.17 Studi toksisitas lain

* : Ringkasan matriks studi merupakan pilihan. Lebih baik berupa narasi tabel dan gambar dengan Ringkasan Studi Nonklinik.
a : Jika studi pada hewan muda telah dilakukan, maka perlu dibuat matriks menggunakan format baku yang sesuai dengan tipe studi dan diletakkan di Bagian 2.4.2.15.

The Common Technical Dossier - Data Studi Nonklinik

2.2.2.1 Farmakologi

Tinjauan

Obat Uji : *(1)*

Jenis studi	Sistem uji	Cara pemberian	Fasilitas Pengujian	Nomor Studi *(4)*	Lokasi *(3)* Vol.	Hal
Farmakodinamik primer *(2)*						
Farmakodinamik sekunder						
Farmakologi keamanan						
Farmakodinamik Interaksi obat						

Catatan: *(1) International Nonproprietary Name (INN)*
(2) Harus ada satu garis untuk setiap laporan farmakologi, dengan urutan yang sama seperti CTD. Laporan yang mencakup GLP Compliance Statement sebaiknya diidentifikasi dalam catatan kaki.
(3) Letak Technical Report dalam CTD sebaiknya ditunjukkan.
(4) Atau No. Laporan (pada semua tabel)

2.2.2.4 Farmakologi Keamanan *(1)* Obat Uji: *(2)*

Sistem Organ yang dinilai	Spesies / *Strain*	Cara Pemberian	Dosis[a] (mg/kg)	Jenis kelamin dan jumlah tiap kelompok	Temuan penting	Kepatuhan terhadap GLP	No. Studi *(3)*

Catatan: (1) Seluruh studi farmakologi keamanan sebaiknya diringkas
(2) International Nonproprietary Name (INN)
(3) Atau No. Laporan (pada semua tabel)
a - Dosis tunggal kecuali jika dinyatakan lain

2.3.2.1 Farmakokinetik

Tinjauan

Obat Uji: *(1)*

Jenis studi	Sistem Uji	Cara Pemberian	Fasilitas Pengujian	No. Studi	Lokasi *(3)* Vol.	Hal
Absorpsi *(2)*						
Distribusi						
Metabolisme						
Ekskresi						
Farmakokinetik interaksi obat						
Lain-lain						

Catatan: (1) International Nonproprietary Name (INN)
(2) Harus ada satu garis untuk setiap laporan farmakologi, dengan urutan yang sama seperti CTD. Laporan yang mengandung GLP Compliance Statement sebaiknya diidentifikasi dalam catatan kaki
(3) Letak Laporan Teknis dalam CTD sebaiknya ditunjukkan.

2.3.2.3 Farmakokinetik: Absorpsi setelah pemberian dosis tunggal

Obat uji : *(1)*

Lokasi dalam CTD : Volume. Halaman
No studi.

Spesies					
Jenis kelamin (J/B)/ jumlah hewan	*(4)*				
Kondisi pemberian pakan					
Pembawa/formulasi					
Cara pemberian					
Dosis (mg/kg)					
Sampel (misal: darah, plasma, serum)					
Analit					
Penetapan Kadar *(2)*					
Parameter farmakokinetik					

Informasi tambahan *(3)*

Catatan:

(1) International Nonproprietary Name (INN)

(2) Misalnya: HPLC, LSC dengan senyawa berlabel ^{14}C

(3) Misalnya, narasi hasil secara singkat, perbedaan spesies, perbedaan jenis kelamin, keterkaitan dengan dosis, atau komentar khusus.

(4) Satu kolom untuk setiap studi yang dilakukan. Sebagai perbandingan, informasi dosis maksimum yang direkomendasikan pada manusia harus dimasukkan.

2.3.2.4. Farmakokinetik : Absorpsi setelah pemberian dosis berulang

(Data dapat ditabulasi seperti format 2.3.2.3 (jika diminta))

Obat Uji :

Format A

2.3.2.5 Farmakokinetik: Distribusi organ

Obat Uji :
Lokasi dalam

CTD: Vol. Halaman

No studi.

Spesies:
Jenis kelamin (J/B) Jumlah hewan :
Kondisi pemberian pakan:
Pembawa/formulasi:
Cara pemberian:
Dosis (mg/kg):
Radionuklida:
Aktivitas spesifik:
Waktu sampling : Kadar (unit)

Jaringan/ organ	T (1)	T (2)	T (3)	T(4)	T(5)	T ½

Informasi tambahan :

Alternatif Format B

2.3.2.5 Farmakokinetik : Distribusi organ

Obat Uji:
Lokasi dalam

CTD: Vol. Halaman

No studi.

Spesies:
Jenis kelamin (J/B)/Jumlah hewan:
Kondisi pemberian pakan
Pembawa/formulasi:
Cara pemberian:
Dosis (mg/kg):
Radionuklida:
Aktivitas spesifik:
Analit/Penetapan Kadar (unit)
Waktu sampling:

Jaringan /organ	Ct		Waktu *sampling* terakhir		
	Kadar	T/P [1)]	Kadar	T/P [1)]	waktu
AUC	t ½				

Informasi tambahan:

[1)](Jaringan)/(Plasma)

2.3.2.6. Farmakokinetik : Ikatan Protein Plasma

Obat uji:

Sistem studi:
Target, sistem, dan metode uji:

Spesies	Konsentrasi yang diuji	% ikatan	Lokasi dalam CTD: No. Studi	Volume	Halaman

Informasi tambahan :

2.3.2.7. Farmakokinetik : Studi pada hewan hamil atau menyusui *(1)*

Obat Uji : *(2)*

			Lokasi dalam CTD: No studi:	Vol.	Halaman
Transfer melalui placenta					
Spesies:					
Usia kehamilan/jumlah hewan :					
Pembawa/formulasi:					
Cara pemberian:					
Dosis (mg/kg) :					
Analit :					
Penetapan Kadar:					
Waktu (jam)					
Kadar/jumlah (% dosis)					
Dam: (3)					
Janin: *(3)*					

Informasi tambahan :

Informasi tambahan:

			Lokasi dalam CTD : No.Studi	Vol.	Halaman
Ekskresi ke dalam air susu					
Spesies:					
Tanggal laktasi/ jumlah hewan:					
Kondisi pemberian pakan:					
Pembawa/formulasi:					
Dosis (mg/kg):					
Analit:					
Penetapan Kadar:					
Waktu (jam):					
Kadar:					
Air susu:					
Plasma:					
Air susu/plasma:					
Bayi baru lahir:					

Informasi tambahan:

Catatan untuk tabel 2.3.2.7

(1) Meskipun data diperoleh dari studi toksikologi reproduksi, hasil harus dicantumkan dalam tabel ini
(2) International Nonproprietary Name (INN)
(3) Jaringan yang diambil sebagai sampel harus dijelaskan (misalnya plasma foe dams, kadar dalam janin)

2.3.2.8 Farmakokinetik: Studi Distribusi lain

Obat Uji :

2.3.2.9 Farmakokinetik: Metabolisme *in vivo* Obat Uji:

Jenis kelamin (J/B)/Jumlah hewan:
Kondisi pemberian pakan:
Pembawa/Formulasi:
Cara Pemberian:
Dosis (mg/kg):
Radionuklida:
Aktivitas spesifik:

				% Senyawa dalam Sampel				Lokasi dalam CTD	
Spesies	Sampel	Waktu atau Periode *Sampling*	% Dosis dalam Sampel	Senyawa Induk	M1	M2	No studi	Vol	Halaman
	Plasma								
	Urin								
	Empedu								
	Feses								
	Plasma								
	Urin								
	Empedu								
	Feses								
	Plasma								
	Urin								
	Empedu								
	Feses								

Informasi tambahan:

Catatan: *Data manusia harus dimasukkan sebagai bahan perbandingan (jika ada)*

2.3.2.10 Farmakokinetik: Metabolisme *in vitro*

Obat Uji:

Lokasi dalam CTD: Vol. Halaman
No. studi

Sistem studi :

Waktu					
Kadar:					
Senyawa					
Senyawa induk					
M-1					
M-2					

Informasi tambahan :

Catatan: Data manusia harus dimasukkan sebagai bahan perbandingan (jika ada).

2.3.2.11 Farmakokinetik: Jalur Metabolisme yang Mungkin Obat Uji:

(Gambarkan peta metabolisme yang mungkin pada spesies hewan dimana reaksi metabolisme terjadi).

2.3.2.12 Farmakokinetik: Induksi/Inhibisi Enzim Metabolisme Obat

Obat Uji:
Lokasi dalam CTD: Vol. Halaman
No. studi

Catatan. Hanya Studi Nonklinik

Jenis studi:

Metode:

Tabel hasil:

Informasi tambahan:

2.3.2.13 Farmakokinetik: Ekskresi	Obat Uji: *(1)*											
Spesies												
Jenis kelamin (J/B) / Jumlah hewan	*(3)*											
Kondisi pemberian pakan												
Pembawa/Formulasi												
Cara pemberian												
Dosis (mg/kg)												
Analit												
Penetapan kadar												
Rute ekskresi *(4)*	Urin	Feses	Total	Urin	Feses	Total	Urin	Feses	Total	Urin	Feses	Total
Waktu												
0 – T jam												
No studi												
Lokasi dalam CTD												
Informasi tambahan: *(2)*												

Catatan:
(1) International Nonproprietary Name (INN)
(2) Misalnya, narasi hasil secara singkat, perbedaan spesies, perbedaan jenis kelamin, keterkaitan dengan dosis, atau komentar khusus.
(3) Harus ada satu kolom untuk setiap studi yang dilaksanakan. Sebagai bahan perbandingan, informasi dosis maksimum yang direkomendasikan pada manusia harus dimasukkan. Dapat dikombinasi dengan tabel Absorpsi (jika sesuai)
(4) Rute lainnya (misalnya empedu, saluran napas) harus ditambahkan (jika studi dilakukan).

2.3.2.14 Farmakokinetik: Ekskresi kedalam empedu Obat Uji:

(Data dapat ditabulasi seperti dalam format 2.3.2.13 (jika diminta)).

2.3.2.15 Farmakokinetik: Interaksi Obat

Obat Uji:
Lokasi dalam CTD: Vol. Halaman
No. Studi.

Jenis studi:

Metode:

Tabel hasil:

Informasi tambahan:

2.3.2.16 Farmakokinetik: Studi Lain

Obat Uji:
Lokasi dalam CTD: Vol. Halaman
No. Studi.

Jenis studi:

Metode:

Tabel hasil:

Informasi tambahan:

2.4.2.1 Toksikologi — Gambaran — Obat Uji: *(1)*

Jenis Studi	Spesies dan Strain	Cara Pemberian	Lama Pemberian Obat	Dosis (mg/kg[a])	Kepatuhan terhadap GLP	Fasilitas Pengujian	Nomor Studi	Lokasi Vol. Hal.
Toksisitas Dosis Tunggal	*(2)*							*(3)*
Toksisitas Dosis berulang								
Genotoksisitas								
Karsinogenisitas								
Toksisitas Reproduksi dan Pengembangan								
Toleransi Lokal								
Studi Toksisitas lainnya								

Catatan: *(1)* *International Nonproprietary Name (INN).*
(2) *Harus ada satu baris untuk setiap laporan toksikologi, dengan urutan yang sama seperti CTD.*
(3) *Harus dicantumkan lokasi Laporan Teknis dalam CTD*
a- Kecuali jika disebutkan lain. Untuk toksisitas dosis berulang, NOAEL tertinggi digarisbawahi.

2.4.2.2 Toksikokinetik — Tinjauan Studi Toksikokinetik — Obat Uji: *(1)*

Jenis Studi	Sistem Uji	Cara Pemberian	Dosis (mg/kg)	Kepatuhan terhadap GLP	Nomor Studi	Lokasi Vol.	Halaman
(2)						*(3)*	

Catatan: (1) International Nonproprietary Name (INN).
(2) Harus ada satu baris untuk setiap laporan toksikokinetik, dengan urutan yang sama seperti CTD (bagian C, Toksikologi).
(3) Harus dicantumkan lokasi Laporan Teknis dalam CTD

2.4.2.3 Toksikokinetik	Tinjauan Studi Toksikokinetik	Obat Uji: *(1)*
	(2)	

Notes: (1) International Nonproprietary Name (INN).
(2) Ringkasan 1-3 halaman (tabel dan/atau gambar) dari data toksikokinetik keadaan tunak harus dicantumkan dalam suatu format yang menggambarkan perbandingan antarspesies, termasuk manusia.

2.4.2.4 Toksikologi		Obat Aktif Kemurnian tertentu *(1)*		Obat Uji *(1)*
No. *Batch*	Kemurnian (%)		Nomor Studi	Jenis Studi
SPESIFIKASI YANG DIAJUKAN:				
(2)				*(3)*

Catatan:
(1) International Nonproprietary Name (INN).
(2) Semua batch yang digunakan dalam studi toksikologi harus dicantumkan secara berurutan.
(3) Studi Toksikologi setiap batch yang digunakan harus dijelaskan.

2.4.2.5 Toksisitas Dosis Tunggal *(1)* Obat Uji: *(2)*

Spesies/ Strain	Cara Pemberian (Pembawa/ Formulasi)	Dosis (mg/kg)	Jenis kelamin dan jumlah per kelompok	Dosis Maksimum Nonletal yang Teramati (mg/kg)	Perkiraan Dosis Mematikan (mg/kg)	Temuan penting	Nomor Studi

Catatan: (1) Semua studi toksisitas dosis tunggal harus diringkas, dengan urutan yang sama seperti CTD. Catatan kaki harus digunakan untuk menunjukkan ciri-ciri khusus, misalnya lama pemberian, kecepatan infus, atau usia subjek uji yang tidak umum.

(2) International Nonproprietary Name (INN).

2.4.2.6. Toksisitas Dosis Berulang — Studi Nonpivotal *(1)* — Artikel uji: *(2)*

Spesies/ Strain	Cara Pemberian (Pembawa/ Formulasi)	Lama Pemberian	Dosis (mg/kg)	Jenis kelamin dan Jumlah per kelompok	NOAEL[a] (mg/kg)	Temuan Penting	Nomor Studi

Catatan: (1) Semua studi toksisitas dosis berulang (termasuk semua studi penentuan dosis toksisitas) yang tidak disebutkan di dalam oleh ICH Guidance M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (November 1997), harus diringkas dengan urutan yang sama seperti CTD. Catatan kaki harus digunakan untuk menunjukkan ciri-ciri khusus, misalnya usia subjek yang tidak lazim.

(2) International Nonproprietary Name (INN).

a – Dosis NOAEL.

2.4.2.7 *(1)* Toksisitas Dosis Berulang *(2)* Judul Laporan — Obat Uji: *(3)*

Spesies/Strain: | Lama Pemberian Obat: | No. Studi.
Lokasi pada
Umur Awal Studi: | Lama waktu pascadosis: | CTD: Vol. Hal.
Tanggal Dosis Pertama: | Cara Pemberian:
Pembawa/Formulasi: | Kepatuhan thd GLP:
Ciri-ciri Khusus:
NOAEL:

Dosis Harian (mg/kg)	0 (Kontrol)							
Jumlah Hewan Uji	J:	B:	J:	B:	J:	B:	J:	B:
Toksikokinetik: AUC ( ) *(4)*	*(5)*							

Temuan Penting

Mati atau dikorbankan	
Berat Badan (%[a])	
Konsumsi Makanan (%[a])	*(5)*
Konsumsi Air ( )	*(5)*
Pengamatan Klinik	
Optalmoskopi	
Elektrokardiografi	

\- Tidak ada temuan penting + Ringan ++ Sedang +++ Berat *(6)*

(7) * - p<0.05 ** - p<0.01
Pada akhir pemberian dosis: Untuk kelompok kontrol, dicantumkan rerata kelompok. Untuk kelompok perlakuan, dicantumkan persentase perbedaan dari kelompok kontrol.

a - Kemaknaan statistik berdasarkan data sebenarnya (bukan berdasarkan persentase perbedaan)

(Bersambung)

2.4.2.7 *(1)* Toksisitas Dosis Berulang — No. Studi. (Sambungan)

Dosis Harian (mg/kg)	0 (Kontrol)							
Jumlah Hewan Uji:	J:	B:	J:	B:	J:	B:	J:	B:
Hematologi:								
Kimia Darah:								
Analisis Urin:								
Berat Organ[a] (%):								
Gross pathology:								
Histopatologi:								
Pemeriksaan Tambahan:								
Evaluasi setelah pemberian obat:								
Jumlah yang Dievaluasi *(8) (9)*								

\- Tidak ada temuan penting.
*

(7) - $p<0.05$ ** - $p<0.01$

a - Berat absolut dan relatif berbeda dari kontrol ke arah yang ditunjukkan. Angka menunjukkan persentase perbedaan untuk berat organ absolut.

Catatan untuk Tabel 2.4.2.7

(1) Tabel dinomori secara berurutan (misalnya, 2.4.2.7A, 2.4.2.7B, 2.4.2.7C).

(2) Harus ada satu tabel untuk setiap studi toksisitas dosis berulang yang disebutkan dalam ICH Guidance M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (November 1997), juga untuk studi toksisitas dosis berulang lain yang dianggap pivotal.

(3) International Nonproprietary Name (INN).

(4) AUC keadaan tunak, Cmax, Css, atau informasi toksikokinetik lain yang menunjang studi. Jika berasal dari studi yang terpisah, nomor studi harus dicantumkan pada catatan kaki.

(5) HANYA TEMUAN PENTING YANG HARUS DITAMPILKAN. Jika ada parameter tambahan (selain dari format baku) yang menunjukkan perubahan yang penting, agar ditambahkan ke dalam tabel. Secara umum, data pada akhir pemberian dosis dapat ditunjukkan; akan tetapi, jika ada temuan penting tambahan pada awal pengamatan, data ini ini harus dicantumkan. Catatan kaki harus digunakan bila diperlukan informasi tambahan tentang pengujian atau hasil studi.

(6) Atau skala lain (jika perlu).

(7) Agar dicantumkan metode analisis statistik.

(8) Semua parameter yang masih menunjukkan perubahan terkait obat agar dicantumkan. Bagian ini harus dihilangkan bila studi tidak melakukan evaluasi postdose.

(9) Jika perlu, informasi mengenai hewan uji yang di-nekropsi lebih awal agar disajikan secara terpisah.

2.4.2.8 *(1)* Genotoksisitas: *In Vitro*

Judul laporan

Obat Uji: *(2)*

Uji untuk Induksi:

Jumlah Kadar Independen:

Nomor Studi.
Lokasi dalam CTD:
Vol. Hal.

Strain:

Jumlah Replikasi Kultur:
Jumlah Sel/Kultur yang Dianalisis:

Sistem Metabolisme:
Pembawa: Untuk Obat uji: Untuk Kontrol Positif:
Perlakuan:
Efek Sitotoksik:
Efek Genotoksik:

Kepatuhan terhadap GLP:
Tanggal Perlakuan:

Aktivasi Metabolik	Obat Uji	Kadar atau Dosis (*(3)*)				
Tanpa Aktivasi		*(4)*				
Dengan Aktivasi						

Catatan:

(1) *Tabel dinomori secara berurutan (misalnya, 2.4.2.8A, 2.4.2.8B). Hasil kadar replikasi agar ditampilkan pada halaman berikut.*

(2) *International Nonproprietary Name (INN).*

(3) *Unit-unit harus dimasukkan.*

(4) *Bila terlihat adanya endapan, hal ini harus disebutkan pada catatan kaki..*

(5) *Agar dicantumkan metode analisis statistik.*

(5) * - $p<0.05$ ** - $p<0.01$

2.4.2.9 *(1)* Genotoksisitas: *In Vivo* Judul Laporan: Obat Uji: *(2)*

Uji untuk Induksi: Jadwal Perlakuan: No. studi.

Lokasi dalam CTD:

Spesies/Strain: Waktu Sampling: Vol. Hal.

Cara

Umur: Pemberian:

Sel yang dievaluasi: Pembawa/Formulasi: Kepatuhan terhadap GLP:

Jumlah Sel yang

Dianalisis/Hewan: Tanggal Pemberian Obat:

Ciri-ciri Khusus:

Efek Toksik/Sitotoksik:

Efek Genotoksik:

Bukti Paparan:

Obat Uji	Dosis (mg/kg)	Jumlah Hewan				

Catatan: *(1) Tabel dinomori secara berurutan (contoh, 2.4.2.9A, 2.4.2.9B).*

(2) International Nonproprietary Name (INN).

(3) Agar dicantumkan metode analisis statistik.

(3) * - p<0.05 ** - p<0.01

2.4.2.10 *(1)* Karsinogenositas — Judul Laporan — Obat Uji: *(2)*

Spesies/Strain: | Lama Pemberian: | No. Studi.
Umur Awal Studi: | Lama Postdose: | Lokasi dalam CTD: Vol. Hal.
Tanggal Pemberian Dosis Pertama: | Cara Pemberian:
Pembawa/Formulasi: | Kepatuhan thd GLP:

Dasar Pemilihan Dosis Tinggi: *(3)*
Ciri-ciri Khusus:

Dosis Harian (mg/kg)	0 (Kontrol)							
Gender	J:	B:	J:	B:	J:	B:	J:	B:
Toksikokinetik: AUC ( ) *(4)*								
Jumlah Hewan								
Saat Awal:								
Mati/Dikorbankan:								
Dikorbankan pada Akhir:								
Bertahan Hidup (%):	*(5)*							
Berat Badan (%[a]):								
Konsumsi Makanan (%[a]):								

(6) * - $p<0.05$ ** - $p<0.01$

a - Pada bulan keenam. Untuk kelompok kontrol, ditunjukkan rerata kelompok. Untuk kelompok perlakuan, ditunjukkan persentase perbedaan dari kontrol. Kemaknaan statistik berdasarkan pada data sebenarnya (bukan pada persentase perbedaan)

(Bersambung)

2.4.2.10 *(1)* Karsinogenisitas No Studi. (lanjutan)

Dosis harian (mg/kg)	(Kontrol))		0 (Kontrol)							
Jumlah yang dievaluasi	J:	B:	J:	B:	J:	B:	J:	B:	J:	B:
Jumlah hewan										
Dengan lesi neoplastik: *(7)*										

Temuan penting:
Patologi *gross*
Histopatologi – Nonneoplastik
Lesi

- Tidak ada temuan penting

* - p<0.05 ** - p<0.01

Catatan untuk Tabel 2.4.2.10

(1) Tabel diberi nomor secara berurutan (misalnya, 2.4.2.10A, 2.4.2.10B). Harus ada satu tabel untuk setiap studi karsinogenisitas.

(2) International Nonproprietary Name (INN).

(3) Dari Pedoman ICH SIC Dose Selection for Carcinogenicity Studies of Pharmaceuticals (Maret 1995).

(4) AUC kadar tunak, Cmax, Css, atau informasi toksikokinetik lain yang mendukung studi. Jika informasi berasal dari studi yang terpisah, nomor studi harus dicantumkan dalam catatan kaki.

(5) Jika parameter tambahan memperlihatkan perubahan terkait Obat, maka parameter tersebut harus ditambahkan ke dalam tabel. Catatan kaki harus digunakan untuk memberikan informasi tambahan tentang pengujian dan hasil (jika perlu).

(6) Metode analisis statistik harus disebutkan.

(7) Lesi terkait Obat harus dicantumkan pertama kali. Kemudian lesi lain dicantumkan secara alfabetis menurut organ dan/atau jaringan.

2.4.2.11 Toksisitas reproduksi dan pengembangan — Studi Nonpivotal *(1)* — Obat Uji *(2)*

Spesies/ Strain	Cara Pemberian Obat (Pembawa / Formulasi)	Periode Pemberian Dosis	Dosis mg/kg	Jumlah per kelompok	Temuan Penting	Nomor Studi

Catatan: *(1)* *Semua studi toksisitas reproduksi (termasuk semua studi penentuan rentang dosis yang relevan), selain dari studi yang disebutkan oleh M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals, November 1997, harus diringkas. Akan tetapi, studi pemeriksaan harus diringkas menggunakan format baku yang lebih rinci.*

(2) *International Nonproprietary Name (INN).*

2.4.2.12 *(1)* Toksisitas reproduksi dan pengembangan - Fertilitas dan Pengembangan Embrio Awal hingga implantasi *(3)*

Judul Laporan: Obat Uji : *(2)*

Desain studi :

Spesies/Strain:

Umur awal studi:

Tanggal pemberian dosis pertama:

Ciri-ciri khusus:

NOAEL:

Lama pemberian Obat: J:

Hari Kawin: *(8)* B:

Hari Bagian-C:

Cara pemberian:

Pembawa/Formulasi:

No. Studi

F_0 Jantan :

F_0 Betina :

F_1 *Litters*:

Dosis harian (mg/kg) 0 (Kontrol)

Jantan Toksikokinetik: AUC ( ) *(4)*

Jumlah hewan yang dievaluasi
Jumlah hewan yang mati atau dikorbankan
Pengamatan klinis
Pengamatan nekropsi
Berat badan (%[a])
Konsumsi makanan (%[a])
Rerata jumlah hari sebelum kawin
Jumlah jantan yang kawin
Jumlah jantan yang subur

(5)

\- Tidak ada temuan penting + Ringan ++ Sedang +++ Berat *(6)*

*(7)** - p<0.05 ** - p<0.01

a - Setelah empat minggu pemberian Obat. Untuk kelompok kontrol, dicantumkan rerata kelompok. Untuk kelompok uji, dicantumkan persentase perbedaan dari kontrol. Kemaknaan statistik berdasarkan data sebenarnya (bukan persen perbedaan). (bersambung)

2.4.2.12 (1) Toksisitas reproduksi dan pengembangan No. Studi (Lanjutan)

Dosis harian (mg/kg) 0 (Kontrol)

Betina Toksikokinetik: AUC ( ) (*4*)

Jumlah yang dievaluasi
Jumlah hewan mati atau dikorbankan
Pengamatan klinis
Pengamatan nekropsi
Berat Badan Sebelum Kawin (%[a])
Berat Badan Sewaktu hamil (%[a])
Konsumsi Makanan Sebelum Kawin (%[a])
Konsumsi Makanan Sewaktu hamil (%[a])
Rerata Jumlah Siklus Estrus/14 hari
Rerata Jumlah Hari Sebelum Kawin
Jumlah Sperma Positif pada Betina
Jumlah Betina yang Hamil
Jumlah Aborsi atau dengan Total Resopsi *Litter*
Rerata Jumlah *Corpora Lutea*
Rerata Jumlah Implantasi
% Rerata Kehilangan Praimplantasi
Rerata Jumlah *conceptuses* hidup
Rerata Jumlah Resorpsi
Jumlah *conceptuses* mati
% rerata kehilangan pascaimplantasi

\- Tidak ada temuan penting. + Ringan ++ Sedang +++ Berat *(6)*

*(7)** - p<0.05 ** - p<0.01

a - Pada akhir periode kawin atau hamil. Untuk kelompok kontrol, dicantumkan rerata kelompok. Untuk kelompok uji, dicantumkan persentase perbedaan dari kontrol. Kemaknaan statistik berdasarkan data sebenarnya (bukan persen perbedaan).

Catatan untuk tabel 2.4.2.12, 2.4.2.13 dan 2.4.2.14

(1) Jika terdapat banyak studi jenis ini, tabel harus diberi nomor secara berurutan (misal, 2.4.2.12A, 2.4.2.12B, 2.4.2.13A, 2.4.2.13B).

(2) International Nonproprietary Name (INN).

(3) Jika digunakan desain studi yang dimodifikasi, tabel harus disesuaikan

(4) AUC kadar tunak, Cmax, atau informasi toksikokinetik lain yang mendukung studi. Jika informasi berasal dari studi yang terpisah, nomor studi harus dicantumkan dalam catatan kaki.

(5) PRESENTASI HASIL DAPAT DILIHAT PADA FORMAT BAKU INI. PENYAJIAN DATA HARUS FLEKSIBEL DAN SESUAI BERDASARKAN ANALISIS STATISTIK DAN DESAIN STUDI YANG OPTIMAL. Jika parameter tambahan memperlihatkan perubahan yang terkait Obat, maka parameter tersebut harus ditambahkan ke dalam tabel. Catatan kaki harus digunakan untuk memberikan informasi tambahan tentang pengujian dan hasil (jika perlu).

(6) Atau skala lain yang sesuai.

(7) Metode analisis statistik harus disebutkan.

(8) Hari Kawin harus disebutkan (misalnya, Hari ke- 0 atau Hari ke-1).

2.4.2.13 (*1*) Toksisitas reproduksi dan pengembangan - Efek pada Pengembangan Embrio janin *(3)*

Judul Laporan:

Obat uji: (*2*)

Desain studi :

Lama pemberian obat:
Hari Kawin: *(8)*

No Studi.

Lokasi dalam CTD: Vol.
Hal.

Species/Strain :
Umur awal studi:
Tanggal pemberian dosis pertama:
Ciri-ciri khusus :

Hari Bagian-C:
Cara pemberian:
Pembawa/Formulasi:

Kepatuhan terhadap GLP:

NOAEL
Fo Betina:
F1 *Litters*:

Dosis harian (mg/kg) 0 (Kontrol)

Dams/Does: Toksikokinetik: AUC ( ) *(4)*

Jumlah hewan hamil
Jumlah hewan mati atau dikorbankan *(5)*
Jumlah aborsi atau Total Resopsi *Litter*
Pengamatan klinis
Pengamatan nekropsi
Berat badan (%[a])
Konsumsi makanan (%[a])
Rerata jumlah *Corpora Lutea*
Rerata jumlah implantasi
Rerata % kehilangan praimplantasi

\- Tidak ada temuan penting + Ringan ++ Sedang +++ Berat *(6)* G = Hari kehamilan

*(7)** - p<0.05 ** - p<0.01

a - Pada akhir periode pemberian Obat. Untuk kelompok kontrol, dicantumkan rerata kelompok. Untuk kelompok uji, dicantumkan persentase perbedaan dari kontrol. Kemaknaan statistik berdasarkan data sebenarnya (bukan persen perbedaan) (Bersambung)

2.4.2.13 *(1)* Toksisitas Reproduksi dan Pengembangan No. Studi. (Bersambung)

Dosis Harian (mg/kg)	0 (Kontrol)
Litters:	
Jumlah *Litter* yang dievaluasi	
Jumlah Janin Hidup	
Rerata jumlah Resorpsi	
Jumlah *Litter* dengan Janin Mati	
Rerata % Kehilangan Pascaimplantasi	
Rerata Berat Badan Janin (g)	
Rasio Jenis Kelamin Janin	
Kelainan Janin:	
External Gross	
Anomali Viseral	
Anomali Rangka	
Total Janin yang terpengaruh (*Litter*)	

\- Tidak ada temuan yang penting

* - $p < 0.05$ ** - $p < 0.01$

2.4.2.14 *(1)* Toksisitas Reproduksi dan Pengembangan - Efek pada Perkembangan Pra dan Pascakelahiran, Termasuk Fungsi Maternal *(3)*

Judul Laporan: Obat Uji: *(2)*

Desain Studi:

Lama Pemberian Obat: No. Studi
Hari Kawin: *(8)*

Spesies/Galur:
Usia Awal Studi
Tanggal Pemberian Dosis Pertama:

Cara Pemberian: Lokasi dalam CTD: Vol. Hal.
Pembawa/Formulasi:
Litter yang Terkumpul/Tidak Terkumpul: Kepatuhan terhadap GLP:

Ciri-ciri Khusus:
NOAEL
F0 Betina:
F1 Jantan:
F1 Betina:

Dosis Harian (mg/kg)		0 (Kontrol)
Fo Betina:	Toksikokinetik: AUC ( ) *(4)*	
	Jumlah yang Hamil	
	Jumlah yang Mati atau dikorbankan	
	Jumlah Aborsi atau Total Resorpsi *Litter*	
	Pengamatan Klinik	
	Pengamatan Nekropsi	
	Berat Badan saat Hamil (%[a])	*(5)*
	Berat Badan saat Laktasi (%[a])	
	Konsumsi Makanan saat Hamil (%[a])	
	Konsumsi Makanan saat Laktasi (%[a])	
	Rerata lama Kehamilan (hari)	
	Kelahiran yang Abnormal	

\- Tidak ada temuan yang penting. + Ringan ++ Sedang +++ Berat *(6)* G = Hari Kehamilan L = Hari Laktasi

*(7)** - $p<0.05$ ** - $p<0.01$

a - Pada akhir kehamilan atau laktasi. Untuk kelompok kontrol, dicantumkan rerata kelompok. Untuk kelompok uji, dicantumkan persentase perbedaan dari kontrol. Kemaknaan statistik berdasarkan data sebenarnya (bukan persen perbedaan) (Bersambung)

2.4.2.14 *(1)* Toksisitas Reproduksi dan Pengembangan

No. Studi
(Lanjutan)

Dosis Harian (mg/kg)		0 (Kontrol)
F1 *Litter:*	Jumlah *Litter* yang dievaluasi	
Sebelum disapih	Rerata Jumlah Implantasi	
	Rerata Jumlah Anak/*Litter*	
	Rerata Jumlah Anak Lahir Hidup /*Litter*	
	Jumlah *Litter* dengan Anak Lahir Mati	
	Anak yang Bertahan Hidup Sampai Hari ke-4	
	Anak yang Bertahan Hidup Sampai Disapih	
	Jumlah Total *Litter* yang Hilang	
	Perubahan Berat Badan Anak[a] (g)	
	Rasio Jenis Kelamin Anak	
	Tanda-Tanda Klinik Anak	
	Pengamatan Pascakematian Anak	
F1 Jantan:	Jumlah anak setelah disapih per *Litter* yang dievaluasi	
Setelah disapih	Jumlah mati atau dikorbankan	
	Pengamatan Klinik	
	Pengamatan nekropsi	
	Perubahan berat badan[b] (g)	
	Konsumsi Makanan (%[c])	
	Pemisahan *Preputial*	
	Fungsi Sensorik	
	Aktivitas Motorik	
	Kemampuan belajar dan mengingat	
	Rerata Jumlah Hari Sebelum Kawin	
	Jumlah Jantan yang Dikawinkan	
	Jumlah Jantan yang Subur	

\- Tidak ada temuan yang penting + Ringan ++ Sedang +++ Berat *(6)*
*(7)** - $p<0.05$ ** - $p<0.01$

a - Sejak lahir sampai disapih
b - Sejak disapih sampai kawin
c - Pada akhir periode setelah disapih. Untuk kelompok kontrol, dicantumkan rerata kelompok. Untuk kelompok uji, dicantumkan persentase perbedaan dari kontrol. Kemaknaan statistik berdasarkan data sebenarnya (bukan persen perbedaan) (Bersambung)

2.4.2.14 *(1)* Toksisitas Reproduksi dan Pengembangan No. Studi (Lanjutan)

Dosis Harian (mg/kg)		0 (Kontrol)
F1 Betina:	Jumlah Anak Setelah Disapih yang Dievaluasi	
Setelah disapih	Jumlah yang Mati atau Dikorbankan	
	Pengamatan Klinik	
	Pengamatan Nekropsi	
	Perubahan Berat Badan Sebelum kawin[a] (g)	
	Perubahan Berat Badan saat Hamil (g)	
	Konsumsi Makanan Sebelum Kawin (%[b])	
	Konsumsi Makanan Saat Hamil (%[B])	
	Rerata Usia Patensi Vagina (Hari)	
	Fungsi Sensorik	
	Aktivitas Motorik	
	Kemampuan belajar dan mengingat	
	Rerata Jumlah Hari Sebelum Kawin	
	Jumlah Betina dengan Positif Sperma	
	Jumlah Betina yang Hamil	
	Rerata Jumlah *Corpora Lutea*	
	Rerata Jumlah Implantasi	
	Rerata % Kehilangan Praimplantasi	
F2 *Litter*:	Rerata jumlah zigot yang hidup/*Litter*	
	Rerata Jumlah Resorpsi	
	Jumlah *Litter* dengan zigot mati	
	Jumlah zigot mati	
	Rerata % kehilangan Pascaimplantasi	
	Berat Badan Janin (g)	
	Rasio Jenis Kelamin janin (% jantan)	
	Anomali Janin	

\- Tidak ada temuan yang penting. + Ringan ++ Sedang +++ Berat *(6)*

*(7)** - p<0.05 ** - p<0.01

a - Sejak disapih sampai kawin.

b - Pada akhir periode *premating* atau kehamilan. Untuk kelompok kontrol, dicantumkan rerata kelompok. Untuk kelompok uji, dicantumkan persentase perbedaan dari kontrol. Kemaknaan statistik berdasarkan data sebenarnya (bukan persen perbedaan).

(Bersambung)

2.4.2.14 *(1)* Toksisitas Reproduksi dan Pengembangan — No. Studi (Lanjutan)

Dosis Harian (mg/kg)		0 (Kontrol)
F1 Betina:		
Setelah disapih	Jumlah anak setelah disapih yang dievaluasi	
	Jumlah yang mati atau dikorbankan yang hampir mati	
	Pengamatan Klinik	
	Pengamatan Nekropsi	
	Perubahan Berat Badan Sebelum Kawin[a] (g)	
	Perubahan Berat Badan saat Hamil (g)	
	Konsumsi Makanan Sebelum Kawin (%[b])	
	Konsumsi Makanan Saat Hamil (%[ab])	
	Rerata usia Patensi Vagina (hari)	
	Fungsi Sensorik	*Catatan: Format*
	Aktivitas Motorik	*Alternatif untuk*
	Kemampuan belajar dan Mengingat	*Kelahiran*
	Rerata Jumlah Hari Sebelum Kawin	*Normal*
	Jumlah Betina dengan Positif Sperma	
	Jumlah Betina yang Hamil	
	Rerata Lama Kehamilan	
	Kelahiran yang Abnormal	
F2 *Litter:*	Jumlah *Litter* yang dievaluasi	
	Rerata Jumlah Implantasi	
	Rerata Jumlah Anak/*Litter*	
	Rerata Jumlah Anak Lahir Hidup/*Litter*	
	Rerata Jumlah Anak Lahir Mati /*Litter*	
	Anak yang Bertahan Hidup sampai Hari Ke-4	
	Anak yang Bertahan Hidup sampai Masa Disapih	
	Perubahan Berat Badan Anak (g)	
	Rasio Jenis Kelamin Anak	
	Tanda-Tanda Klinik Anak	
	Pengamatan Nekropsi anak	

\- Tidak ada temuan yang penting. + Ringan ++ Sedang +++ Berat *(6)*

*(7)** - $p<0.05$ ** - $p<0.01$

a - Sejak lahir sampai kawin.

b - Pada akhir periode sebelum kawin atau kehamilan. Untuk kontrol, digunakan nilai rerata kelompok. Untuk kelompok Obat, digunakan nilai persen perbedaan dari kontrol. Kebermaknaan statistik berdasarkan data aktual (bukan nilai persen perbedaan).

2.4.2.16 Toleransi Lokal *(1)* Obat Uji: *(2)*

Spesies/ Galur	Cara Pemberian	Dosis (mg/kg)	Jenis Kelamin dan Jumlah per Kelompok	Temuan yang Bermakna	Nomor Studi

Catatan: *(1)* Semua studi toleransi lokal harus diringkas.
(2) International Nonproprietary Name (INN).

2.3.2.17 Studi Toksisitas Lokal
(*1*)

Obat uji: (*2*)

Spesies/ Galur	Cara Pemberian	Durasi Pemberian Dosis	Dosis (mg/kg)	Jenis Kelamin dan Jumlah per Kelompok	Temuan yang Bermakna	Nomor Studi

Catatan: *(1)* Semua studi toksisitas lokal harus ringkas.
(2) International Nonproprietary Name (INN).

KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA,

ttd.

PENNY K. LUKITO

LAMPIRAN IX
PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA
NOMOR 24 TAHUN 2017
TENTANG
KRITERIA DAN TATA LAKSANA REGISTRASI OBAT

DOKUMEN KLINIK

Dokumen klinik terdiri dari Tinjauan Studi Klinik *(Clinical Overview)*, Ringkasan Studi Klinik (*Clinical Summary*), Matriks Studi Klinik (*Tabular Listing of All Clinical Studies*), dan Laporan Studi Klinik *(Clinical Study Reports)*.

SUBBAGIAN A: TINJAUAN STUDI KLINIK

Tinjauan Studi Klinik ini dimaksudkan untuk memberikan analisis kritis terhadap data klinik di dokumen teknis umum *(Common Technical Dossier/ CTD)*.

Tinjauan Studi Klinik mengacu pada data Registrasi yang ada dalam Ringkasan Studi Klinik komprehensif, Laporan Studi Klinik individual dan laporan lain yang relevan; terutama menyajikan kesimpulan dan implikasi dari data tersebut, dan tidak sekadar rekapitulasi. Secara khusus, Ringkasan Studi Klinik menyajikan ringkasan faktual yang rinci tentang informasi klinik dalam CTD, dan Tinjauan Studi Klinik memberikan pembahasan ringkas dan interpretasi temuan tersebut bersama dengan informasi relevan lainnya (misalnya, data hewan yang relevan atau isu mutu produk yang mungkin memiliki dampak klinik).

Tinjauan Studi Klinik digunakan oleh Badan Pengawas Obat dan Makanan untuk mengkaji Registrasi pada bagian klinik. Tinjauan ini juga menjadi referensi mengenai temuan klinik keseluruhan bagi penilai yang terlibat dalam mengkaji bagian lain dalam proses Registrasi. Tinjauan Studi Klinik menyajikan kekuatan dan keterbatasan program pengembangan dan hasil studi, menganalisis manfaat dan risiko penggunaan produk Obat dan menjelaskan bagaimana hasil studi menunjang bagian penting informasi Obat.

Untuk mencapai tujuan tersebut Tinjauan Studi Klinik haruslah:

- Menggambarkan dan menjelaskan pendekatan keseluruhan terhadap pengembangan klinik suatu produk Obat, termasuk keputusan desain studi.
- Menilai mutu desain dan kinerja studi, termasuk pernyataan mengenai kepatuhan terhadap Cara Uji Klinik yang Baik.
- Memberikan tinjauan singkat mengenai temuan klinik, termasuk keterbatasan yang penting untuk diketahui (misalnya, kurangnya perbandingan dengan pembanding aktif yang relevan, atau tidak adanya informasi tentang beberapa populasi subjek, tentang *endpoint* yang terkait, atau pada penggunaannya dalam terapi kombinasi).
- Memberikan evaluasi tentang manfaat dan risiko berdasarkan kesimpulan studi klinik yang relevan, termasuk interpretasi bagaimana temuan efikasi dan keamanan menunjang dosis yang diajukan dan indikasi target, serta

evaluasi terhadap bagaimana informasi Obat dan pendekatan lainnya akan mengoptimalkan manfaat dan mengelola risiko.

- Membahas khasiat atau isu keamanan tertentu yang dihadapi dalam pengembangan, dan bagaimana hal-hal ini dievaluasi dan diselesaikan.
- Mengeksplorasi isu yang belum terselesaikan, menjelaskan mengapa isu tersebut tidak harus dianggap sebagai hambatan dalam memberikan persetujuan, dan menjelaskan rencana untuk mengatasinya.
- Menjelaskan dasar dari aspek-aspek penting atau aspek yang tidak biasa dari informasi Obat.

Tinjauan Studi Klinik umumnya merupakan dokumen singkat (sekitar tiga puluh halaman) tetapi panjangnya bergantung pada kompleksitas pengajuan. Disarankan untuk menggunaan grafik dan tabel dalam isi teks untuk meringkas dan memudahkan pemahaman, tetapi bukan berarti materi yang disajikan lengkap di bagian lain diulang pada Tinjauan Studi Klinik. Dianjurkan untuk menyesuaikan isi Tinjauan Studi Klinik dengan keterangan yang lebih rinci dalam Ringkasan Studi Klinik atau Laporan Studi Klinik.

ISI TINJAUAN STUDI KLINIK

1. Alasan Pengembangan Obat.
2. Tinjauan Biofarmasetika.
3. Tinjauan Farmakologi Klinik.
4. Tinjauan Khasiat.
5. Tinjauan Keamanan.
6. Kesimpulan Manfaat dan Risiko.

PEMBAHASAN ISI TINJAUAN STUDI KLINIK

1. Alasan Pengembangan Obat

   Pembahasan tentang alasan pengembangan haruslah:

   - Mengidentifikasi kelas farmakologi Obat.
   - Mendeskripsikan kondisi patofisiologi/klinis tertentu yang dimaksudkan akan diobati, dicegah, atau didiagnosis oleh produk Obat (indikasi target).
   - Merangkum latar belakang ilmiah yang menunjang penelitian produk Obat untuk indikasi yang diteliti.
   - Menjelaskan secara singkat program pengembangan klinik Obat, termasuk studi klinik yang sedang berlangsung maupun yang direncanakan dan dasar keputusan untuk mengajukan Registrasi.
   - Menjelaskan kesesuaian atau ketidaksesuaian terhadap standar terkini terkait desain, pelaksanaan dan analisis studi yang mengacu pada literatur terpublikasi. Diidentifikasi pedoman regulasi (setidaknya dari wilayah dimana Tinjauan Studi Klinik ini diajukan), disertai pembahasan dan penerapannya.

2. Tinjauan Biofarmasetika

   Pada bagian ini dijelaskan analisis kritis terkait bioavailabilitas yang mungkin mempengaruhi khasiat dan/atau keamanan dari formulasi yang akan dipasarkan (misalnya, bentuk sediaan/proporsionalitas kekuatan,

perbedaan antara formulasi yang akan dipasarkan dengan yang digunakan dalam uji klinik, dan pengaruh makanan terhadap paparan).

3. Tinjauan Farmakologi Klinik

Pada bagian ini dijelaskan analisis kritis terhadap farmakokinetik (PK), farmakodinamik (PD), dan data *in vitro* dengan mempertimbangkan semua data yang relevan dan mendukung kesimpulan yang diambil. Bila ada hasil yang tidak lazim dan berpotensi menjadi masalah, harus dijelaskan.

Bagian ini membahas:

- Farmakokinetik (PK), misalnya perbandingan PK pada subjek sehat, subjek sakit, dan populasi khusus; PK terkait dengan faktor intrinsik (misalnya umur, jenis kelamin, ras, gangguan ginjal dan hati) dan terkait dengan faktor ekstrinsik (misalnya merokok, obat-obatan yang dikonsumsi secara bersamaan, diet); kecepatan dan besarnya absorpsi, distribusi, termasuk ikatan protein plasma; jalur metabolik khusus, termasuk pengaruh kemungkinan polimorfisme genetik dan pembentukan metabolit aktif dan tidak aktif, ekskresi, perubahan farmakokinetik yang tergantung pada waktu, isu stereokimia; interaksi PK yang relevan secara klinik dengan Obat atau bahan lainnya.
- Farmakodinamik (PD), misalnya informasi tentang mekanisme kerja, seperti ikatan reseptor; *onset* dan/atau *offset* aksi; hubungan antara pengaruh farmakodinamik yang diharapkan dan tidak diharapkan dengan dosis atau konsentrasi plasma (yaitu, hubungan PK/PD); dukungan PD terhadap dosis yang diajukan dan interval pemberian dosis; interaksi PD yang relevan secara klinik dengan produk Obat atau bahan lainnya, serta respon akibat perbedaan genetik.
- Interpretasi hasil dan implikasi studi imunogenisitas, studi mikrobiologi klinik atau studi PD spesifik untuk golongan Obat sejenis.

4. Tinjauan Khasiat

Pada bagian ini menjelaskan analisis kritis terhadap data klinik yang berkaitan dengan khasiat Obat sesuai target populasi. Analisis ini harus mempertimbangkan semua data yang relevan, baik positif maupun negatif, dan harus menjelaskan mengapa dan bagaimana data tersebut menunjang indikasi yang diajukan. Dilakukan identifikasi terhadap studi yang dianggap relevan untuk evaluasi khasiat, dan harus dicantumkan alasan mengapa studi yang cukup dan berpembanding baik dianggap tidak relevan. Studi yang dihentikan secara prematur harus dicatat dan dipertimbangkan dampaknya.

Hal-hal berikut harus dipertimbangkan:

- Gambaran populasi subjek yang relevan, termasuk gambaran demografis, stadium penyakit, setiap kovariat yang berpotensi penting lainnya, setiap populasi subjek utama yang dikeluarkan dari studi yang penting, serta partisipasi anak dan lanjut usia (ICH E11 dan E7). Harus dilakukan pembahasan terhadap perbedaan antara populasi yang diteliti dengan populasi yang akan menerima Obat setelah dipasarkan.
- Implikasi dari desain studi, termasuk pemilihan subjek, durasi studi, serta pemilihan *endpoint* dan kelompok pembanding. Perhatian khusus harus diberikan untuk *endpoint* dengan hasil studi yang masih terbatas. Penggunaan *surrogate endpoint* harus dijustifikasi. Validasi dari setiap skala yang digunakan harus dibahas.

- Pada studi noninferioritas yang digunakan untuk menunjukkan khasiat, bukti yang diberikan harus menunjang penentuan bahwa penelitian tersebut memiliki sensitivitas dalam penetapan kadar dan dalam memberikan justifikasi pemilihan margin noninferioritas (ICH E10).
- Metode statistik dan masalah yang dapat mempengaruhi interpretasi hasil studi (misalnya, modifikasi penting terhadap desain studi, termasuk penilaian *endpoint* dan analisis yang direncanakan seperti yang ditetapkan dalam protokol asli, dukungan terhadap setiap analisis yang tidak direncanakan, prosedur untuk menangani data yang hilang, dan koreksi untuk beberapa *endpoint*).
- Persamaan dan perbedaan hasil antara berbagai studi, atau dalam berbagai subkelompok subjek yang berbeda di dalam studi, dan pengaruhnya pada interpretasi data khasiat.
- Hubungan yang diamati antara khasiat, dosis dan regimen dosis untuk masing-masing indikasi, baik dalam populasi secara keseluruhan maupun dalam berbagai subkelompok subjek yang berbeda (ICH E4).
- Pada produk yang ditujukan untuk penggunaan jangka panjang, bukti khasiat yang berkaitan dengan pemeliharaan khasiat jangka panjang dan penentuan dosis jangka panjang. Perkembangan toleransi harus dipertimbangkan.
- Data yang menunjukkan bahwa hasil pengobatan dapat ditingkatkan melalui pemantauan konsentrasi dalam plasma (jika ada), dan dokumentasi untuk rentang konsentrasi dalam plasma yang optimal.
- Relevansi klinik dari besarnya efek yang diamati.
- Sifat dan besarnya manfaat klinik yang diharapkan dan justifikasinya jika hasil studi menggunakan *surrogate endpoint.*
- Khasiat pada populasi khusus. Jika khasiat diklaim dengan data klinik yang tidak memadai dalam populasi, harus didukung dengan data ekstrapolasi khasiat dari populasi umum.

5. Tinjauan Keamanan

Pada bagian ini menjelaskan ringkasan analisis kritis tentang data keamanan, mencatat hasil yang dapat menunjang dan memberikan justifikasi informasi Obat yang diajukan.

Analisis kritis terhadap keamanan harus mempertimbangkan:

- Karakteristik efek yang tidak diinginkan dari kelas farmakologi. Pendekatan yang diambil untuk memantau efek yang sama.
- Pendekatan khusus untuk monitoring efek yang tidak diinginkan tertentu (misalnya pada mata, perpanjangan interval QT).
- Toksikologi hewan yang relevan dan informasi mutu produk. Temuan yang mempengaruhi atau dapat mempengaruhi evaluasi keamanan dalam penggunaan klinik.
- Sifat populasi subjek dan luasnya pemaparan, baik untuk Obat uji maupun pembanding. Terbatasnya *database* keamanan, misalnya berkaitan dengan kriteria inklusi/eksklusi dan demografi subjek yang diteliti serta implikasi keterbatasan yang berkaitan dengan prediksi keamanan produk di pasaran.

- Efek yang tidak diinginkan, yang lazim dan tidak serius. Pembahasan harus singkat, fokus pada kejadian dengan frekuensi yang relatif tinggi, kejadian yang lebih sering dibandingkan pada plasebo dan kejadian yang diketahui terjadi pada pembanding aktif atau Obat lain dari kelas terapi yang sama. Kejadian yang lebih atau kurang umum atau bermasalah (mempertimbangkan lamanya dan derajat kejadian yang diamati) dengan Obat uji dibandingkan dengan pembanding aktif harus diberi perhatian khusus.
- Kejadian tidak diinginkan yang serius (KTDS). Bagian ini harus membahas jumlah dan frekuensi kejadian tidak diinginkan (KTD) yang serius, termasuk kematian, dan KTD lain yang bermakna (misalnya, kejadian yang mengarah ke penghentian atau modifikasi dosis), dan harus membahas hasil yang diperoleh Obat uji versus pembanding. Setiap kesimpulan tentang hubungan kausal dengan Obat harus dicantumkan. Hasil temuan uji laboratorium yang merefleksikan kemungkinan efek medis yang serius harus dipertimbangkan.
- Persamaan dan perbedaan hasil antar penelitian, dan pengaruhnya terhadap interpretasi data keamanan.
- Perbedaan angka KTD dalam subkelompok populasi, seperti yang ditentukan oleh faktor demografi, berat badan, penyakit yang terjadi bersamaan, terapi yang dilakukan bersamaan, atau metabolisme polimorfisme.
- Hubungan antara KTD dengan dosis, regimen dosis, dan durasi pengobatan.
- Keamanan jangka panjang (E1a).
- Metode untuk mencegah, mengurangi, atau mengelola KTD.
- Reaksi karena overdosis, potensi untuk ketergantungan, *rebound phenomena* dan penyalahgunaan, atau kurangnya data mengenai masalah ini.
- Pengalaman pemasaran di seluruh dunia. Hal-hal berikut ini harus dibahas secara singkat:
  - Luasnya pengalaman di seluruh dunia,
  - Setiap masalah keamanan baru atau berbeda yang teriidentifikasi,
  - Tindak lanjut regulatori yang berkaitan dengan keamanan.

6. Kesimpulan Manfaat dan Risiko

Pada bagian ini menjelaskan seluruh kesimpulan yang diperoleh pada bagian sebelumnya tentang biofarmasetika, farmakologi klinik, khasiat dan keamanan Obat dan untuk memberikan penilaian keseluruhan dari manfaat dan risiko penggunaannya dalam praktik klinik. Selain itu, implikasi dari setiap penyimpangan dari saran regulatori atau pedoman dan setiap keterbatasan data harus dibahas. Penilaian ini mencakup aspek-aspek penting dari informasi Obat yang diajukan dan juga mempertimbangkan risiko dan manfaat Obat ketika dibandingkan dengan pengobatan alternatif yang tersedia atau tanpa pengobatan pada penyakit dimana tanpa pengobatan merupakan pilihan yang secara medis dapat diterima. Jika ada risiko terhadap individu selain penerima Obat, risiko ini harus dijelaskan (misalnya, risiko munculnya *strain* bakteri yang resisten terhadap Obat dengan meluasnya penggunaan antibiotik untuk penyakit ringan).

Analisis manfaat dan risiko umumnya ringkas, tetapi harus menjelaskan hal-hal penting sebagai berikut:

- Khasiat Obat untuk setiap indikasi yang diajukan.
- Temuan keamanan yang bermakna dan tindakan yang dapat meningkatkan keamanan.
- Hubungan dosis-respon dan dosis-toksisitas, rentang dosis optimal dan regimen dosis.
- Khasiat dan keamanan pada subpopulasi, misalnya yang ditentukan oleh umur, jenis kelamin, kelompok etnis, fungsi organ, keparahan penyakit dan polimorfisme genetik.
- Data pada anak dalam kelompok usia yang berbeda, jika ada, dan rencana program pengembangan pada anak.
- Risiko terhadap subjek jika terjadi interaksi, baik yang telah dikenal maupun berpotensi terjadi, termasuk interaksi Obat-Obat maupun makanan-Obat, dan rekomendasi penggunaan Obat.
- Pengaruh potensial dari Obat yang mungkin mempengaruhi kemampuan untuk mengemudi atau mengoperasikan alat berat.

Contoh isu dan masalah yang mungkin memerlukan pembahasan lebih rinci tentang manfaat dan risiko mencakup:

- Obat diajukan untuk pengobatan penyakit nonfatal tetapi berpotensi menyebabkan keracunan serius, seperti tanda karsinogenisitas, teratogenisitas, potensi proaritmia (pengaruh pada interval QT), atau tanda ke arah hepatotoksisitas.
- Penggunaan yang diajukan didasarkan atas *surrogate endpoint* dan ada toksisitas penting yang terdokumentasi dengan baik.
- Penggunaan Obat yang aman dan/atau efektif sulit dipilih atau membutuhkan pendekatan manajemen yang memerlukan keahlian khusus dokter atau edukasi subjek.

SUBBAGIAN B: RINGKASAN STUDI KLINIK

Dokumen pada bagian ini tidak diperlukan untuk Registrasi Variasi Minor.

Ringkasan Studi Klinik dimaksudkan untuk menyajikan ringkasan rinci dari informasi klinik pada CTD. Termasuk di dalamnya informasi yang ada pada Laporan Studi Klinik, informasi dari metaanalisis atau analisis antarstudi yang laporan lengkapnya telah dimasukkan ke dalam Laporan Studi Klinik dan data pascapemasaran untuk Obat yang telah dipasarkan di negara lain.

Perbandingan dan analisis hasil antarstudi yang dijelaskan di dokumen ini difokuskan pada observasi faktual. Sebaliknya, dokumen Tinjauan Studi Klinik CTD menyajikan analisis kritis dari program studi klinik dan hasil-hasilnya, termasuk pembahasan dan interpretasi temuan klinik.

Panjang Ringkasan Studi Klinik sangat bervariasi tergantung pada informasi yang disampaikan, tetapi diharapkan Ringkasan Studi Klinik antara 50 – 400 halaman (tidak termasuk tabel-tabel yang dilampirkan).

ISI RINGKASAN STUDI KLINIK

1. RINGKASAN STUDI BIOFARMASETIKA DAN METODE ANALISIS TERKAIT
   1.1 Latar belakang dan tinjauan.
   1.2 Ringkasan hasil studi individual.
   1.3 Perbandingan dan analisis hasil dari berbagai studi.
   Lampiran 1.

2. RINGKASAN STUDI FARMAKOLOGI KLINIK
   2.1 Latar belakang dan tinjauan.
   2.2 Ringkasan hasil dari studi individual.
   2.3 Perbandingan dan analisis hasil dari berbagai studi.
   2.4 Studi khusus.
   Contoh 1: Immunogenisitas.
   Contoh 2: Mikrobiologi klinik.
   Lampiran 2.

3. RINGKASAN KHASIAT KLINIK
   3.1 Latar belakang dan tinjauan khasiat klinik.
   3.2 Ringkasan hasil dari studi individual.
   3.3 Perbandingan dan analisis hasil dari berbagai studi.
   3.4 Analisis informasi klinik yang relevan dengan pemberian dosis yang direkomendasikan.
   3.5 Khasiat yang persisten dan/atau efek toleransi.
   Lampiran 3.

4. RINGKASAN KEAMANAN KLINIK
   4.1 Paparan terhadap Obat.
   4.2 Efek yang tidak diinginkan.
   4.3 Evaluasi laboratorium klinik.
   4.4 Tanda vital, temuan fisik dan observasi lain yang berhubungan dengan keamanan.
   4.5 Keamanan pada kelompok dan situasi khusus.
   4.6 Data pascapemasaran.
   Lampiran 4.

5. SINOPSIS STUDI INDIVIDUAL

PEDOMAN RINCI RINGKASAN STUDI KLINIK

1. RINGKASAN STUDI BIOFARMASETIKA DAN METODE ANALISIS TERKAIT

   1.1 Latar Belakang dan Tinjauan

   Bagian ini menjelaskan tinjauan menyeluruh tentang proses pengembangan formulasi, performa bentuk sediaan secara *in vitro* dan *in vivo*, pendekatan umum dan penggunaan rasional dalam pengembangan profil bioavailabilitas (BA), bioekivalensi (BE), dan disolusi *in vitro*.

   Pedoman dan literatur yang menjadi rujukan dalam merencanakan dan melakukan studi harus disebut. Subbagian ini juga harus menyajikan tinjauan metode analisis yang digunakan, dengan penekanan pada karakteristik kinerja validasi penetapan kadar

(misalnya rentang linearitas, sensitivitas, spesifisitas), dan kontrol kualitas (misalnya keakuratan dan presisi). Subbagian ini sebaiknya tidak menyajikan informasi rinci tentang studi individual.

1.2 Ringkasan Hasil Studi Individual

Disajikan matriks yang memuat seluruh studi biofarmasetika bersama dengan deskripsi naratif dari hasil studi individual yang memberikan data *in vitro* dan *in vivo* yang penting dan informasi yang relevan dengan BA dan BE (lihat *Lampiran* 1 pada Bagian IV ini). Deskripsi naratif harus singkat, dan menjelaskan desain dan hasil yang kritis. Studi yang sama dapat dideskripsikan bersamaan dengan menekankan hasil studi individual dan perbedaan di antara studi tersebut. Narasi ini dapat diringkas dari sinopsis ICH E3. Rujukan atau *link* elektronik laporan lengkap setiap studi harus dimasukkan di dalam narasi.

1.3 Perbandingan dan Analisis Hasil dari Antarstudi

Bagian ini menjelaskan ringkasan dari seluruh studi disolusi *in vitro*, BA, dan studi BA komparatif terhadap Zat Aktif atau Obat, dengan perhatian khusus pada perbedaan hasil antarstudi. Tinjauan ini merangkum temuan dalam teks dan tabel (lihat *Lampiran* 1 pada Bagian IV ini) dan harus mempertimbangkan hal-hal berikut:

- Pengaruh formulasi dan perubahan dalam proses pembuatan Obat terhadap disolusi *in vitro* dan BA, serta kesimpulan tentang BE. Jika Obat yang mengandung zat yang kompleks (misalnya protein) mengalami perubahan formulasi dan proses pembuatan, dapat dilakukan studi farmakokinetik (PK) yang membandingkan Obat sebelum dan sesudah perubahan untuk memastikan karakteristik PK tidak berubah karena perubahan tersebut. Walaupun studi ini dianggap sebagai studi BE, umumnya tidak hanya menilai pelepasan Zat Aktif dari Obat, namun studi tersebut tetap harus dilaporkan. Perlu dicatat juga bahwa penelitian PK saja tidak cukup untuk menjamin kemiripan di antara Obat-obat tersebut. Pada kondisi tertentu, studi farmakodinamik (PD), studi klinik atau data antigenisitas mungkin diperlukan. Hasil studi tersebut (jika diperlukan) harus dicantumkan pada bagian dokumen yang tepat.
- Bukti tentang pengaruh makanan terhadap BA dan kesimpulan BE yang terkait dengan jenis makanan atau waktu makan (jika sesuai).
- Bukti tentang korelasi antara disolusi *in vitro* dengan BA, termasuk pengaruh pH terhadap disolusi, dan kesimpulan yang berhubungan dengan spesifikasi disolusi.
- Bioavailabilitas komparatif, termasuk kesimpulan BE untuk berbagai kekuatan bentuk sediaan.
- Bioavailabilitas komparatif antara formulasi studi klinik (untuk studi klinik yang memberikan bukti khasiat) dengan formulasi yang akan dipasarkan.
- Sumber dan besarnya variabilitas intra dan antarsubjek yang diamati untuk masing-masing formulasi dalam studi BA komparatif.

Lampiran 1.

Tabel dan gambar diletakkan di dalam teks pada Subbagian yang sesuai sehingga dokumen mudah dibaca. Tabel-tabel yang panjang dapat disajikan pada lampiran di akhir Subbagian.

Tabel 1.1 dan 1.2 merupakan contoh format tabel untuk memberikan informasi dan hasil yang terkait dengan studi bioavailabilitas dan disolusi *in vitro*. Contoh tersebut memberikan hasil dan mengidentifikasi jenis dan desain studi. Tabel juga mencantumkan hasil studi BE dan memasukkan rasio *mean* (uji/rujukan) untuk C_{max} dan AUC serta *confidence interval* 90%, atau metrik terkini yang direkomendasikan untuk penilaian BE.

Tabel ini tidak dimaksudkan sebagai format baku, tetapi hanya untuk memberi ilustrasi tentang jenis informasi yang harus dipertimbangkan oleh Pendaftar dalam mendesain tabel untuk studi biofarmasetika. Pendaftar juga harus memutuskan apakah informasi dan hasil studi tersebut paling baik disajikan dalam bentuk tabel, teks, atau gambar. Jika penyajian hasil paling baik dalam bentuk teks dan gambar, maka tabel mungkin hanya digunakan untuk membuat daftar studi yang dilakukan.

Lihat Matriks: Format Baku Matriks Ringkasan Studi Klinik

2. RINGKASAN STUDI FARMAKOLOGI KLINIK

2.1 Latar Belakang dan Tinjauan

Pada bagian ini menjelaskan gambaran keseluruhan tentang studi farmakologi klinik. Studi ini termasuk studi klinik yang dilakukan untuk mengevaluasi farmakokinetika (PK) manusia, farmakodinamika (PD), dan studi *in vitro* yang dilakukan dengan sel manusia, jaringan, atau materi terkait proses PK (biomaterial manusia). Untuk produk vaksin, harus menjelaskan data respon imun yang mendukung pemilihan dosis, jadwal pemberian dosis, dan formulasi produk akhir. Jika sesuai, data relevan yang dirangkum pada Bagian 1, 3 dan 4 Subbagian C juga dapat dirujuk agar mendapatkan gambaran yang komprehensif tentang pendekatan dan alasan pengembangan farmakokinetika, farmakodinamika, PK/PD dan biomaterial manusia. Bab ini sebaiknya tidak memasukkan informasi studi individual rinci.

Bab ini dimulai dengan tinjauan singkat tentang studi biomaterial manusia yang dilakukan dan bertujuan untuk membantu interpretasi data PK dan PD. Studi tentang permeabilitas (misalnya absorpsi usus, lintasan sawar darah otak), ikatan protein, metabolisme hepatik, dan interaksi Obat yang berbasis metabolik sangat relevan, dan harus diikuti dengan tinjauan singkat tentang studi klinik yang dilakukan untuk mengkarakterisasi PK dan PD dari Obat, termasuk hubungan PK/PD pada subjek sehat dan subjek sakit. Aspek penting dari desain studi dan data analisis harus dicatat misalnya pemilihan dosis tunggal atau berulang yang digunakan, populasi penelitian, pemilihan *endpoint* PD, dan apakah pendekatan tradisional atau pendekatan populasi yang digunakan untuk mengumpulkan dan menganalisis data dalam menilai PK atau PD.

2.2 Ringkasan Hasil Studi Individual

Disajikan matriks yang memuat seluruh studi farmakologi klinik bersama dengan deskripsi naratif dari hasil studi individual yang memberikan data *in vitro* dan *in vivo* yang penting dan informasi yang relevan dengan PK, PD dan hubungan PK/PD (lihat *Lampiran* 2 pada Bagian IV ini). Deskripsi naratif harus singkat dan menjelaskan desain dan hasil yang kritis. Studi yang sama dapat dideskripsikan bersamaan dengan menekankan hasil studi individual dan perbedaan di antara studi tersebut. Rujukan atau *link* elektronik laporan lengkap setiap studi harus dimasukkan di dalam narasi.

Ringkasan studi respon kadar (PK/PD) atau respon dosis dengan *endpoint* farmakodinamik dicantumkan pada bagian ini. Tetapi dalam beberapa kasus, jika studi respon dosis PD terkontrol baik atau respon kadar (PK/PD) memberikan bukti khasiat atau keamanan, maka studi tersebut harus dicantumkan pada Bagian 3 atau 4 dan cukup dirujuk pada bagian ini.

2.3 Perbandingan dan Analisis Hasil dari Berbagai Studi

Pada bagian ini menggunakan hasil dari seluruh studi biomaterial manusia dan studi PK, PD dan PK/PD untuk menggambarkan karakteristik PK, PD dan hubungan PK/PD Obat. Pembahasan mencakup hasil yang terkait dengan variabilitas intra dan antarindividual yang mempengaruhi hubungan farmakokinetik.

Bagian ini (menggunakan teks dan tabel) dengan mencantumkan seluruh data dari berbagai studi yang berhubungan dengan hal-hal berikut:

- Studi metabolisme Obat dan interaksi Obat-Obat secara *in vitro* serta studi implikasi kliniknya.
- Studi PK pada manusia, termasuk estimasi terbaik dari parameter standar dan sumber variabilitas. Fokus pada bukti yang mendukung dosis dan individualisasi dosis pada target populasi dan populasi khusus misalnya anak atau lanjut usia, atau subjek dengan gangguan fungsi hati atau ginjal.
- Perbandingan antara PK dosis tunggal dan dosis berulang.
- Analisis PK populasi, seperti hasil berdasarkan sampel yang jarang antarstudi yang menerangkan variasi antarindividual dalam PK atau PD Zat Aktif Obat.
- Hubungan respon-dosis atau respon-kadar. Pembahasan ini harus fokus pada bukti yang mendukung pemilihan dosis dan interval dosis yang diteliti pada studi klinik yang penting. Selain itu, informasi yang mendukung petunjuk dosis pada Label yang diajukan harus dibahas pada Bagian 3.4.
- Inkonsistensi utama pada *database* biomaterial manusia, PK atau PD.

2.4 Studi Khusus

Pada bagian ini mencakup studi dengan data khusus yang relevan terhadap Obat tertentu. Untuk studi imunogenisitas dan studi lain yang datanya mungkin berkorelasi dengan studi PK, PD, keamanan,

dan/atau data khasiat, penjelasan tentang korelasi tersebut harus dirangkum. Pengaruh yang berpotensi pada PK, PD, keamanan dan/atau khasiat harus dipertimbangkan di bagian lain yang sesuai dari Ringkasan Studi Klinik, dengan rujukan silang ke bagian ini. Studi klinik yang membahas isu keamanan khusus sebaiknya tidak dilaporkan di sini, tetapi dilaporkan di Bagian 4.

Contoh 1: Imunogenisitas

Untuk produk protein dan produk lain yang reaksi imunologis khususnya telah diukur, data mengenai imunogenisitas dirangkum pada bagian ini. Untuk vaksin atau produk lain yang dimaksudkan untuk meningkatkan reaksi imun tertentu, data imunogenisitas dijelaskan di Subbagian Khasiat, Ringkasan Khasiat Klinik. Metode penetapan kadar yang digunakan dijelaskan dengan singkat dan informasi tentang kinerjanya dirangkum (misalnya sensitivitas, spesifisitas, reliabilitas, dan validitas).

Data tentang insidensi, titer, waktu onset dan durasi respon antibodi dirangkum untuk masing-masing jenis penetapan kadar antibodi yang digunakan (misalnya, IgG dengan ELISA, netralisasi). Hubungan antara pembentukan antibodi terhadap penyakit, pengobatan yang dilakukan bersamaan, dosis, durasi, regimen, dan formulasi, hendaknya dijelaskan dan dirangkum. Obat yang dimaksudkan untuk pengobatan kronis dan berkelanjutan, data tentang dampak terputusnya pengobatan terhadap antigenisitas harus dianalisis dan dirangkum.

Penting untuk merangkum analisis dari korelasi imunogenisitas yang berpotensi relevan secara klinik, misalnya untuk menentukan sejauh mana antibodi jenis tertentu atau dalam titer tertentu berkorelasi dengan perubahan pada PK, perubahan pada PD, hilangnya khasiat, hilangnya profil KTD, atau perkembangan KTD. Perhatian khusus harus diberikan pada kejadian yang mungkin dimediasi secara imunologis (misalnya *serum sickness*) dan kejadian yang mungkin diakibatkan oleh ikatan substansi endogen yang bereaksi silang oleh antibodi kepada Obat yang diberikan.

Contoh 2: Mikrobiologi Klinik

Untuk antimikroba atau antivirus, studi *in vitro* yang menjelaskan karakteristik spektrum aktivitas merupakan bagian penting dari program studi yang relevan terhadap khasiat klinik. Studi khasiat klinik yang mencakup karakterisasi paparan isolat klinik sebagai bagian dari penentuan khasiat dimasukkan ke dalam Bagian 3. Tetapi studi yang mengevaluasi temuan seperti pola paparan *in vitro* dari *strain* bakteri yang berasal dari negara lain dapat dijelaskan di sini.

Lampiran 2.

Tabel dan gambar harus dimasukkan ke dalam teks pada bagian yang sesuai jika hal itu memudahkan pembacaan dokumen. Tabel yang panjang disajikan pada lampiran di bagian akhir.

Tabel 2.1 disajikan sebagai contoh format berbentuk tabel untuk melaporkan informasi dan hasil yang berhubungan dengan studi farmakokinetik interaksi Obat-Obat. Tabel sejenis dapat disiapkan untuk studi PK/PD, studi respon-dosis, studi tentang pengaruh terhadap biomaterial manusia, dan studi PK populasi. Tabel ini tidak dimaksudkan sebagai format baku, tetapi hanya untuk memberi ilustrasi jenis informasi yang harus dipertimbangkan oleh sponsor dalam mendesain tabel mereka sendiri. Pendaftar juga harus memutuskan apakah informasi dan hasil studi farmakologi klinik paling baik disajikan dalam tabel, teks, atau gambar untuk memperjelas. Jika hasil paling baik disajikan dalam bentuk teks dan gambar, tabel mungkin hanya mencantumkan studi yang dilakukan.

Dalam mendesain tabel, untuk berbagai jenis studi farmakologi klinik seperti yang ditulis dalam daftar di bawah, Pendaftar harus mempertimbangkan untuk memasukkan informasi berikut ini. Contoh ini hanya sebagai ilustrasi, sponsor harus memutuskan informasi mana yang perlu disajikan.

- Studi metabolisme yang menggunakan biomaterial manusia: biomaterial yang digunakan (misalnya mikrosom, hepatosit), Obat *probe*, alur enzimatik dan % kontribusi serta parameter kinetik yang relevan (misalnya, V_{max}, K_m).
- Studi *in vitro* tentang interaksi Obat-Obat menggunakan biomaterial manusia: harus dijelaskan studi tentang Obat lain yang menghambat Obat Baru, metabolit yang dihambat, jalur enzimatik yang terpengaruh, rentang kadar inhibitor yang digunakan, nilai-nilai IC_{50} dan K_i, dan mekanisme inhibisi yang diajukan. Untuk studi tentang Obat Baru yang menghambat Obat lain, Obat dan metabolit yang dihambat harus djelaskan, bersama dengan informasi yang disebutkan di atas.
- Studi PK populasi: kovariat yang diteliti, jumlah dan jenis subjek, ringkasan parameter statistik dan estimasi akhir dari *mean* (± simpangan baku) untuk parameter PK.

Lihat Matriks: Format Baku Matriks Ringkasan Studi Klinik

3. RINGKASAN KHASIAT KLINIK

Jika suatu Obat efektif untuk lebih dari satu indikasi, maka harus disajikan terpisah untuk masing-masing indikasi pada Bagian 3, meskipun indikasi yang berhubungan erat dapat disajikan bersama-sama. Jika lebih dari satu Bagian 3 yang diajukan, maka Bagian tersebut diberi tanda 3A, 3B, 3C dan seterusnya.

3.1 Latar Belakang dan Tinjauan Khasiat Klinik

Bagian ini menggambarkan studi berpembanding dan studi lain yang berhubungan dengan indikasi yang diajukan. Hasil studi yang berhubungan dengan keamanan dibahas pada Bagian 4.

Bagian ini dimulai dengan tinjauan ringkas tentang desain studi berpembanding yang dilakukan untuk mengevaluasi khasiat. Studi tersebut mencakup respon-dosis, perbandingan khasiat, khasiat jangka panjang dan studi khasiat pada subset populasi. Desain studi harus dijelaskan, seperti randomisasi, pembutaan (*blinding*), pilihan perlakuan pembanding, pilihan populasi subjek, gambaran

desain yang tidak biasa seperti *crossover*, atau *randomised withdrawal design*, penggunaan periode *run-in*, metode pengayaan lain, durasi penelitian, dan rencana analisis hasil studi. Meskipun bagian ini difokuskan pada investigasi klinik, data nonklinik dan data farmakologi klinik dapat juga dirujuk seperlunya untuk memberikan ringkasan komprehensif tentang pengalaman pada manusia yang terkait dengan khasiat. Bagian ini sebaiknya tidak memasukkan informasi studi individu secara rinci.

3.2 Ringkasan Hasil Studi Individual

Disajikan matriks yang memuat seluruh studi terkait khasiat Obat bersama dengan deskripsi naratif dari studi yang penting (lihat *Lampiran* 3 pada Bagian IV ini). Deskripsi naratif harus singkat, dan menjelaskan desain dan hasil yang kritis. Studi yang sama dapat dideskripsikan bersamaan dengan mencatat hasil studi individual dan perbedaan di antara studi tersebut. Untuk studi yang juga berkontribusi pada analisis keamanan, narasi studi harus mencakup informasi tentang paparan Obat uji atau pembanding terhadap subjek studi, dan bagaimana data keamanan dikumpulkan. Narasi ini dapat diringkas dari sinopsis ICH E3. Rujukan atau *link* elektronik laporan lengkap setiap studi harus dimasukkan di dalam narasi.

3.3 Perbandingan dan Analisis Hasil dari Berbagai Studi

Teks, gambar, dan tabel digunakan sesuai kebutuhan (lihat *Lampiran* 3 pada Bagian IV), Bagian 3.3 merangkum semua data karakterisasi khasiat Obat, termasuk analisis seluruh data. Inkonsistensi utama pada data terkait khasiat disebutkan dan bagian yang memerlukan eksplorasi mendalam diidentifikasi.

Bagian ini menjelaskan dua jenis analisis: perbandingan hasil studi individual, dan analisis data yang digabung dari berbagai studi. Rincian analisis yang lebih lengkap disajikan di bagian yang terpisah, yaitu diletakkan di Laporan Studi Klinik.

Bagian ini disesuaikan dengan bukti penting pada Bagian 2, seperti data yang mendukung bagian dosis dan cara penggunaan Obat pada Label. Data ini termasuk dosis dan interval dosis yang direkomendasikan, bukti yang terkait dengan individualisasi dosis, dan perlunya modifikasi dosis untuk kelompok khusus (misalnya subjek anak atau lanjut usia, atau subjek dengan gangguan hati atau ginjal), dan data yang relevan dengan hubungan respon-dosis atau respon-kadar (PK/PD).

3.3.1 Populasi Studi

Karakteristik demografi dan *baseline* subjek dari berbagai studi khasiat dijelaskan. Hal-hal berikut ini harus dijelaskan:

- Karakteristik penyakit (misalnya keparahan, durasi) dan pengobatan sebelumnya pada subjek studi, dan kriteria inklusi/eksklusi studi.
- Perbedaan pada karakteristik *baseline* dari populasi studi atau kelompok studi yang berbeda.

- Perbedaan antara populasi yang dimasukkan dalam analisis khasiat dan populasi subjek keseluruhan yang diharapkan akan menerima Obat tersebut jika kelak dipasarkan sebaiknya juga dicatat.
- Penilaian jumlah subjek yang *drop out* dari studi, waktu *withdrawal* (hari atau kunjungan studi tertentu selama masa studi atau *follow up*), serta alasan untuk tidak melanjutkan.

Penyajian dalam bentuk tabel yang menggabungkan dan membandingkan populasi dari berbagai studi akan bermanfaat.

3.3.2 Perbandingan Hasil Khasiat dari Seluruh Studi

Hasil seluruh studi yang didesain untuk mengevaluasi khasiat Obat harus dirangkum dan dibandingkan, termasuk studi yang tidak dapat disimpulkan atau memberikan hasil yang negatif. Perbedaan penting dalam desain studi seperti *endpoint*, kelompok pembanding, durasi studi, metode statistik populasi subjek, dan dosis harus diidentifikasi.

Perbandingan hasil dari berbagai studi difokuskan kepada *endpoint* primer yang dijelaskan sebelumnya. Akan tetapi jika *endpoint* primer melibatkan variabel atau titik waktu yang berbeda dalam studi khasiat yang berbeda, maka diperlukan penjelasan mengenai perbandingan antarstudi tentang elemen data penting yang didapatkan dari seluruh studi. Jika hasil dianggap penting seiring dengan waktu, maka hasil studi dapat ditampilkan dalam gambar yang menggambarkan perubahan seiring waktu pada setiap studi.

Derajat kepercayaan (*Confidence intervals*/CI) untuk efek pengobatan diberikan untuk membantu interpretasi. Jika plasebo dan Obat uji menunjukkan perbedaan perubahan dari *baseline*, maka nilai *baseline* dan besarnya pengaruh pada kelompok perlakuan, termasuk plasebo dan pembanding aktif (jika digunakan), harus dibuat tabel atau teks yang menjelaskan suatu gambar. Jika tujuan pengujian pembanding aktif adalah untuk menunjukkan ekivalensi atau noninferioritas, maka perbedaan rasio hasil antara perlakuan tersebut harus diberikan dalam derajat kepercayaan (*Confidence intervals*/CI). Hasil harus dievaluasi menggunakan kriteria yang didefinisikan sebelumnya untuk menentukan ekivalensi atau noninferioritas. Alasan untuk kriteria dan dukungan untuk menentukan bahwa studi tersebut mempunyai sensitivitas *assay* harus dijelaskan (lihat ICH E10).

Perbedaan hasil yang penting di antara studi yang mempunyai desain serupa harus dibahas. Perbandingan faktor antarstudi yang mungkin berkontribusi terhadap perbedaan hasil berbagai studi dijelaskan.

Jika dilakukan metaanalisis terhadap studi klinik, harus jelas apakah analisis ini dilakukan menurut protokol yang ditentukan sebelumnya atau merupakan *post hoc exercise*.

Perbedaan dalam desain studi atau populasi, atau dalam pengukuran khasiat antara berbagai studi harus dijelaskan agar dapat dilakukan penilaian terhadap relevansi dan validitas hasil dan kesimpulan (lihat ICH E9). Penjelasan yang rinci tentang metodologi dan hasil metaanalisis harus dijelaskan dalam laporan yang terpisah (Laporan Studi Klinik).

3.3.3 Perbandingan Hasil dalam Subpopulasi

Hasil studi individual atau tinjauan analisis khasiat dalam populasi khusus dirangkum pada bagian ini. Tujuan perbandingan ini adalah untuk menunjukkan apakah pengaruh perlakuan yang diklaim teramati secara konsisten pada semua subpopulasi yang relevan, terutama mereka yang mempunyai alasan khusus untuk diperhatikan. Perbandingan ini mungkin saja menyoroti variasi khasiat yang besar yang kemudian memerlukan investigasi dan pembahasan lebih dalam. Namun demikian, analisis semacam ini terbatas (ICH E9), dan penting untuk dicatat bahwa tujuan analisis tersebut bukan untuk memberikan dasar untuk klaim tertentu ataupun untuk memperbaiki bukti khasiat pada situasi di mana hasil keseluruhan tidak sesuai dengan yang diharapkan.

Mengingat terbatasnya ukuran sampel dalam studi individual, analisis terhadap berbagai studi harus dilakukan untuk mengevaluasi pengaruh faktor demografi (umur, jenis kelamin, dan ras) terhadap khasiat. Faktor khusus dapat muncul dari hal yang umum (misalnya, golongan lanjut usia) atau dari isu khusus yang berhubungan dengan farmakologi Obat atau yang muncul pada awal pengembangan Obat. Khasiat pada populasi anak harus dianalisis secara rutin pada pengajuan indikasi untuk anak. Jika analisis data terlalu luas, dilakukan analisis khasiat yang rinci dan diletakkan pada Laporan Studi Klinik dengan hasil analisisnya dijelaskan pada bagian ini.

3.4 Analisis Informasi Klinik yang Relevan terhadap Rekomendasi Pemberian Dosis

Bagian ini menjelaskan ringkasan terpadu dan analisis dari seluruh data yang terkait dengan hubungan efektivitas respon-dosis atau respon kadar dalam darah (termasuk hubungan dosis-kadar dalam darah), sehingga memberi kontribusi pada pemilihan dosis dan pilihan interval dosis. Data yang relevan dari studi nonklinik dapat dirujuk, dan data yang relevan dari studi farmakokinetik, studi farmakologi klinik lain, serta studi klinik dengan ataupun tanpa pembanding dirangkum untuk menggambarkan hubungan respon-dosis atau respon kadar dalam darah. Untuk studi farmakokinetik

dan farmakodinamik yang datanya dirangkum pada Bagian 2.2, akan lebih tepat menggunakan data tersebut dalam ringkasan ini disesuaikan dengan ringkasan pada Bagian 2.2, tanpa pengulangan.

Walaupun interpretasi tentang bagaimana data ini mendukung rekomendasi pemberian dosis dicantumkan dalam dokumen Tinjauan Studi Klinik, hasil studi individual dan analisis lintas studi yang akan digunakan untuk mendukung rekomendasi pemberian dosis (termasuk pemberian dosis awal dan maksimal yang direkomendasikan, metode titrasi dosis, dan petunjuk lain mengenai individualisasi dosis) harus dirangkum di sini. Setiap penyimpangan yang teridentifikasi dari hubungan respon-dosis atau respon kadar dalam darah karena nonlinieritas farmakokinetik, efek yang tertunda, toleransi, induksi enzim, dan lain-lain harus dijelaskan.

Harus dijelaskan setiap perbedaan dalam hubungan respon-dosis yang dihasilkan dari usia subjek, jenis kelamin, ras, penyakit, atau faktor lain. Setiap perbedaan dalam respon farmakokinetik atau farmakodinamik juga dibahas dan disesuaikan dengan Bagian 2. Bagaimana perbedaan tersebut terlihat, bahkan jika tidak ditemukan perbedaan harus dijelaskan (misalnya, penelitian khusus pada subpopulasi, analisis hasil khasiat oleh subkelompok, atau penentuan kadar Obat uji).

3.5. Persistensi Khasiat dan/atau Pengaruh Toleransi

Informasi persistensi atau khasiat dari waktu ke waktu harus dirangkum. Jumlah subjek yang data khasiat jangka panjangnya tersedia, dan lamanya pemaparan, harus dijelaskan. Setiap bukti toleransi (hilangnya pengaruh terapi seiring dengan waktu) harus dicatat. Pemeriksaan terhadap hubungan antara perubahan dosis seiring waktu dan khasiat jangka panjang mungkin akan berguna.

Studi berpembanding yang didesain untuk mengumpulkan data khasiat jangka panjang harus menjadi fokus utama, dan studi tersebut harus jelas dibedakan dari studi lain yang lebih longgar seperti *open extension studies*. Perbedaan ini juga berlaku untuk studi yang khusus didesain untuk mengevaluasi pengaruh toleransi dan *withdrawal*. Data tentang *withdrawal* atau *rebound effect* yang terkait dengan keamanan produk disajikan pada bagian keamanan (lihat Bagian 4).

Dalam uji khasiat jangka panjang, pengaruh penghentian terapi di awal atau peralihan ke terapi lainnya terhadap penilaian hasil harus dipertimbangkan. Isu ini juga berguna untuk uji jangka pendek dan harus disebutkan ketika membahas hasil studi, jika diperlukan.

Lampiran 3

Tabel dan gambar harus dimasukkan ke dalam teks pada Bab yang sesuai jika hal itu dapat memudahkan pembacaan dokumen. Tabel yang panjang dapat disajikan pada lampiran di akhir bab.

Tabel harus mencantumkan semua studi yang berkaitan dengan evaluasi khasiat (termasuk studi yang dihentikan atau belum

selesai, studi yang gagal menunjukkan efektivitas karena suatu alasan, studi yang tersedia hanya sebagai publikasi, studi yang dilaporkan dalam laporan lengkap (ICH E3), dan studi yang dijelaskan dalam laporan singkat), dan harus menyajikan hasil paling penting dari studi tersebut. Perlu diketahui bahwa analisis interim yang tidak direncanakan pada studi yang sedang berjalan biasanya tidak diperlukan. Bila Bagian 3 lebih dari satu untuk sebuah pendaftaran Obat dengan lebih dari satu indikasi, biasanya setiap bagian memiliki lampiran sendiri dengan tabel.

Tabel ilustrasi untuk Obat antihipertensi disajikan sebagai contoh, tetapi contoh ini tidak selalu relevan untuk setiap pendaftaran Obat. Secara umum, pendaftaran Obat akan memerlukan tabel dan/atau gambar yang dikembangkan secara khusus untuk kelas Obat tertentu dan studi yang dilakukan.

Tabel 3.1 Gambaran studi khasiat klinik dan keamanan
Tabel 3.2 Hasil studi khasiat
Lihat Matriks: Format Baku Matriks Ringkasan Studi Klinik

4. RINGKASAN KEAMANAN KLINIK

Bagian ini menjelaskan ringkasan data yang relevan dengan keamanan dalam populasi subjek yang dituju, dengan menggabungkan semua hasil laporan studi klinik individu serta laporan lain yang relevan, misalnya analisis terpadu data keamanan yang secara rutin diserahkan ke beberapa negara.

Tampilan data yang terkait keamanan dapat dipertimbangkan pada tiga tingkatan (ICH E3):

- Luasnya paparan (dosis, durasi, jumlah subjek, jenis subjek) harus diteliti untuk menentukan sejauh mana keamanan dapat dinilai dari *database*.
- Kejadian umum yang tidak diinginkan dan perubahan dalam uji laboratorium diidentifikasi, diklasifikasikan, dan dirangkum.
- KTDS (didefinisikan dalam ICH E2A) dan KTD lain yang bermakna (didefinisikan dalam ICH E3) harus diidentifikasi dan dirangkum. Frekuensi kejadian tersebut harus diperiksa selama studi berlangsung, terutama untuk Obat yang digunakan secara kronis.

Profil keamanan Obat yang dijelaskan berdasarkan analisis seluruh data keamanan klinik harus diuraikan secara rinci, jelas dan objektif, dengan menggunakan tabel dan gambar.

4.1. Paparan terhadap Obat

4.1.1 Rencana Evaluasi Keamanan Menyeluruh dan Narasi Studi Keamanan

Rencana evaluasi keamanan menyeluruh harus dijelaskan singkat, termasuk pertimbangan khusus dan pengamatan data nonklinik, pengaruh kelas farmakologi yang relevan, dan sumber data keamanan (uji berpembanding, studi terbuka, dan lain-lain). Sebuah matriks seluruh studi klinik yang menyajikan pengelompokan data keamanan

harus disertakan (lihat *lampiran 4* di Bagian IV ini). Selain studi yang mengevaluasi khasiat dan keamanan, dan studi tanpa pembanding yang menghasilkan informasi keamanan, bagian ini juga mencakup studi yang mempertimbangkan masalah keamanan khusus, contohnya studi untuk membandingkan angka KTD untuk dua terapi, untuk menilai keamanan dalam subset demografi tertentu, untuk mengevaluasi fenomena *withdrawal* atau *rebound*, atau untuk mengevaluasi KTD tertentu (misalnya sedasi, fungsi seksual, pengaruh terhadap kemampuan mengemudi, tidak adanya efek kelas yang tidak diinginkan). Studi tentang indikasi yang belum diajukan dan studi yang sedang berlangsung saat ini juga disertakan jika memberikan kontribusi terhadap analisis keamanan.

Deskripsi naratif studi tersebut harus disajikan, kecuali untuk deskripsi naratif studi yang memberikan kontribusi data khasiat maupun keamanan dimasukkan dalam Bagian 3.2 dan disesuaikan pada bagian ini. Narasi harus cukup rinci untuk memudahkan penilai dalam memahami paparan subjek studi terhadap Obat uji atau pembanding, dan memahami bagaimana data keamanan dikumpulkan (termasuk metode yang digunakan dan sejauh mana pengawasan terhadap keamanan subjek yang terlibat dalam studi individual). Jika beberapa studi tidak dianalisis secara terpisah melainkan dikelompokkan untuk analisis keamanan, maka hal itu harus dicatat, dan deskripsi naratif tunggal dapat disajikan.

4.1.2 Tingkat Keterpaparan Menyeluruh

Tabel (lihat contoh dalam *lampiran 4* pada Bagian IV) dan teks yang sesuai harus dibuat untuk merangkum tingkat pemaparan Obat pada seluruh tahap pengembangan studi klinik. Tabel tersebut menunjukkan jumlah subjek yang terpapar dalam berbagai jenis studi dan pada berbagai dosis, rute, dan durasi. Jika digunakan beberapa dosis dan/atau jangka waktu pemaparan yang berbeda, maka hal ini dapat dikelompokkan. Jadi, untuk setiap dosis atau rentang dosis, durasi keterpaparan dapat dirangkum menurut jumlah subjek yang terpapar pada periode waktu tertentu, seperti 1 hari atau kurang, 2 hari sampai 1 minggu, 1 minggu sampai 1 bulan, 1 bulan sampai 6 bulan, 6 bulan sampai 1 tahun, lebih dari 1 tahun (ICH E3). Pada pendaftaran Obat, penting juga mengidentifikasi subkelompok diagnostik dan/atau kelompok yang menerima terapi tertentu secara bersamaan yang dianggap relevan dengan penilaian keamanan.

Setiap subjek dapat memperoleh dosis sesuai kebutuhan, berupa dosis maksimum, dosis dengan paparan terlama, dan/atau dosis harian rata-rata. Dalam beberapa kasus, dosis kumulatif dapat dipertimbangkan. Dosis dapat diberikan sebagai dosis harian yang sebenarnya atau berdasarkan mg/kg atau mg/m^2, sesuai kebutuhan. Jika

tersedia, data kadar Obat (misalnya kadar Obat pada saat KTD, kadar plasma maksimum, daerah di bawah kurva/AUC) dapat membantu menghubungkan subjek individual dengan KTD atau perubahan variabel laboratorium.

Diasumsikan bahwa semua subjek yang terlibat dan menerima setidaknya satu dosis pengobatan, masuk dalam analisis keamanan. Jika tidak, harus dijelaskan.

4.1.3 Demografi dan Karakteristik lain Populasi Studi

Tabel ringkasan harus menyajikan tinjauan karakteristik demografi (Tabel 4.2) populasi yang terpapar Obat selama proses pengembangan. Pilihan rentang usia yang digunakan harus mempertimbangkan pembahasan dalam ICH E7 [Studi yang mendukung Populasi Khusus: Geriatri] dan ICH E11 [Studi Klinik Obat pada Populasi Pediatri]. Jika paparan relatif dari kelompok demografi dalam studi berpembanding berbeda dari paparan menyeluruh, harus disediakan tabel yang terpisah.

Tabel harus menunjukkan karakteristik yang relevan dari populasi studi dan jumlah subjek dengan karakteristik khusus. Karakteristik tersebut dapat mencakup:

- Keparahan penyakit.
- Perawatan di rumah sakit.
- Gangguan fungsi ginjal.
- Keadaan sakit yang terjadi bersamaan.
- Penggunaan Obat lain pada saat yang sama.
- Lokasi geografis.

Jika karakteristik tersebut didistribusikan secara berbeda dalam studi berpembanding versus *database* keseluruhan, harus dibuat tabel untuk kedua kelompok tersebut.

Teks yang menyertai tabel tersebut harus menyebutkan ketidakseimbangan (jika ada) antara Obat dan plasebo dan/atau pembanding terkait salah satu karakteristik demografi di atas, terutama jika dapat mengakibatkan perbedaan hasil keamanan.

Jika subjek tertentu dikeluarkan dari studi (karena keadaan sakit yang terjadi bersamaan, keparahan penyakit, Obat yang dikonsumsi secara bersamaan), maka harus dicantumkan.

Tabel demografis untuk setiap indikasi harus dibuat terpisah, meskipun indikasi yang terkait erat dapat disatukan jika karakteristik subjek studinya serupa sehingga risikonya diyakini sama.

4.2. Kejadian Tidak Diinginkan (KTD)

4.2.1. Analisis Kejadian Tidak Diinginkan (KTD)

Data tentang frekuensi KTD dijelaskan dalam teks dan tabel. Teks dicantumkan pada Bagian 4.2.1 yang sesuai

dan tabel yang tidak dicantumkan dalam teks ditempatkan dalam *Lampiran 4*.

Seluruh KTD atau KTD yang memburuk setelah pengobatan dimulai ("tanda dan gejala yang muncul karena pengobatan," KTD yang tidak terlihat pada *baseline* dan yang memburuk walaupun telah ada pada saat *baseline*) harus diringkas dalam tabel yang mencantumkan setiap kejadian, jumlah subjek yang mengalami kejadian dan frekuensi munculnya kejadian pada subjek yang mendapat Obat yang diteliti, dengan Obat pembanding dan plasebo. Tabel tersebut juga dapat menyajikan hasil dari setiap dosis dan dapat dimodifikasi untuk menunjukkan antara lain angka KTD berdasarkan keparahan, onset terapi atau penilaian kausalitas.

Jika sebagian besar data keamanan yang relevan berasal dari jumlah studi yang terbatas (misalnya satu atau dua studi), atau jika populasi subjek yang terlibat dalam studi tersebut sangat berbeda, penyajian data berdasarkan studi lebih sesuai. Jika data keterpaparan yang relevan tidak tercantum dalam studi yang terbatas, pengelompokan studi dan penggabungan hasil untuk meningkatkan ketepatan estimasi dan kepekaan terhadap perbedaan harus dipertimbangkan.

Penggabungan data keamanan dari berbagai studi harus dilakukan dengan hati-hati karena dalam beberapa kasus, interpretasi bisa menjadi sulit dan penggabungan tersebut dapat mengaburkan perbedaan nyata. Dalam kasus di mana perbedaan terlihat jelas, akan lebih tepat menyajikan data berdasarkan studi. Hal berikut ini harus dipertimbangkan:

- Penggabungan data paling tepat dilakukan untuk studi dengan desain yang mirip, misalnya mirip dalam dosis, lama, metode menentukan KTD, dan dalam populasi.
- Jika KTD berbeda secara nyata di berbagai studi individual yang terkumpul, estimasi gabungan kurang informatif.
- Studi dengan pola KTD yang tidak biasa harus disajikan secara terpisah.
- Kedalaman analisis tergantung pada keseriusan KTD dan kekuatan bukti bahwa kejadian tersebut disebabkan oleh Obat. Perbedaan tingkat keterkaitan Obat, kejadian serius atau kejadian yang menyebabkan penghentian atau perubahan dosis memerlukan investigasi lebih dalam, sedangkan KTD lainnya tidak perlu analisis yang rumit.
- Pemeriksaan pada subjek yang mengalami kelainan nilai laboratorium yang ekstrim ("*outlier*") bermanfaat dalam mengidentifikasi subkelompok individu yang berisiko terhadap KTD tertentu.

Kelompok studi yang dapat digunakan dalam analisis keamanan gabungan adalah sebagai berikut:

- Seluruh studi berpembanding atau bagian dari studi berpembanding, seperti studi berpembanding plasebo, berpembanding positif, berpembanding positif tertentu, atau studi tentang indikasi tertentu (yang dilakukan di populasi yang berbeda). Pengelompokan ini dapat memberikan informasi terbaik mengenai KTD yang lebih umum dan dapat membedakan kejadian terkait Obat dari kejadian spontan. Angka pada kelompok pembanding dan perlakuan harus dibandingkan.
- Seluruh studi, tidak termasuk studi jangka pendek pada subjek sehat. Pengelompokan ini berguna untuk mengevaluasi kejadian yang lebih jarang.
- Seluruh studi yang menggunakan *regimen* atau rute dosis tertentu, atau terapi lain secara bersamaan.
- Studi dimana laporan KTD diungkapkan melalui daftar periksa (*checklist*) atau langsung ditanyakan, atau studi dimana kejadiannya adalah sukarela.
- Gabungan studi menurut wilayah/negara.

Pembahasan dua kelompok pertama bermanfaat, sedangkan kelompok lainnya akan bervariasi tergantung Obat yang dibahas, dan dipengaruhi oleh pemeriksaan hasil studi individual. Metode yang digunakan, harus diketahui bahwa setiap angka hanya perkiraan kasar, seperti halnya hasil studi tunggal.

Jika data dari beberapa studi akan digabungkan, harus dijelaskan alasan memilih metode penggabungan. Menggabungkan pembilang kejadian dan penyebut untuk studi dapat dilakukan. Metode lain untuk mengumpulkan hasil seluruh studi adalah dengan menghitung data berdasarkan ukuran studi atau variansinya.

Jika angka KTD dalam studi klinik sangat berbeda, perbedaan tersebut harus dicatat dan didiskusikan alasannya (misalnya, perbedaan dalam populasi studi, pemberian dosis, atau dalam metode pengumpulan data KTD).

KTD harus dijelaskan sesuai dengan penjelasan dalam laporan studi individual (ICH E3). Dalam menggabungkan data dari beberapa studi, gunakan istilah standar untuk menggambarkan kejadian tersebut dan kumpulkan sinonim dibawah istilah tunggal. Hal ini dapat dilakukan dengan kamus standar internasional dan terminologinya. Penelitian dimana KTD menyebabkan perubahan terapi (penghentian penggunaan Obat, perubahan dosis, kebutuhan terapi tambahan) dapat membantu menilai aspek klinik KTD tersebut. Angka tersebut dapat ditambahkan pada tabel KTD, atau dapat disajikan dalam tabel terpisah. Jumlah seluruh penghentian penggunaan Obat dari setiap studi dapat bermanfaat dan juga penting

mencantumkan KTD yang menyebabkan penghentian tersebut dalam tabel terpisah.

4.2.1.1 Kejadian Tidak Diinginkan (KTD) yang Umum

Matriks yang menyajikan angka KTD (lihat *Lampiran 4* pada Bagian IV ini) digunakan untuk membandingkan angka pada kelompok uji dan pembanding. Penggabungan kategori keparahan kejadian dan kategori kausalitas dapat bermanfaat untuk analisis ini. Kategori kausalitas dilaporkan dan penyajian datanya harus mencakup total KTD (baik dianggap terkait atau tidak terkait dengan pengobatan) karena evaluasi kausalitas bersifat subjektif dan dapat mengabaikan KTD yang terkait pengobatan. Perbandingan angka KTD antara kelompok uji dan kelompok pembanding dalam studi individual dirangkum pada bagian ini. Memasukkan angka dalam tabel pada studi yang dipilih (lihat tabel 4.4 contoh, pada *Lampiran 4*) seringkali bermanfaat.

Pemeriksaan mendalam terhadap KTD yang lebih umum yang kemungkinan terkait Obat dapat pula bermanfaat (misalnya kejadian yang menunjukkan respon-dosis dan/atau perbedaan angka antara Obat dan plasebo) untuk hubungannya dengan faktor yang relevan, termasuk:

- dosis;
- dosis mg/kg atau mg/m^2;
- *regimen* dosis;
- lama perlakuan;
- dosis total;
- karakteristik demografi seperti umur, jenis kelamin, ras;
- penggunaan Obat lain secara bersamaan;
- gambaran *baseline* lain seperti status ginjal;
- hasil khasiat;
- kadar Obat, jika tersedia.

Rangkuman hasil pemeriksaan waktu onset dan durasi untuk kejadian yang terkait dengan Obat juga bermanfaat.

Evaluasi statistik yang ketat terhadap kemungkinan hubungan antara KTD dengan masing-masing faktor di atas seringkali tidak perlu. Penyajian awal dan pemeriksaan data dapat memperlihatkan bahwa tidak ada bukti hubungan yang bermakna dengan demografi atau gambaran *baseline* lainnya sehingga tidak diperlukan analisis lebih lanjut dari faktor tersebut. Analisis tersebut tidak perlu disajikan dalam laporan. Jika analisis keamanan terlalu luas untuk disajikan secara rinci dalam laporan,

sebaiknya disajikan sebagai laporan terpisah dalam Laporan Studi Klinik, dan dirangkum pada bagian ini.

Dalam keadaan tertentu, *life tabel* atau analisis serupa mungkin lebih informatif daripada melaporkan data KTD yang belum diolah.

4.2.1.2 Kematian

Tabel pada *Lampiran 4* pada Bagian IV harus mencantumkan seluruh kematian yang terjadi saat studi (termasuk kematian yang terjadi setelah penghentian pengobatan, misalnya dalam waktu tiga puluh hari atau sebagaimana ditentukan dalam protokol studi. Begitu juga kematian lainnya yang terjadi kemudian yang mungkin disebabkan oleh proses selama masa studi). Dikecualikan dari daftar ini adalah kematian yang terkait penyakit sesuai protokol dan tidak berhubungan dengan Obat yang diteliti, baik dalam studi dengan kondisi kematian tinggi seperti kanker stadium lanjut atau dalam studi dimana kematian adalah *endpoint* primer studi (namun demikian, diasumsikan bahwa kematian tersebut masih akan dilaporkan dalam laporan studi individual E3 ICH). Kematian tersebut masih harus diteliti lagi untuk mencari pola tak terduga diantara tahapan studi, dan selanjutnya dianalisis jika terdapat perbedaan yang tidak dapat dijelaskan. Kematian harus diteliti secara individual dan dianalisis berdasarkan angka dalam studi individual dan gabungan studi, dengan mempertimbangkan kematian total dan kematian dengan penyebab khusus. Hubungan dengan faktor yang tercantum dalam bagian 4.2.1.1 juga harus dipertimbangkan. Kematian dalam populasi subjek yang penyebabnya dapat diduga (misalnya karena serangan jantung dan kematian mendadak pada populasi angina) dianggap tidak informatif, tetapi satu kematian saja karena aritmia terkait perpanjangan interval QT, anemia aplastik, atau penyakit hati dapat menjadi informatif. Perhatian khusus harus diberikan sebelum terjadi kematian yang tidak biasa karena penyakit yang terjadi bersamaan.

4.2.1.3 Kejadian Tidak Diinginkan yang Serius (KTDS) Lainnya

Ringkasan seluruh KTDS (selain kematian tetapi termasuk KTDS yang dianggap terkait dengan kematian) harus dilaporkan. KTD yang terjadi setelah penghentian Obat harus dilaporkan. Pelaporan harus mencakup kelainan nilai laboratorium yang utama, kelainan tanda vital,

dan kelainan pemeriksaan fisik yang dianggap sebagai KTDS menurut definisi ICH E2A. Hasil analisis KTDS di berbagai studi harus dilaporkan. Frekuensi KTDS harus diperiksa terutama untuk Obat yang digunakan secara kronis. Hubungan yang mungkin terjadi dengan faktor yang tercantum dalam Bagian 4.2.1.1 juga harus dipertimbangkan.

4.2.1.4 Kejadian Tidak Diinginkan (KTD) yang Bermakna Lainnya

Kelainan hematologi dan laboratorium lain (selain yang memenuhi definisi serius) dan setiap kejadian yang menyebabkan intervensi penting (penghentian Obat uji sebelum waktunya, pengurangan dosis, atau terapi tambahan yang dilakukan bersamaan) selain yang dilaporkan sebagai KTDS, harus dilaporkan.

Kejadian yang menyebabkan penghentian Obat uji sebelum waktunya menandakan masalah keamanan penting dan harus mendapatkan perhatian khusus dalam analisis keamanan Obat untuk dua alasan. Pertama, untuk kejadian yang terduga (berdasarkan aktivitas farmakologis), kebutuhan untuk menghentikan (atau mengubah) pengobatan menandakan keparahan kejadian tersebut dan dirasakan pentingnya bagi subjek dan dokter.

Kedua, penghentian dapat mewakili suatu kejadian terkait Obat, namun belum tentu terkait dengan Obat. KTD yang menyebabkan penghentian pengobatan harus dianggap sebagai kejadian yang mungkin terkait dengan Obat bahkan jika kejadian tersebut awalnya tidak terlihat dan bahkan jika kejadian tersebut dianggap mewakili penyakit yang *intercurrent.* Alasan penghentian pengobatan dini harus dibahas dan jumlahnya harus dibandingkan diantara studi, dengan kelompok plasebo dan/atau dengan uji berpembanding aktif. Selain itu, data studi harus diperiksa untuk menemukan hubungan yang mungkin dengan faktor yang tercantum pada Bagian 4.2.1.1.

4.2.1.5 Analisis Kejadian Tidak Diinginkan (KTD) Berdasarkan Sistem Organ atau Sindroma

Penilaian kausalitas dan faktor risiko kematian, KTDS dan KTD bermakna lainnya seringkali sulit dilakukan karena tidak umum. Pengelompokan kejadian tersebut, termasuk kejadian yang kurang penting untuk patofisiologi terkait, dapat menjadi hal penting dalam memahami profil keamanan. Misalnya, hubungan antara

penanganan kematian mendadak dapat menjadi lebih jelas jika dilihat dalam konteks kasus *syncope*, jantung berdebar, dan aritmia tanpa gejala.

Oleh karena itu, merangkum KTD berdasarkan sistem organ akan bermanfaat, sehingga kejadian tersebut dapat dianggap sebagai kejadian terkait Obat, termasuk kelainan laboratorium. Penyajian KTD berdasarkan sistem organ ini harus ditempatkan pada Bagian 4.2.1.5 (4.2.1.5.1; 4.2.1.5.2; dan lain-lain), dan diberi judul sesuai sistem organ yang dibahas. Daftar sistem organ harus disebutkan dan dasar pengelompokan kejadian harus ditentukan dengan tepat untuk menyajikan data KTD Obat. Jika beberapa KTD muncul sebagai sindrom (misalnya sindrom influenza, sindrom pelepasan sitokin), sponsor dapat membuat beberapa Bagian 4.2.1.5 khusus untuk sindrom, bukan untuk sistem organ.

Data dan ringkasan yang sama tidak boleh diulang di lebih dari satu Subbab pada Bab 4.2.1. Namun ringkasan penyajian dapat ditempatkan dalam satu Subbab dan disesuaikan dengan bagian lain.

4.2.2 Narasi

Narasi sebaiknya hanya dibuat untuk kejadian tertentu yang dianggap penting untuk penilaian ringkasan Obat. Letak narasi individual tentang kematian subjek, KTDS lain, dan KTD yang bermakna lainnya dalam pengajuan Registrasi dianggap penting karena aspek kliniknya (seperti yang dijelaskan di laporan studi individual dalam ICH E3) harus dirujuk di sini untuk kemudahan penilai. Narasi tersebut harus menjadi bagian dari laporan studi individual. Jika tidak ada laporan studi individual (misalnya jika banyak studi terbuka digabungkan dalam analisis keamanan dan tidak dijelaskan secara individual), narasi dapat ditempatkan dalam Laporan Studi Klinik, Bab 5.3.

4.3. Evaluasi Data Laboratorium Klinik

Bagian ini menjelaskan kaitan antara perubahan hasil laboratorium dengan penggunaan obat. Kelainan hasil laboratorium yang jelas dan menyebabkan intervensi penting dilaporkan dalam Bagian 4.2.1.3 atau 4.2.1.4. Jika data tersebut juga disajikan dalam bagian ini, duplikasi laporan harus dibuat jelas untuk penilai. Evaluasi ditentukan dari hasil uji laboratorium yang ada, tetapi uraian analisis harus disajikan pada bagian ini. Untuk setiap analisis, perbandingan antara kelompok uji dan kelompok pembanding harus dilakukan. Selain itu, rentang nilai laboratorium normal harus dicantumkan dalam setiap analisis (ICH E3). Bila memungkinkan, nilai laboratorium disajikan dalam satuan standar internasional.

Tinjauan singkat tentang perubahan utama nilai laboratorium dalam berbagai studi klinik harus disajikan. Data laboratorium mencakup hematologi, kimia klinik, urinalisis dan data lainnya yang sesuai. Masing-masing parameter di setiap waktu selama studi (misalnya pada setiap kunjungan) harus dijelaskan pada tiga tingkatan berikut:

- *Central Tendency*, yaitu nilai rata-rata (*mean*) dan median kelompok,
- Rentang nilai dan jumlah subjek dengan nilai abnormal atau dengan nilai abnormal ukuran tertentu (misalnya 2 kali batas atas normal, 5 kali batas atas; pilihan harus dijelaskan). Ketika data digabungkan dari beberapa senter studi dengan perbedaan nilai laboratorium normal, metodologi penggabungan harus dijelaskan. Analisis perubahan subjek individual menurut kelompok uji dapat ditunjukkan dengan berbagai pendekatan (misalnya tabel geser, lihat contoh dalam ICH E3),
- Kelainan klinik individual yang penting, termasuk yang mengarah pada penghentian pengobatan. Kebermaknaan perubahan nilai laboratorium dan kemungkinan hubungannya dengan pengobatan harus dinilai (misalnya dengan menganalisis gambaran tersebut sebagai keterkaitannya dengan dosis, kaitannya dengan kadar Obat, ketidakmunculannya pada terapi lanjutan, *dechallenge* positif, *rechallenge* positif, dan sifat terapi yang dilakukan bersamaan). Keterkaitan yang mungkin dengan faktor lain yang tercantum dalam Bagian 4.2.1.1 juga harus dipertimbangkan.

4.4. Tanda Vital, Temuan Fisik, dan Observasi Lain terkait Keamanan

Cara penyajian observasi studi silang dan perbandingan tanda vital (misalnya detak jantung, tekanan darah, suhu, laju pernapasan), berat badan dan data lain (misalnya elektrokardiogram, sinar-X) yang berkaitan dengan keamanan harus sama dengan cara penyajian variabel laboratorium. Jika ada bukti mengenai pengaruh Obat, hubungan respon-dosis, hubungan respon-kadar Obat atau hubungan dengan variabel individu (misalnya penyakit, demografi, terapi yang diberikan bersamaan), hal ini harus diidentifikasi dan relevansi klinik dari observasi tersebut dijelaskan. Perhatian khusus harus diberikan pada perubahan yang tidak dievaluasi sebagai variabel khasiat dan pada perubahan yang dianggap sebagai KTD. Perhatian khusus juga harus diberikan untuk studi yang dirancang untuk mengevaluasi masalah keamanan tertentu, misalnya studi tentang perpanjangan interval QT.

4.5. Keamanan pada Kelompok dan Situasi Khusus

4.5.1 Kelompok Subjek

Bagian ini merangkum data keamanan yang terkait dengan individualisasi terapi atau manajemen subjek berdasarkan demografi, usia, jenis kelamin, tinggi, berat, massa tubuh tanpa lemak, polimorfisme genetik, komposisi tubuh, penyakit lain dan disfungsi organ. Pada pengajuan indikasi untuk anak, keamanan pada populasi

anak harus secara rutin dianalisis. Analisis dampak terhadap hasil keamanan disajikan dalam bagian lain tetapi dirangkum di sini, bersama dengan informasi kinetik atau informasi lain yang berkaitan, misalnya pada subjek dengan penyakit ginjal atau hati, lingkungan medis, penggunaan Obat lain (lihat 4.5.2, Interaksi Obat), tembakau, alkohol, dan kebiasaan makanan. Sebagai contoh, jika interaksi dengan alkohol ditunjukkan oleh profil metabolik, hasil studi, pengalaman pascapemasaran, atau oleh informasi mengenai Obat sejenis, informasi tersebut harus disajikan di sini. Jika sejumlah besar subjek dengan kondisi komorbid seperti hipertensi, penyakit jantung, atau diabetes dilibatkan dalam penelitian, analisis dilakukan untuk menilai apakah kondisi komorbid tersebut mempengaruhi keamanan Obat yang diteliti. Penyesuaian dengan tabel atau penjelasan KTD harus dilakukan ketika analisis terhadap subkelompok tersebut telah dilakukan.

4.5.2 Interaksi Obat

Studi tentang potensi interaksi Obat dengan makanan atau Obat dengan Obat dirangkum dalam Bagian Ringkasan Studi Farmakologi Klinik dalam ACTD. Dampak terhadap keamanan interaksi tersebut dirangkum di sini, berdasarkan farmakokinetik, farmakodinamik, atau observasi klinik. Setiap perubahan yang teramati dalam profil KTD, perubahan kadar Obat dalam darah yang dianggap berkaitan dengan risiko, atau perubahan efek Obat yang terkait dengan terapi lain disajikan di sini.

4.5.3 Penggunaan pada Kehamilan dan Menyusui

Informasi keamanan penggunaan Obat pada kehamilan atau menyusui selama pengembangan klinik atau dari sumber lain dirangkum di sini.

4.5.4 Overdosis

Informasi klinik terkait overdosis, termasuk tanda/gejala, temuan laboratorium dan pengukuran terapetik/pengobatan serta antidotum (jika tersedia) dirangkum dan dibahas. Informasi tentang khasiat antidotum spesifik dan dialisis disajikan jika ada.

4.5.5 Penyalahgunaan Obat

Studi/informasi terkait penyelidikan potensi ketergantungan terhadap Zat Aktif baru pada hewan dan manusia dirangkum dan disesuaikan dengan Ringkasan Nonklinik. Populasi subjek yang rentan harus diidentifikasi.

4.5.6 Penghentian dan Efek Balik (*Withdrawal* dan *Rebound)*

Informasi atau hasil studi terkait efek balik (*rebound*) dirangkum. Kejadian yang muncul, atau bertambah parah

setelah penghentian Obat (*withdrawal*) pada studi aktif atau tersamar ganda (*double blind)* harus diperiksa untuk melihat apakah hal itu disebabkan penghentian Obat. Penekanan khusus diberikan kepada studi yang mengevaluasi *withdrawal* dan/atau *rebound.*

Data tentang toleransi dirangkum dalam Bagian 3.5 pada Ringkasan Khasiat Klinik.

4.5.7 Pengaruh pada Kemampuan Mengemudikan Kendaraan, Mengoperasikan Mesin atau Penurunan Kemampuan Mental

Data keamanan terkait gangguan indra, koordinasi, atau faktor lain yang akan mengurangi kemampuan berkendara, mengoperasikan mesin atau mengurangi kemampuan mental dirangkum di sini, termasuk KTD yang dilaporkan dalam monitoring keamanan (misalnya mengantuk) dan studi khusus tentang pengaruh Obat terhadap kemampuan berkendara, mengoperasikan mesin atau penurunan kemampuan mental.

4.6 Data Pascapemasaran

Jika Obat sudah dipasarkan, seluruh data pascapemasaran yang tersedia (terpublikasi dan tidak terpublikasi, termasuk laporan keamanan periodik terkini jika tersedia) harus dirangkum. Laporan keamanan periodik terkini dimasukkan dalam Laporan Studi Klinik. Perkiraan jumlah subjek yang terpapar dikelompokkan berdasarkan indikasi, dosis, rute, durasi pengobatan, dan lokasi geografi. Metodologi yang digunakan untuk memperkirakan jumlah subjek yang terpapar harus dijelaskan. Perkiraan rincian demografi dari sumber manapun harus disajikan jika ada.

Matriks kejadian serius yang dilaporkan setelah Obat dipasarkan disajikan, termasuk adanya potensi interaksi Obat yang serius.

Setiap temuan pasca pemasaran di subkelompok dijelaskan.

Lampiran 4

Matriks disajikan untuk merangkum hasil penting dari seluruh studi yang terkait dengan evaluasi keamanan dan khususnya untuk mendukung Label Obat.

Tabel dan gambar disisipkan dalam teks pada bagian yang sesuai jika hal tersebut memudahkan pembacaan dokumen. Tabel dapat disajikan dalam lampiran di akhir bagian.

Ringkasan Studi Klinik memerlukan tabel dan gambar yang dibuat untuk menjelaskan Obat, kelas Obat, dan indikasi klinik tertentu.

Lihat Bagian 4.2.1, 4.2.2.3, dan 4.3 pada pedoman ini untuk pembahasan tambahan mengenai isi tabel-tabel Bagian 4.

Tabel 4.1 <u>Paparan Obat pada subjek studi berdasarkan dosis harian rata-rata dan durasi pemaparan.</u>

Tabel 4.2 <u>Profil demografi subjek pada studi berpembanding.</u>

Tabel 4.3 Insiden kejadian tidak diinginkan (KTD) dalam gabungan studi berpembanding aktif dan plasebo.

Tabel 4.4 Insiden kejadian tidak diinginkan (KTD) pada studi terbesar.

Tabel 4.5 Subjek yang *withdrawal* dari studi: studi berpembanding.

Tabel 4.6 Daftar kematian.

Lihat matriks: Format baku matriks Ringkasan Studi Klinik.

5. SINOPSIS STUDI INDIVIDUAL

Berdasarkan Pedoman ICH E3 (Struktur dan Isi Laporan Studi Klinik), sinopsis studi klinik dimasukkan dalam setiap Laporan Studi Klinik.

Bagian ini harus mencakup tabel berjudul Matriks Studi Klinik, dijelaskan dalam pedoman Laporan Studi Klinik, diikuti dengan seluruh sinopsis studi yang disusun dengan urutan yang sama seperti dalam Laporan Studi Klinik.

Satu sinopsis disiapkan untuk setiap studi yang digunakan di semua negara. Panjang sinopsis biasanya hingga tiga halaman, tetapi sinopsis untuk studi yang lebih kompleks dapat lebih panjang, misalnya sepuluh halaman. Dalam sinopsis individu, tabel dan gambar digunakan seperlunya untuk menambah kejelasan.

SUBBAGIAN C: MATRIKS STUDI KLINIK

Matriks seluruh studi klinik dan informasi terkait harus tersedia. Matriks harus mencakup jenis informasi setiap studi yang diidentifikasi dalam Tabel 1 Bagian ini. Informasi lain dapat dimasukkan dalam tabel ini jika dianggap perlu. Urutan matriks studi mengikuti urutan yang dijelaskan dalam Subbagian D: Laporan Studi Klinik.

Tabel 1. Matriks Keseluruhan Studi Klinik

	Identitas Studi	Lokasi Laporan Studi	Tujuan Studi	Desain Studi dan Jenis Pembanding	Produk Uji; Regimen Dosis, Rute Pemberian	Jumlah Subjek	Subjek Sehat atau Diagnosis Subjek	Durasi Pengobatan	Status Studi; Jenis Laporan
BA	001	Vol 3, Bab. 1.1, hal. 183	BA IV absolut vs Tablet	Studi silang *(cross-over)*	Tablet, 50mg dosis tunggal, oral, 10 mg IV	20	Subjek sehat	Dosis tunggal	Selesai; Ringkasan
BE	002	Vol 4, Bab. 1.2, hal. 254	Membandingkan formulasi Obat dalam studi klinik dan yang akan dipasarkan	Studi silang	Formulasi 2 tablet, 50 mg, oral	32	Subjek sehat	Dosis tunggal	Selesai; Ringkasan
PK	1010	Vol 6, Bab. 3.3, hal. 29	Menetapkan PK	Studi silang	Tablet, 50mg dosis tunggal, oral	50	Insufisiensi Renal	Dosis tunggal	Selesai; Lengkap
PD	020	Vol 6, Bab.4.2, hal. 147	*Bridging-study* antar wilayah/negara	Acak, berpembanding-plasebo	Tablet, 50mg, dosis berulang, oral, setiap 8 jam	24 (12 Obat, 12 plasebo)	Subjek dengan hipertensi primer	2 minggu	Masih berjalan; Laporan Sementara
Khasiat	035	Vol 10, Bab.5.1, hal. 1286	Khasiat & keamanan jangka panjang; Analisis Populasi PK	Acak, berpembanding -aktif	Tablet, 50mg, oral, setiap 8 jam	300 (152 Obat uji, 148 pembanding aktif)	Subjek dengan hipertensi primer	48 minggu	Selesai; Lengkap

SUBBAGIAN D: LAPORAN STUDI KLINIK

PENDAHULUAN

Subbagian ini menjelaskan tentang penyusunan Laporan Studi Klinik, data klinik lain, dan rujukan dalam dokumen teknis umum *(Common Technical Dossier/ CTD)* untuk pendaftaran Obat yang digunakan manusia. Indonesia mempersyaratkan Laporan Studi khusus untuk evaluasi klinik.

SUSUNAN LAPORAN STUDI KLINIK DAN INFORMASI TERKAIT

1. DAFTAR ISI LAPORAN STUDI KLINIK

2. LAPORAN STUDI KLINIK

   2.1. Laporan Studi Biofarmasetika
   - 2.1.1. Laporan studi ketersediaan hayati (BA).
   - 2.1.2. Laporan studi perbandingan ketersediaan hayati (BA) dan bioekivalensi (BE).
   - 2.1.3. Laporan studi korelasi *in vitro-in vivo.*
   - 2.1.4. Laporan metode bioanalisis dan analisis untuk studi pada manusia.

   2.2. Laporan Studi terkait Farmakokinetik Menggunakan Biomaterial Manusia
   - 2.2.1. Laporan studi ikatan protein plasma.
   - 2.2.2. Laporan studi metabolisme hati dan interaksi Obat.
   - 2.2.3. Laporan studi menggunakan biomaterial manusia lainnya.

   2.3. Laporan Studi Farmakokinetika (PK) pada Manusia
   - 2.3.1. Laporan studi PK pada subjek sehat dan tolerabilitas awal.
   - 2.3.2. Laporan studi PK pada subjek dan laporan tolerabilitas awal.
   - 2.3.3. Laporan studi PK pada populasi.

   2.4. Laporan Studi Farmakodinamika (PD) pada Manusia
   - 2.4.1. Laporan studi PD dan PK/PD pada subjek sehat.
   - 2.4.2. Laporan studi PD dan PK/PD pada subjek.

   2.5. Laporan Studi Khasiat dan Keamanan
   - 2.5.1. Laporan studi klinik berpembanding terkait klim indikasi.
   - 2.5.2. Laporan studi klinik tanpa pembanding.
   - 2.5.3. Laporan analisis data dari lebih dari satu studi, termasuk analisis formal terpadu, metaanalisis, dan *bridging analysis.*
   - 2.5.4. Laporan studi klinik lain.

3. Laporan Pengalaman Pascapemasaran

4. Formulir Laporan Kasus dan Daftar Subjek Individual

PEDOMAN PENYUSUNAN LAPORAN STUDI KLINIK DAN INFORMASI TERKAIT

Pedoman ini memberikan rekomendasi struktur Laporan Studi Klinik dan informasi terkait untuk menyederhanakan penyiapan dan pengkajian dokumen serta memastikan kelengkapannya. Penempatan laporan ditentukan oleh tujuan utama studi. Setiap laporan studi hanya akan muncul dalam satu bagian. Jika ada beberapa tujuan, studi tersebut harus disesuaikan dengan bagian lain.

Penjelasan seperti "tidak ada" atau "tidak ada studi yang dilakukan" diberikan bila tidak ada laporan atau informasi yang tersedia untuk Bagian atau Subbagian.

1. DAFTAR ISI LAPORAN STUDI

Daftar Isi Laporan Studi harus tersedia.

Daftar Isi untuk Subbagian D mencakup seluruh bab yang tercantum dalam pedoman CTD hingga subbagian terkecil untuk mengidentifikasi seluruh komponen penting dari Registrasi yang diajukan (misalnya, 5.1.1 *Placebo Controlled Trials*).

Ilustrasi bagian dari Daftar Isi Subbagian E

5. Indikasi Z - Laporan Studi Khasiat dan Keamanan

5.1 Indikasi Z - Laporan Studi Klinik Berpembanding terkait Klim Indikasi

5.1.1 Indikasi Z – Studi Berpembanding Plasebo
Studi xx-xxx: Studi tersamar ganda, berpembanding plasebo Obat A untuk Indikasi Z
Studi yy-yyy: Studi tersamar ganda... ...

5.1.2 Indikasi Z – Studi Berpembanding Aktif
Studi zz-zzz: Studi tersamar ganda, berpembanding aktif Obat A vs Obat C untuk Indikasi Z

5. Indikasi Q - Laporan Studi Khasiat dan Keamanan

5.1 Indikasi Q - Laporan Studi Klinik Berpembanding terkait Klim Indikasi

2. LAPORAN STUDI KLINIK

2.1. Laporan Studi Biofarmasetika

Studi Bioavailabilitas (BA) menilai kecepatan dan luasnya pelepasan Zat Aktif dari Obat. Studi perbandingan BA atau Bioekivalensi (BE) dapat menggunakan *endpoint* kinetik, dinamik, klinik, atau disolusi *in vitro*, dan dapat berupa dosis tunggal atau dosis berulang. Apabila tujuan utama studi adalah untuk menilai kinetik Obat dan juga mencakup informasi BA, laporan studi disampaikan pada Bagian 1, dan dirujuk pada Bagian 1.1 dan/atau 1.2.

2.1.1. Laporan Studi Ketersediaan Hayati (BA)
Studi BA pada Bagian ini harus mencakup:

1) Studi yang membandingkan pelepasan dan ketersediaan sistemik Zat Aktif dari bentuk sediaan padat oral dengan ketersediaan sistemik Zat Aktif yang diberikan secara intravena atau sebagai bentuk sediaan oral cair,
2) Studi tentang proporsionalitas bentuk sediaan, dan
3) Studi tentang pengaruh makanan.

2.1.2. Laporan Studi Perbandingan BA dan BE

Studi di bagian ini membandingkan jumlah dan luasnya pelepasan Zat Aktif dari Obat yang sejenis (misalnya, tablet dengan tablet, tablet dengan kapsul). Studi perbandingan BA atau BE dapat mencakup perbandingan antara:

1) Obat yang digunakan dalam studi klinik yang mendukung keefektifan dan Obat yang akan dipasarkan,
2) Obat yang digunakan dalam studi klinik yang mendukung keefektifan dan Obat yang digunakan dalam bets stabilitas, dan
3) Obat sejenis dari produsen yang berbeda.

2.1.3. Laporan Studi Korelasi *In Vitro-In Vivo*

Studi disolusi *in vitro* yang menyajikan informasi BA, termasuk studi yang digunakan untuk mencari korelasi data *in vitro* dengan *in vivo*, ditempatkan pada Bagian 1.3.

Laporan uji disolusi *in vitro* yang digunakan untuk kontrol mutu bets dan/atau pelulusan bets ditempatkan di Bagian Mutu pada CTD.

2.1.4. Laporan Metode Bioanalisis dan Analisis untuk Studi pada Manusia

Metode bioanalisis dan/atau analisis untuk studi biofarmasetika atau disolusi *in vitro* biasanya disajikan dalam Laporan Studi Individual. Jika suatu metode digunakan dalam banyak studi, metode tersebut dan validasinya dimasukkan dalam Bagian 1.4 dan dirujuk dalam Laporan Studi Individual yang sesuai.

2.2. Laporan Studi terkait Farmakokinetika Menggunakan Biomaterial Manusia

Biomaterial manusia adalah istilah yang digunakan untuk protein, sel, jaringan dan materi lain yang berasal dari manusia yang digunakan secara *in vitro* atau *ex vivo* untuk menilai sifat kinetik dari Zat Aktif. Contohnya termasuk kultur koloni sel manusia yang digunakan untuk menilai permeabilitas melalui membran biologis dan proses transpor, dan albumin manusia yang digunakan untuk menilai ikatan protein plasma. Yang terpenting adalah penggunaan biomaterial manusia seperti hepatosit dan/atau mikrosom hati untuk mempelajari alur metabolisme dan menilai interaksi Obat-Obat dengan alur ini.

Studi menggunakan biomaterial untuk membahas sifat lain (misalnya kemandulan atau farmakodinamika) sebaiknya tidak ditempatkan pada Subbagian Laporan Studi Klinik, tetapi pada Bagian Studi Nonklinik (Bagian III).

2.2.1. Laporan Studi Ikatan Protein Plasma
Laporan studi ikatan protein *ex vivo* disajikan di sini. Data ikatan protein dari studi kinetik darah dan/atau plasma disajikan dalam Bagian 3.

2.2.2. Laporan Studi Metabolisme Hati dan Interaksi Obat
Laporan studi metabolisme hati dan interaksi Obat dengan jaringan hati disajikan di sini.

2.2.3. Studi Menggunakan Biomaterial Manusia Lainnya
Laporan studi menggunakan biomaterial lainnya disajikan di sini.

2.3. Laporan Studi Farmakokinetik (PK) pada Manusia

Penilaian kinetik Obat pada subjek sehat dan/atau pasien dianggap penting untuk merancang strategi pemberian dosis dan tahapan titrasi dosis, untuk mengantisipasi dampak penggunaan bersamaan dengan Obat lain, dan untuk menafsirkan perbedaan farmakodinamik yang teramati. Penilaian ini harus memberikan penjelasan bagaimana tubuh menangani Obat seiring waktu, dengan fokus pada kadar plasma maksimum (paparan puncak), daerah di bawah kurva (paparan total), bersihan, dan akumulasi Obat induk serta metabolitnya, khususnya yang memiliki aktivitas farmakologi.

Studi PK yang laporannya dimasukkan dalam Bagian 3.1 dan 3.2 umumnya dirancang untuk (1) mengukur kadar Obat dan metabolit dalam plasma seiring waktu, (2) mengukur kadar Obat dan metabolit dalam urin atau feses jika diperlukan, dan/atau (3) mengukur ikatan Obat dan metabolit terhadap protein atau sel darah merah.

Pada kondisi tertentu, studi PK dapat mencakup pengukuran distribusi Obat ke jaringan, organ, atau cairan tubuh (misalnya, cairan sinovial atau serebrospinal), dan hasil studi distribusi ini dimasukkan pada Bagian 3.1 dan 3.2. Studi ini memberikan karakteristik kinetik Obat dan informasi absorpsi, distribusi, metabolisme, dan ekskresi Obat dan metabolit aktif pada subjek sehat dan/atau pasien. Studi tentang keseimbangan massa dan perubahan dalam kinetik terkait dosis (misalnya penentuan proporsionalitas dosis) atau waktu (misalnya karena induksi enzim atau pembentukan antibodi) merupakan hal yang penting dan harus disajikan pada Bagian 3.1 dan/atau 3.2. Selain menggambarkan kinetik rata-rata pada subjek sehat dan pasien, kinetik juga menggambarkan rentang variabilitas individu.

2.3.1. Laporan Studi PK pada Subjek Sehat dan Tolerabilitas Awal

Laporan studi PK dan tolerabilitas awal pada subjek sehat ditempatkan pada bab ini.

2.3.2. Laporan Studi PK pada Subjek dan Tolerabilitas Awal
Laporan studi PK dan tolerabilitas awal pada subjek ditempatkan pada bab ini.

2.3.3. Laporan Studi PK pada Populasi
Laporan studi PK pada populasi berdasarkan sampel terbatas yang diperoleh dari studi klinik termasuk studi khasiat dan keamanan ditempatkan pada bab ini.

2.4. Laporan Studi Farmakodinamika (PD) pada Manusia

Laporan studi dengan tujuan utama menentukan pengaruh PD Obat pada manusia ditempatkan pada bab ini. Sedangkan laporan studi yang tujuan utamanya untuk menentukan khasiat atau untuk mengumpulkan data keamanan, ditempatkan pada Bab 5.

Bagian ini mencakup laporan (1) studi sifat-sifat farmakologi yang diketahui atau diduga berkaitan dengan efek klinik yang diinginkan (*biomarker*), (2) studi jangka pendek tentang efek klinik utama, dan (3) studi PD tentang sifat-sifat lainnya yang tidak terkait dengan efek klinik yang diinginkan. Karena hubungan kuantitatif antara pengaruh farmakologi ini terhadap dosis dan/atau konsentrasi Obat dan metabolit dalam plasma biasanya penting, informasi PD seringkali dikumpulkan dalam studi respon-dosis atau bersama dengan informasi kadar Obat dalam studi PK (studi respon-kadar atau PK/PD). Hubungan antara pengaruh PK dan PD yang tidak diperoleh dalam studi berpembanding baik seringkali dievaluasi menggunakan model yang sesuai dan digunakan sebagai dasar untuk merancang studi respon-dosis lebih lanjut atau, dalam beberapa kasus, untuk menafsirkan pengaruh perbedaan kadar dalam subset populasi.

Studi penemuan dosis, PD dan/atau PK-PD dapat dilakukan pada subjek sehat dan/atau subjek, dan juga dapat dimasukkan ke dalam studi yang mengevaluasi keamanan dan khasiat suatu indikasi klinik. Laporan studi penemuan dosis, PD dan/atau PK/PD yang dilakukan pada subjek sehat ditempatkan pada Bab 4.1, sedangkan laporan studi yang dilakukan pada subjek ditempatkan dalam Bab 4.2.

Dalam beberapa kasus, informasi PD jangka pendek, penemuan dosis, dan/atau PK-PD yang ditemukan dalam studi farmakodinamik pada subjek akan memberikan kontribusi data pada penilaian khasiat, karena informasi tersebut menunjukkan pengaruh pada *surrogate marker* yang dapat diterima (misalnya, tekanan darah) atau pada *endpoint* manfaat klinik (misalnya, pengurang rasa sakit). Studi PD mungkin juga berisi informasi keamanan klinik penting. Ketika studi-studi ini menjadi bagian dari bukti khasiat atau keamanan, studi-studi ini dianggap sebagai studi khasiat klinik dan keamanan yang harus disertakan dalam Bab 5, bukan di Bab 4.

2.4.1. Laporan Studi PD dan PK/PD terhadap Subjek Sehat
Studi PD dan/atau PK/PD yang mempunyai tujuan nonterapi pada subjek sehat ditempatkan pada bab ini

2.4.2. Laporan Studi Subjek PD dan PK/PD
Studi PD dan/atau PK/PD pada subjek harus ditempatkan dalam bab ini.

2.5. Laporan Studi Khasiat dan Keamanan

Bab ini mencakup laporan seluruh studi klinik khasiat dan/atau keamanan Obat yang dilakukan oleh sponsor, termasuk seluruh studi yang telah selesai maupun yang masih berjalan untuk indikasi yang diajukan maupun tidak diajukan. Laporan studi harus tersaji rinci sesuai studi dan perannya dalam pendaftaran Obat. ICH E3 menggambarkan isi laporan lengkap untuk studi yang memberikan bukti khasiat dan keamanan. Laporan singkat dapat dibuat untuk beberapa studi (lihat ICH E3 dan pedoman masing-masing negara).

Dalam Bab 5, studi-studi disusun menurut desain (berpembanding, tanpa pembanding) dan dalam studi berpembanding, menurut jenis pembandingnya. Dalam setiap bab, studi digolongkan lebih lanjut, diurutkan berdasarkan kelengkapan dan ringkasnya studi (ICH E3), dengan studi yang laporannya lengkap disajikan lebih dahulu. Laporan terpublikasi dengan data yang terbatas atau tidak memiliki data lanjutan ditempatkan terakhir pada bab ini.

Jika pengajuan pendaftaran mencakup beberapa indikasi terapi, laporan disusun dalam Bab 5 yang terpisah untuk setiap indikasi. Pada kasus tersebut, jika studi khasiat klinik relevan dengan hanya salah satu indikasi yang diajukan, studi tersebut dimasukkan dalam Bab 5 yang sesuai. Sedangkan jika studi khasiat klinik relevan dengan beberapa indikasi, laporan studi dimasukkan dalam Bab 5 yang tepat dan dirujuk seperlunya pada Bab 5 lain, misalnya, Bab 5A, Bab 5B.

2.5.1. Laporan Studi Klinik Berpembanding terkait Klim Indikasi
Laporan Studi Klinik Berpembanding diurutkan menurut jenis pembanding:

- Pembanding plasebo (dapat mencakup kelompok pembanding lainnya, seperti pembanding aktif atau dosis lain).
- Tanpa pembanding.
- Respon-Dosis (tanpa plasebo).
- Pembanding aktif (tanpa plasebo).
- Pembanding Eksternal (*Historical*), terlepas dari Pembanding.

Dalam setiap jenis pembanding, studi harus disusun berdasarkan durasi pengobatan jika relevan dengan

penilaian efek Obat. Studi tentang indikasi selain dari yang diajukan, tetapi mendukung khasiat untuk indikasi yang diajukan, dimasukkan dalam Bab 5.1.

Apabila suatu studi farmakodinamik memberikan kontribusi bukti khasiat, studi tersebut dimasukkan dalam Bab 5.1. Studi berpembanding plasebo, baik dilakukan di awal ataupun di akhir, ditempatkan pada Bab 5.1. Studi keamanan berpembanding, termasuk studi dalam kondisi yang tidak untuk didaftarkan, juga dilaporkan dalam Bab 5.1.

2.5.2. Laporan Studi Klinik tanpa Pembanding

Laporan studi klinik tanpa pembanding (misalnya, laporan studi keamanan *open-label*) ditempatkan disini, termasuk studi dalam kondisi yang tidak untuk didaftarkan.

2.5.3. Laporan Analisis Data dari Lebih dari Satu Studi

Banyak masalah klinik dalam pengajuan pendaftaran Obat dapat diatasi dengan analisis data dari beberapa studi. Hasil analisis semacam ini dirangkum dalam dokumen Ringkasan Studi Klinik, tetapi penjelasan rinci dan penyajian hasil analisis tersebut penting untuk interprestasinya. Jika rincian analisis terlalu luas untuk dilaporkan dalam dokumen ringkasan, rincian tersebut disajikan dalam laporan terpisah yang diletakkan pada Bab 5.3. Contoh laporan pada bagian ini adalah: laporan dari metaanalisis formal atau analisis eksplorasi ekstensif tentang khasiat untuk memperkirakan besarnya pengaruh pada semua subjek dan/atau pada subpopulasi tertentu, dan laporan tentang analisis keamanan terpadu yang menilai faktor-faktor seperti kecukupan *database* keamanan, perkiraan angka kejadian, dan keamanan yang terkait variabel seperti dosis, demografi, dan Obat-obat yang digunakan secara bersamaan.

2.5.4. Laporan Studi Klinik Lain

Bab ini mencakup:

- Laporan interim analisis studi-studi terkait klim indikasi.
- Laporan studi keamanan berpembanding yang tidak dilaporkan di tempat lain.
- Laporan studi dengan atau tanpa pembanding yang tidak terkait klim indikasi.
- Laporan terpublikasi tentang pengalaman klinik Obat yang tidak termasuk dalam Bab 5.1. Namun, jika literatur dinilai penting untuk menunjukkan atau membuktikan khasiat, literatur tersebut dimasukkan dalam Bab 5.1.
- Laporan studi yang sedang berlangsung.

3. LAPORAN PENGALAMAN PASCAPEMASARAN

Untuk produk yang saat ini dipasarkan, laporan yang merangkum pengalaman pemasaran (termasuk semua pengamatan terhadap keamanan yang bermakna) harus disertakan dalam item 6.

4. FORMULIR LAPORAN KASUS DAN DAFTAR SUBJEK INDIVIDUAL (SESUAI PERMINTAAN)

Formulir laporan kasus dan daftar data subjek individual yang dijelaskan dalam Lampiran 16.3 dan 16.4 pada pedoman laporan studi klinik ICH, ditempatkan dalam bab ini, dalam urutan yang sama seperti laporan studi klinik dan diindeks menurut studi.

BAGIAN E: DAFTAR PUSTAKA

Daftar pustaka, termasuk artikel terpublikasi yang penting, catatan pertemuan resmi, atau pedoman/saran regulasi lain dicantumkan di sini, termasuk seluruh rujukan yang disebutkan dalam Tinjauan Studi Klinik dan Ringkasan Studi Klinik atau dalam laporan teknis individual yang ada dalam Laporan Studi Klinik. Salinan dokumen yang dirujuk harus tersedia jika diminta.

MATRIKS: FORMAT BAKU MATRIKS RINGKASAN STUDI KLINIK

1.1 Ringkasan studi ketersediaan hayati.
1.2 Ringkasan studi disolusi *in vitro.*

2.1 Ringkasan studi PK interaksi Obat-Obat.

3.1 Gambaran studi khasiat dan keamanan klinik.
3.2 Hasil studi khasiat.

4.1 Paparan Obat terhadap subjek studi berdasarkan rata-rata dosis harian dan durasi paparan formulasi intravena.
4.2 Profil demografi subjek dalam studi berpembanding.
4.3 Insidensi kejadian yang tidak diharapkan dalam *database* gabungan uji berpembanding aktif dan plasebo.
4.4 KTD dalam *database* gabungan studi berpembanding aktif dan Berpembanding plasebo.
4.5 *Withdrawal* subjek oleh studi: studi berpembanding.
4.6 Daftar kematian.

Tabel 1.1. Ringkasan Studi Ketersediaan Hayati

Studi Ref. No.	Tujuan Studi	Desain Studi	Perlakuan (Dosis, Bentuk sediaan, Rute) [Identitas Produk]	Subjek (No.(M/F) Jenis Usia: rata-rata (kisaran)	Parameter rata-rata (+/- SD)						Lokasi Laporan Studi
					C_{max} (mg/L)	T_{max} (hr)	AUC* (mg/Lxhr)	C_{min}** (mg/L)	$T_{1/2}$ (hr)	Lain-lain	
192 (Jepang)	Studi BA relatif pilot yang membandingkan absorpsi bets tablet 200 mg dengan bets pembanding 200 mg.	Terbuka, acak, *cross-over*, dosis 200 mg tunggal	200 mg Tab., p.o. [17762] 200 mg Tab., p.o. [19426]	20 (10/10) Subjek sehat 27 y (20-35)	83 ± 21 80 ± 32	1 0.5	217 ± 20 223 ± 19		3.1 2.9		
195 (Japan)	Studi BA terbanding xx pada kondisi puasa dan kondisi makan	Terbuka, acak, *cross-over*, dosis tunggal	200mg Tab, p.o. [19426]	30 (15/15) Subjek sehat 32 y (26-50)	83 ± 21 120 ± 30	1 2	217 ± 20 350 ± 40				

AUC*: AUC_{TAU} or AUC_{inf}
C_{min}**: Untuk studi dosis berulang

Tabel 1.2. Ringkasan Studi Disolusi *In Vitro*

Studi Ref. No.	Identitas Produk / No. Bets	Bentuk sediaan	Kondisi	Jumlah Unit Dosis	Waktu pengumpulan Rata-rata % Terdisolusi (kisaran)	Lokasi Laporan Studi
1821	979-03	25 mg Kap.	Disolusi: Peralatan 2 (USP) Kecepatan Rotasi: 50 rpm Medium/suhu: air 37°	12	10 20 30 (min) 42 (32-49) 71 (58-85) 99 (96-100) (%)	

Tabel 2.1 Ringkasan Studi PK Interaksi Obat-Obat

Studi/ Protokol # (negara)	Identitas Produk / Bets # (NME)	Tujuan Studi	Desain Studi	# Subjeks Masuk/ selesai (L/P)	HV/P[1] (Usia: rata-rata, kisaran)	Perlakuan		Parameter Farmakokinetik Rata-rata (%CV) Substrat Obat					Rata-rata rasio[2] *Confidence interval*		Lokasi
						Substrat	Obat yang berinteraksi	C_{max}	T_{max}	AUC	$T_{1/2}$	CL/kg	C_{max}	AUC	
001 (USA)	19B Bets 0034	Pengaruh warfarin terhadap Obat X	Acak, *Cross over*	(8L/4P)/ (7L/4P)	HV (34, 20-41)	Obat X 100 mg bid x 7d	Plasebo	45 (18) mcg/mL	2.0 (30) hr	456 (24) mcg*hr/ mL	4.25 (30) hr	0.05 (20) mL/min/kg	1.16 1.01-1.30	1.16 1.03-1.34	
						Obat X 100 mg bid x 7d	Warfarin 10 mg qd x 7d	52 (20) mcg/mL	2.1 (35) hr	530 (27) mcg*hr/ mL	4.75 (35) hr	0.04 (22) mL/min/kg			
001 (USA)	19B Bets 0034	Pengaruh Obat X terhadap warfarin	Acak, *Cross over*	(8L/4P)/ (7L/4P)	HV (34, 20-41)	Warfarin 10 mg qd x 7d	Plasebo	12 (25) mcg/mL	1.5 (30) hr	60 (37) mcg*hr/ mL	40 (35) hr	0.04 (30) mL/min/kg	1.08 0.92-1.24	1.07 0.92-1.18	
						Warfarin 10 mg qd x 7d	Obat X 100 mg bid x 7d	13 (20) mcg/mL	1.45 (27) hr	64 (39) mcg*hr/ mL	42 (37) hr	0.39 (34) mL/min/kg			
002 (UK)	19B2 Bets 0035	Pengaruh Cimetidine terhadap Obat X	*Cross over, Single sequence*	(4L/8P) (4L/8P)	HV (30, 19-45)	Obat X 50 mg bid x 5d	Plasebo	49 (18) mcg/mL	2.1 (30) hr	470 (24) mcg*hr/ mL	4.4 (30) hr	0.05 (20) mL/min/kg	1.22 1.03-1.40	1.36 1.11-1.53	
						Obat X 50 mg bid x 5d	Cimetidine 200 mg bid x 5d	60 (10) mcg/mL	2.2 (30) hr	640 (24) mcg*hr/ mL	5.2 (30) hr	0.03 (20) mL/min/kg			

[1] HV=Relawan sehat, P=Subjek

[2] Nilai untuk substrat dengan Obat berinteraksi/nilai dengan plasebo

Tabel 3.1 Gambaran Studi Khasiat dan Keamanan Klinik

Studi ID	Jumlah Senter Studi Lokasi(s)	Mulai Studi Status keikutsertaan, tanggal Total keikutsertaan/ Tujuan keikutsertaan	Desain Jenis pembanding	Obat Uji & Pembanding Dosis, Rute & Rejimen	Tujuan Studi	# subjek menurut perlakuan masuk/ selesai	Durasi	Jenis kelamin L/P Median Usia (Kisaran)	Diagnosis Kriteria Inklusi	*Endpoint* Primer
PG-2476	1 U. Antartika	Agust-94 SelesaiApr 98 50 / 50	Acak, *double blind*, paralel Plasebo	PT: 30 mg po bid Pbo	Khasiat dan Keamanan	27/24 23/21	4 minggu	27/23 38 (20-64)	Hipertensi Ringan Diastolik 90-100 Sistolik 150-170	Perubahan tekanan sistolik dan diastolik dari *baseline* dalam 4 minggu.
PG-2666	4 Afiliasi Dokter Florida, Smith & Jones CRO	Mei-98 Masih berlangsung pada Mei 2001 126/400	Acak, *open label*, paralel Plasebo dan respon-dosis	PT: 100 mg po bid PT: 50 mg po bid PT: 25 mg po bid Plasebo	Khasiat dan Keamanan, Khasiat dan Keamanan jangka panjang	34/30 30/28 34/32 28/26	4 minggu, diikuti *open label* 12 minggu	66/60 55 (24-68)	Hipertensi Ringan Sistolik 150-170 Diastolik 90-100	Perubahan tekanan sistolik dan diastolik dari *baseline* dalam 4 minggu dan 12 minggu.

Tabel 3.2 Hasil Studi Khasiat

Studi	Perlakuan	# Masuk/Selesai	Tekanan Darah Sistolik dan Diastolik Rata-Rata			*Endpoint* Primer	Uji Statistik / nilai *p*	*Endpoint* Sekunder	Komentar lain
			Baseline	20 minggu	40 minggu	Substrat-Plasebo Perubahan TDD dalam 40 minggu		% normal** (Analisis ITT)	
PG-2678	PT: 100 mg po bid	34/30	162/96	140/85	138/84	6		88	
	PT: 50 mg po bid	30/28	165/97	146/87	146/87	4		78	
	PT: 25 mg po bid	34/32	167/96	148/88	148/88	2		50	
	PT: 10 mg po bid	26/20	162/95	153/93	153/93	-4		20	
	Plasebo	28/26	166/97	160/92	159/91			30	

**Berikan penjelasan

Tabel 4.1 Paparan Obat pada Subjek Berdasarkan Rata-Rata Dosis Harian dan Durasi Paparan Formulasi Intravena

N= *Cut off Date*:

Durasi (Minggu)	Rata-rata Dosis Harian (mg)							
	0 < Dosis ≤ 5 mg	5 < Dosis ≤ 10 mg	10 < Dosis ≤ 20 mg	20 < Dosis ≤ 30 mg	30 < Dosis ≤ 50 mg	50 mg < Dosis	Total (Dosis)	Persen
0 < Dur ≤ 1								
1 < Dur ≤ 2								
2 < Dur ≤ 4								
4 < Dur ≤ 12								
12 < Dur ≤ 24								
24 < Dur ≤ 48								
48 < Dur ≤ 96								
Dur >96								
Total (Setiap Durasi)								
Persen								

Tabel serupa dapat dibuat untuk median, untuk modal, dan untuk dosis maksimum, atau untuk dosis paparan terpanjang. Tabel yang sama dapat dibuat untuk gabungan studi dan subkelompok, misalnya atas dasar pengelompokan usia, jenis kelamin, faktor etnis, kondisi komorbiditas, penggunaan Obat-obatan secara bersamaan, atau kombinasi dari faktor-faktor ini.

Dosis juga dapat dinyatakan sebagai mg/kg, mg/m^2, atau dalam kadar Obat dalam plasma jika data tersebut tersedia.

Tabel 4.2 Profil Demografi Subjek dalam Studi Berpembanding

Cut off Date:

	Kelompok Perlakuan		
	Produk Uji N =	Plasebo N =	Kontrol aktif N =
Usia (tahun)			
Mean ± SD	50 ± 15		
Kisaran	20-85		
Kelompok			
<18	N (%)	N (%)	N (%)
18 - 40	N (%)	N (%)	N (%)
40 - 64	N (%)	N (%)	N (%)
65 - 75	N (%)	N (%)	N (%)
>75	N (%)	N (%)	N (%)
Jenis Kelamin			
Perempuan	N (%)	N (%)	N (%)
Laki-laki	N (%)	N (%)	N (%)
Ras			
Asia	N (%)	N (%)	N (%)
Berkulit hitam	N (%)	N (%)	N (%)
Kaukasia	N (%)	N (%)	N (%)
Lainnya	N (%)	N (%)	N (%)
Faktor-Faktor Lain			

Tabel 4.3 Kejadian Tidak Diinginkan (KTD) dalam *Database* Gabungan Studi Berpembanding Aktif dan Plasebo

Sistem Tubuh/KTD	Obat Uji			Plasebo	Pembanding Aktif 1	Pembanding Aktif 2	
	Semua dosis n = 1685	10 mg n = 968	20 mg n = 717	n = 425	20 mg n = 653	50 mg n = 334	100 mg n = 546
Tubuh secara keseluruhan							
Pusing	19 (1%)	7 (1%)	12 (2%)	6 (1%)	23 (4%)	1 (<1%)	3 (1%)
Dll							
Kardiovaskular							
Hipotensi Postural	15 (1%)	10 (1%)	5 (1%)	2 (<1%)	7 (1%)	6 (2%)	12 (2%)
Dll							
Gastrointestinal							
Konstipasi							

Tabel 4.4 Insidensi Kejadian Tidak Diinginkan (KTD) dalam Studi Individual

	Kejadian yang Dilaporkan Menurut Kelompok Uji							
Sistem Tubuh/KTD	Studi 95-0403			Studi 96-0011		Studi 97-0007		Studi 98-0102s
	Obat x 60 mg bid N =104	Obat x 30 mg bid N =102	Plasebo N = 100	Obat x 60 mg bid N = 500	Plasebo N = 495	Obat x 60 mg bid N = 200	Obat y 100 mg qd N = 200	Obat x 60 mg bid N = 800
Tubuh secara keseluruhan								
Pusing	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Dll	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Kardiovaskular								
Hipotensi Postural								
Dll								
Gastrointestinal								
Konstipasi								

Tabel 4.5 Subjek yang *Withdrawal*[1] dari Studi: Studi Berpembanding

Cut off Date:

Studi		Total *Withdrawal*				Alasan *Withdrawal*			Jumlah tanpa data khasiat pasca-*withdrawal*
		Total	Laki-laki/ Perempuan	Usia > 65	Ras (Jelaskan Pengelompokan) / / /	KTD N (%)	*Lack of efficacy* N (%)	Lainnya N (%)	N (%)
Studi	Obat X	N (%)	N (%) / N (%)	N (%)	N (%) / N (%) / N (%)				
XXX	Plasebo								
Studi	Obat X								
AAA	Pembanding A								
Studi	Obat X								
BBB	Pembanding B								
Studi	Obat X								
CCC	Pembanding C								
Seluruh Studi									

Catatan: data *withdrawal* dapat dibagi menurut tingkat dosis, jika hal tersebut berguna.
[1]Subjek yang *withdrawal* adalah yang diikutsertakan tapi tidak menyelesaikan studi (termasuk subjek yang menghentikan pengobatan atau berpindah ke pengobatan lain dan/atau menghilang dari studi)

Tabel 4.6 Daftar Kematian Perlakuan: Obat Uji *Cut off Date*:

Studi / Sumber[1]	Senter	Identitas Subjek	Usia (tahun)	Jenis Kelamin	Dosis (mg)	Durasi Paparan (Hari)	Diagnosis	Sebab kematian	Pengobatan Lain	Kondisi Medis Lain	Letak Narasi

[1]PM = Kematian dari pengalaman pascapemasaran

Daftar ini meliputi seluruh kematian yang memenuhi aturan inklusi, baik yang timbul dari studi klinik atau dari sumber sekunder, misalnya pengalaman pascapemasaran.
Dalam pendaftaran elektronik, *link* ke narasi atau dokumentasi lain mengenai kejadian tersebut harus ada.
Catatan kaki harus menjelaskan syarat memasukkan kematian ke dalam tabel, misalnya seluruh kematian yang terjadi selama periode paparan Obat atau dalam jangka waktu hingga tiga puluh hari setelah penghentian Obat dan juga yang terjadi kemudian namun akibat KTD yang mempunyai onset selama paparan atau selama tiga puluh hari masa *follow-up*.
Daftar serupa harus disajikan untuk subjek yang terpapar plasebo dan pembanding aktif.

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LAMPIRAN X
PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA
NOMOR 24 TAHUN 2017
TENTANG
KRITERIA DAN TATA LAKSANA REGISTRASI OBAT

INFORMASI MINIMAL YANG HARUS DICANTUMKAN PADA INFORMASI PRODUK

A. RINGKASAN KARAKTERISTIK PRODUK/BROSUR

1. Nama Obat
2. Bentuk sediaan
3. Pemerian Obat
4. Komposisi Obat (nama dan kekuatan Zat Aktif)
5. Indikasi
6. Posologi dan cara pemberian
7. Kontraindikasi
8. Peringatan – Perhatian
9. Interaksi Obat
10. Kehamilan dan menyusui
11. Efek pada pengendara dan menjalankan mesin (jika perlu)
12. Efek samping
13. Overdosis dan pengobatan (jika ada)
14. Cara kerja Obat, dan/atau Farmakodinamik dan/atau Farmakokinetik
15. Data keamanan nonklinik (jika perlu)
16. Daftar Eksipien
17. Ketidaktercampuran (jika perlu)
18. Cara penyimpanan
19. Stabilitas/batas penggunaan setelah direkonstitusi atau setelah wadah dibuka (*in use stability*) (jika perlu)
20. Jenis dan besar kemasan
21. Bentuk sediaan dan kemasan lain yang terdaftar (jika perlu)
22. Nomor Izin Edar
23. Nama Pendaftar dan/atau pemilik Obat sesuai dengan ketentuan yang berlaku
24. Alamat Pendaftar dan/atau pemilik Obat sesuai dengan ketentuan yang berlaku
25. Nama produsen
26. Alamat produsen
27. Nama industri pemberi lisensi (jika perlu)
28. Alamat industri pemberi lisensi (jika perlu)

29. Petunjuk penggunaan
30. Cara rekonstitusi (jika ada)
31. Tanggal disetujui pertama kali/Registrasi Ulang (jika perlu)
32. Tanggal perubahan Informasi Produk (jika perlu)
33. Golongan Obat
34. Peringatan khusus, misalnya:
    a. Harus dengan resep dokter
    b. Tanda peringatan Obat bebas terbatas (P.No.1- P.No.6)
    c. Kotak peringatan
    d. Bersumber/bersinggungan babi
    e. Kandungan alkohol

B. INFORMASI PRODUK UNTUK PASIEN (Contoh) *)

1. Nama Obat
2. Bentuk sediaan
3. Pemerian Obat
4. Komposisi Zat Aktif/Apa yang terkandung dalam Obat?
5. Kekuatan Obat
6. Indikasi/Untuk apa Obat digunakan?
7. Posologi dan cara pemberian/Berapa banyak dan seberapa sering Obat ini boleh digunakan? Apa yang harus dilakukan bila lupa minum Obat ini?
8. Kontraindikasi/Pada keadaan apa Anda tidak diperbolehkan menggunakan Obat ini?
9. Peringatan dan Perhatian/Apa yang perlu diperhatikan bila menggunakan Obat ini? (seperti: apa yang terjadi jika Obat dihentikan)
10. Interaksi Obat/Obat dan makanan apa yang harus dihindari jika menggunakan Obat ini?
11. Kehamilan dan menyusui/Apakah boleh digunakan pada wanita hamil dan menyusui?
12. Efek pada pengendara dan menjalankan mesin/Apakah boleh mengendarai dan menjalankan mesin selama minum Obat ini? (jika perlu)
13. Efek samping/Efek yang tidak diinginkan yang mungkin terjadi
14. Overdosis/Tanda dan gejala kelebihan dosis (jika perlu)
15. Pengobatan overdosis/Apa yang harus dilakukan bila menggunakan Obat ini melebihi dosis yang dianjurkan? (jika perlu)
16. Cara penyimpanan/Bagaimana cara menyimpan Obat ini?
17. Batas penggunaan setelah direkonstitusi atau setelah wadah dibuka/ Berapa lama Obat ini dapat digunakan setelah kemasan dibuka? (jika perlu)
18. Petunjuk penggunaan

19. Cara rekonstitusi/Bagaimana cara melarutkan Obat ini? (jika perlu)
20. Nomor Izin Edar
21. Nama Pendaftar dan/atau pemilik Obat sesuai dengan ketentuan yang berlaku
22. Alamat Pendaftar dan/atau pemilik Obat sesuai dengan ketentuan yang berlaku
23. Tanggal perubahan (jika perlu)
24. Peringatan Khusus, misalnya:
    a. Harus dengan resep dokter
    b. Tanda peringatan Obat bebas terbatas (P. No. 1 - P. No. 6)
    c. Kotak peringatan
    d. Bersumber/bersinggungan babi
    e. Kandungan alkohol

Keterangan:
*) Informasi Produk untuk Pasien dapat dijelaskan dalam bentuk penjelasan atau pertanyaan-jawaban.

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LAMPIRAN XI
PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
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KRITERIA DAN TATA LAKSANA REGISTRASI OBAT

INFORMASI MINIMAL YANG HARUS DICANTUMKAN PADA KEMASAN (LABEL)

No	Informasi yang harus dicantumkan	Bungkus Luar	*Catch Cover*/ Amplop	Etiket	Blister/ Strip	Blister (kemasan terkecil pada Obat Bebas dan Obat Bebas Terbatas)	Etiket Ampul/ Vial
1.	Nama Obat	√	√	√	√	√	√
2.	Bentuk sediaan	√	√	√	(-)	√	√ e)
3.	Besar kemasan (unit)	√	√	√	(-)	(-)	√
4.	Nama dan kekuatan Zat Aktif	√	√	√	√	√	√
5.	Nama dan alamat Pendaftar	√	√	√	√ d)	√	√ d)
6.	Nama dan alamat produsen	√	√	√	√ d)	√	√ f)
7.	Nama dan alamat pemberi lisensi	√	√	√	√ d)	√	(-)
8.	Cara pemberian	√	√	√	(-)	(-)	√
9.	Nomor Izin Edar	√	√	√	√	√	√
10.	Nomor bets	√	√	√	√	√	√
11.	Tanggal produksi	√	√	(-)	(-)	√	(-)
12.	Batas kedaluwarsa	√	√	√	√	√	√
13.	Indikasi	√ a)	√	√ b)	(-)	√	(-)
14.	Posologi	√ a)	√	√ b)	(-)	√	(-)
15.	Kontraindikasi	√ b)	√	√ b)	(-)	√	(-)
16.	Efek samping	√ b)	√	√ b)	(-)	√	(-)
17.	Interaksi Obat	√ b)	√	√ b)	(-)	√	(-)
18.	Peringatan – Perhatian	√ b)	√	√ b)	(-)	√	(-)
19.	Peringatan khusus, misalnya:						
	a. "Harus dengan resep dokter"	√	√	√	√	(-)	√ e)
	b. Tanda peringatan (P. No. 1 – P. No. 6)	√	√	√	(-)	√	(-)
	c. Kotak peringatan	√	√	√	(-)	√	(-)
	d. "Bersumber babi/bersinggungan"	√	√	√	(-)	(-)	√
	e. Kandungan alkohol	√	√	√	(-)	(-)	√
20.	Cara penyimpanan Obat (termasuk cara penyimpanan setelah rekonstitusi)	√	√	√	(-)	√	(-)
21.	Label khusus, misalnya:						
	a. Harga Eceran Tertinggi (HET)	√	√	√	√	√	√ e)
	b. Logo golongan Obat (Obat keras/bebas terbatas/bebas)	√	√	√	√	√	(-)
	c. Logo generik (khusus untuk Obat Generik)	√	√	√	√	√	√ e)
	d. Identitas yang mampu telusur untuk menjamin keabsahan produk	√ c)	√ c)	√ c)	√ c)	√ c)	√ c)

Keterangan:

a) : harus dicantumkan untuk Obat bebas dan Obat bebas terbatas, untuk Obat keras dapat merujuk pada Informasi Produk untuk Pasien.
b) : informasi dapat merujuk pada Informasi Produk untuk Pasien.
c) : penerapan identitas yang mampu telusur untuk menjamin keabsahan produk diatur dengan Peraturan Kepala Badan.
d) : dicantumkan nama Pendaftar/nama produsen/nama pemberi lisensi.

e) : dikecualikan untuk ampul atau vial kurang dari 10 mL.
f) : untuk alamat hanya nama negara.

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LAMPIRAN XII
PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
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KRITERIA DAN TATA LAKSANA REGISTRASI OBAT

PERNYATAAN PENDAFTAR

Saya yang bertanda tangan di bawah ini:

Nama : .....
Jabatan : .....
Nomor telepon : .....
Nomor fax : .....
Alamat *e-mail* : .....

menyatakan bahwa semua informasi dalam dokumen registrasi untuk produk sebagai berikut :

Nama obat: .....
Komposisi zat aktif dan kekuatan per unit dosis: .....
Bentuk sediaan: .....
Jenis dan besar kemasan: .....
Pendaftar: .....
Produsen: .....
Kategori registrasi (agar diuraikan dengan rinci): .....

adalah terkini dan benar. Saya menyatakan bahwa saya telah memeriksa dan bertanggung jawab atas:

1. Kelengkapan dokumen yang diserahkan.
2. Kebenaran semua informasi yang tercantum dalam dokumen registrasi.
3. Kebenaran dan keabsahan dokumen yang dilampirkan untuk menunjang registrasi.
4. Penerapan Pedoman CPOB secara penuh pada semua fasilitas produksi yang terkait dalam proses produksi dan pengawasan obat.
5. Formula obat sesuai dengan formula induk dan catatan bets.
6. Prosedur pembuatan sama dengan yang ditetapkan dalam formula induk dan catatan bets.
7. Data zat aktif dan eksipien pada dokumen registrasi sesuai dengan bets zat aktif dan eksipien yang digunakan.

8. Tiap bets zat aktif dan eksipien telah diuji dan memenuhi spesifikasi sebelum digunakan dalam proses produksi obat.
9. Tiap bets kemasan telah diuji dan memenuhi spesifikasi sebelum digunakan dalam proses produksi obat.
10. Tiap bets obat telah diuji dan memenuhi spesifikasi pelulusan obat sebelum dipasarkan.
11. Penanggung jawab pelulusan obat yang akan dipasarkan adalah personel yang kompeten sesuai dengan Pedoman CPOB.
12. Prosedur pengujian obat tervalidasi/terverifikasi sesuai Pedoman CPOB.
13. Tersedia prosedur tetap untuk penanganan penarikan kembali obat dari peredaran.
14. Semua dokumen registrasi tersedia untuk dievaluasi selama proses inspeksi dan audit regulatori.
15. Uji klinik (jika ada) dilakukan sesuai dengan Pedoman Cara Uji Klinik yang Baik (CUKB).
16. Tidak melakukan perubahan apapun di luar perubahan yang diajukan*).

Apabila pernyataan yang kami berikan tidak sesuai dengan yang sebenarnya, maka kami bersedia proses registrasi tersebut dibatalkan dan dikenai sanksi sesuai ketentuan yang berlaku.

.....,Tanggal
Materai
(Nama Jelas)
(Jabatan)

Keterangan:
*) : Khusus untuk Registrasi Variasi

KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
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PENNY K. LUKITO

LAMPIRAN XIII
PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA
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TENTANG
KRITERIA DAN TATA LAKSANA REGISTRASI OBAT

KELENGKAPAN DOKUMEN PRAREGISTRASI

A. DOKUMEN ADMINISTRATIF

1. Surat pengantar.
2. Sertifikat dan dokumen administratif lain sesuai Lampiran 6.
3. Dokumen pertimbangan penetapan jalur 100 (seratus) Hari.
   - 3.1. Justifikasi bahwa Obat diindikasikan untuk penyakit serius dan langka *(Orphan Drug)*, dan/atau
   - 3.2. Justifikasi bahwa Obat diindikasikan untuk terapi penyakit serius yang mengancam nyawa manusia (*life saving*), dan/atau mudah menular kepada orang lain, dan/atau belum ada atau kurangnya pilihan terapi lain yang aman dan efektif, dan/atau
   - 3.3. Dokumen penunjang untuk program kesehatan masyarakat.
4. Dokumen pertimbangan penetapan jalur 120 (seratus dua puluh) Hari.

   Dokumen penunjang untuk persyaratan Registrasi yang telah disetujui di negara referensi *(reference country)* dengan sistem evaluasi yang telah dikenal baik:

   - 4.1. Informasi status peredaran dilengkapi bukti yang sahih.
   - 4.2. Dokumen *assessment report* lengkap dari badan otoritas terkait dalam bahasa Inggris dari tiga negara referensi, dengan persyaratan indikasi dan posologi yang diajukan mirip dengan yang disetujui untuk ketiga negara referensi tersebut.

     Ketentuan Registrasi dengan negara referensi:

     - 4.2.1. Seluruh aspek terkait mutu Obat, termasuk tetapi tidak terbatas pada sumber bahan baku, Formula, tempat produksi, spesifikasi rilis dan *shelf life*, harus sama dengan yang disetujui di negara referensi.
     - 4.2.2. Obat yang diajukan bukan merupakan Obat yang memerlukan evaluasi khusus terkait adanya perbedaan pola penyakit, pola resistensi dan/atau kebijakan program nasional, seperti antiinfeksi, antivirus (Hepatitis C; HIV), antimalaria, Obat Tuberkulosa, Produk Biologi, dan Obat target terapi.

     Namun demikian, persetujuan negara referensi tidak menjadi dasar utama untuk memberikan Izin Edar.

   - 4.3. Surat pernyataan yang menyatakan bahwa seluruh aspek mutu Obat sama dengan yang disetujui di negara referensi, termasuk pernyataan bahwa *Drug Master File (DMF)* yang diserahkan ke Badan POM sama dengan yang diserahkan ke negara referensi, jika dipersyaratkan.

5. Dokumen pertimbangan penetapan jalur 300 (tiga ratus) Hari.

   Untuk Registrasi Baru Obat Baru, Produk Biologi, atau Registrasi Variasi Major indikasi baru/posologi baru yang tidak termasuk dalam jalur 100 Hari dan 120 Hari maka akan dilakukan evaluasi melalui jalur 300 Hari.

6. Dokumen Obat terkait paten (jika perlu)

   6.1. Surat pernyataan terkait paten.

   6.2. Hasil penelusuran paten dari Direktorat Jenderal Kekayaan Intelektual.

   6.3. Hasil kajian mandiri paten.

B. DOKUMEN MUTU

1. Ringkasan Dokumen Mutu *(Quality overall summary).*
2. Informasi tentang bahan bersumber hewan yang digunakan dalam proses pembuatan Zat Aktif dan Obat.
3. DMF atau dokumen setara dari produsen Zat Aktif untuk Zat Aktif yang belum pernah digunakan untuk produksi Obat yang disetujui di Indonesia (jika perlu).
4. Data ekivalensi (ringkasan/protokol) atau justifikasi tidak diperlukan uji ekivalensi.

C. DOKUMEN NONKLINIK (jika perlu)

1. Tinjauan studi nonklinik *(Nonclinical overview).*
2. Matriks ringkasan studi nonklinik *(Nonclinical tabulated summary).*

D. DOKUMEN KLINIK (jika perlu)

1. Tinjauan studi klinik (*Clinical overview).*
2. Matriks sinopsis studi klinik *(Tabulated study synopses).*

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LAMPIRAN XIV
PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
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KRITERIA DAN TATA LAKSANA REGISTRASI OBAT

KELENGKAPAN DOKUMEN REGISTRASI BARU

A. Kategori Registrasi Baru

Secara rinci, kategori Registrasi Baru terdiri atas:

a. Kategori 1 :
Registrasi Obat Baru dan Produk Biologi, termasuk Produk Biosimilar, meliputi:
1.1 Registrasi Obat Baru dengan Zat Aktif baru, atau Produk Biologi;
1.2 Registrasi Obat Baru atau Produk Biologi dengan kombinasi baru;
1.3 Registrasi Obat Baru atau Produk Biologi dengan bentuk sediaan baru atau kekuatan baru;
1.4 Registrasi Obat Baru atau Produk Biologi dengan rute pemberian baru;
1.5 Registrasi Produk Biosimilar.

b. Kategori 2 :
Registrasi Obat Generik dan Obat Generik Bermerek, meliputi:
2.1. Registrasi Obat Generik dan Obat Generik Bermerek yang memerlukan uji klinik;
2.2. Registrasi Obat Generik dan Obat Generik Bermerek yang tidak memerlukan uji klinik.

c. Kategori 3 :
Registrasi sediaan lain yang mengandung Obat dengan teknologi khusus, dapat berupa *transdermal patch*, *implant*, dan *beads*.

B. Kelengkapan Dokumen Registrasi Baru

No.		KATEGORI							
		1					2		3
		1.1	1.2	1.3	1.4	1.5	2.1	2.2	
BAGIAN I: KELENGKAPAN DOKUMEN ADMINISTRATIF DAN INFORMASI PRODUK									
A. DOKUMEN ADMINISTRATIF									
1	Surat pengantar	v	v	v	v	v	v	v	v
2	Formulir Registrasi	v	v	v	v	v	v	v	v
3	Pernyataan Pendaftar	v	v	v	v	v	v	v	v
4	Sertifikat dan Dokumen administratif (sesuai dengan status produksi: Obat Produksi Dalam Negeri, kontrak, lisensi, ekspor atau impor) sesuai Lampiran 6	v	v	v	v	v	v	v	v
5	Hasil praregistrasi	v	v	v	v	v	v	v	v
6	Kuitansi/bukti pembayaran	v	v	v	v	v	v	v	v
7	Dokumen terkait paten								
	7.1. Surat pernyataan terkait paten	v[a)]	v[a)]	v[a)]	v[a)]	v[b)]	v[b)]	v[b)]	
	7.2. Hasil penelusuran paten dari Direktorat Jenderal Kekayaan Ilmiah	v[a)]	v[a)]	v[a)]	v[a)]	v[b)]	v[b)]	v[b)]	

No.		KATEGORI							
		1					2		3
		1.1	1.2	1.3	1.4	1.5	2.1	2.2	
	7.3. Kajian mandiri terkait paten	v[a)]	v[a)]	v[a)]	v[a)]	v[b)]	v[b)]	v[b)]	
8	Surat keterangan dari produsen mengenai penggunaan bahan baku bersumber dari hewan atau bahan baku bersumber dari tumbuhan (termasuk tetapi tidak terbatas pada gelatin; laktosa monohidrat; magnesium stearat; bahan-bahan yang mengandung asam lemak seperti stearat, oleat, palmitat; gliserin dan jenis lemak hidrogenasi; DHA; asam arakhidonat; eudragit) (jika perlu) Jika bersumber dari hewan disertai dengan informasi sumber hewan dan surat keterangan bebas BSE/TSE	v	v	v	v	v	v	v	v
9	Surat pernyataan bermaterai dari produsen mengenai penggunaan bahan yang bersumber babi/*porcine* (jika perlu)	v	v	v	v	v	v	v	v
B. INFORMASI PRODUK DAN LABEL									
1	Informasi Produk	v	v	v	v	v	v	v	v
2	Label	v	v	v	v	v	v	v	v
3	Foto atau gambar Obat dan kemasan sesuai asli	v	v	v	v	v	v	v	v
BAGIAN II: KELENGKAPAN DOKUMEN MUTU									
Sub Bagian A. Ringkasan Dokumen Mutu (RDM)		v	v	v	v	v	v	v	v
Sub. Bagian B. Dokumen Mutu									
	S. ZAT AKTIF								
	S.1. Informasi Umum								
	1.1. Tata nama	v	v[c)]	v[c)]	v[c)]	v	v	v	v
	1.2. Rumus kimia	v	v[c)]	v[c)]	v[c)]	v	v	v	v
	1.3. Sifat-sifat umum	v	v[c)]	v[c)]	v[c)]	v	v	v	v
	S.2. Proses produksi dan sumber Zat Aktif								
	2.1. Produsen	v	v[c)]	v[c)]	v[c)]	v	v	v	v
	2.2. Uraian dan kontrol proses pembuatan	v	v[c)]	v[c)]	v[c)]	v			v
	2.3. Kontrol terhadap bahan	v	v[c)]	v[c)]	v[c)]	v			v
	2.4. Kontrol terhadap tahapan kritis dan senyawa antara	v	v[c)]	v[c)]	v[c)]	v			v
	2.5. Validasi proses dan/atau evaluasi	v	v[c)]	v[c)]	v[c)]	v			v
	2.6. Pengembangan proses pembuatan	v	v[c)]	v[c)]	v[c)]	v			v
	S.3. Karakterisasi								
	3.1. Elusidasi dari struktur dan karakterisasi	v	v[c)]	v[c)]	v[c)]	v			v
	3.2. Bahan pengotor	v	v[c)]	v[c)]	v[c)]	v			v
	S.4. Spesifikasi dan metode pengujian Zat Aktif								
	4.1. Spesifikasi	v	v[c)]	v[c)]	v[c)]	v	v	v	v
	4.2. Prosedur analisis	v	v[c)]	v[c)]	v[c)]	v	v	v	v
	4.3. Validasi prosedur analisis	v	v[c)]	v[c)]	v[c)]	v	v[d)]	v[d)]	v
	4.4. Analisis bets	v	v[c)]	v[c)]	v[c)]	v	v	v	v
	4.5. Justifikasi spesifikasi	v	v[c)]	v[c)]	v[c)]	v			v
	S.5. Baku pembanding	v	v[c)]	v[c)]	v[c)]	v	v	v	v
	S.6. Spesifikasi dan pengujian kemasan	v	v[c)]	v[c)]	v[c)]	v			v

No.		KATEGORI							
		1					2		3
		1.1	1.2	1.3	1.4	1.5	2.1	2.2	
	S.7. Stabilitas	v	v[c)]	v[c)]	v[c)]	v	v	v	v
	P. OBAT								
	P.1. Pemerian dan Formula	v	v	v	v	v	v	v	v
	P.2. Pengembangan produk								
	2.1. Informasi studi pengembangan	v	v	v	v	v	v	v	v
	2.2. Komponen Obat	v	v	v	v	v	v	v	v
	2.3. Obat	v	v	v	v	v	v	v	v
	2.4. Pengembangan proses pembuatan	v	v	v	v	v	v	v	v
	2.5. Sistem kemasan	v	v	v	v	v	v	v	v
	2.6. Atribut mikrobiologi	v	v	v	v	v			v
	2.7. Kompatibilitas	v	v	v	v	v	v	v	v
	P.3. Prosedur Pembuatan								
	3.1. Produsen Obat	v	v	v	v	v	v	v	v
	3.2. Formula bets	v	v	v	v	v	v	v	v
	3.3. Proses pembuatan dan kontrol proses	v	v	v	v	v	v	v	v
	3.4. Kontrol terhadap tahapan kritis dan produk antara	v	v	v	v	v	v	v	v
	3.5. Validasi proses dan/atau laporan	v	v	v	v	v	v	v	v
	P.4. Spesifikasi dan metode pengujian Eksipien								
	4.1. Spesifikasi	v	v	v	v	v	v	v	v
	4.2. Prosedur analisis	v	v	v	v	v	v	v	v
	4.3. Eksipien bersumber dari hewan dan/atau manusia	v	v	v	v	v	v	v	v
	4.4. Eksipien baru	v	v	v	v	v	v	v	v
	P.5. Spesifikasi dan metode pengujian Obat								
	5.1. Spesifikasi	v	v	v	v	v	v	v	v
	5.2. Prosedur analisis	v	v	v	v	v	v	v	v
	5.3. Laporan validasi metode analisis	v	v	v	v	v	v	v	v
	5.4. Analisis bets	v	v	v	v	v	v	v	v
	5.5. Karakterisasi zat pengotor	v	v	v	v	v	v	v	v
	5.6. Justifikasi spesifikasi	v	v	v	v	v	v	v	v
	P.6. Baku pembanding	v	v	v	v	v	v	v	v
	P.7. Spesifikasi dan metode pengujian kemasan	v	v	v	v	v	v	v	v
	P.8. Stabilitas	v	v	v	v	v	v	v	v
	P.9. Bukti ekivalensi						v		
Sub Bagian C. Daftar pustaka		v	v	v	v	v	v	v	v
BAGIAN III: KELENGKAPAN DOKUMEN NONKLINIK									
Sub Bagian A. Tinjauan studi nonklinik		v	v	v[e)]	v	v			v[f)]
Sub Bagian B. Ringkasan dan matriks studi nonklinik		v	v	v[e)]	v	v			v[f)]
1	Ringkasan studi nonklinik	v	v	v[e)]	v	v			v[f)]
2	Isi ringkasan dan matriks studi nonklinik	v	v	v[e)]	v	v			v[f)]
3	Ringkasan matriks studi nonklinik	v	v	v[e)]	v	v			v[f)]
Sub Bagian C. Laporan studi nonklinik (jika perlu)		v[i)]	v[i)]	v[e)i)]	v[i)]	v[i)]			v[f)i)]

No.		KATEGORI							
		1					2		3
		1.1	1.2	1.3	1.4	1.5	2.1	2.2	
1	Daftar isi laporan studi nonklinik	v[i]	v[i]	v[e)i]	v[i]	v[i]			v[f)i]
2	Laporan studi								
	2.1. Farmakologi	v[i]	v[i]	v[e)i]	v[i]	v[h)i]			v[f)i]
	2.2. Farmakokinetik	v[i]	v[i]	v[e)i]	v[i]	v[h)i]			v[f)i]
	2.3. Toksikologi	v[i]	v[i]	v[e)i]	v[i]	v[i]			v[f)i]
Sub Bagian D. Daftar Pustaka		v[i]	v[i]	v[i]	v[i]	v[i]	v[i]	v[i]	v[i]
BAGIAN IV: KELENGKAPAN DOKUMEN KLINIK									
Sub Bagian A. Tinjauan studi klinik		v	v	v	v	v	v[g]		v
Sub Bagian B. Ringkasan studi klinik							v[g]		
1	Ringkasan studi biofarmasetika dan metode analisis terkait	v	v	v	v	v			v
2	Ringkasan studi farmakologi klinik	v	v	v	v	v			v
3	Ringkasan khasiat klinik	v	v	v	v	v			v
4	Ringkasan keamanan klinik	v	v	v	v	v			v
5	Sinopsis studi individual	v	v	v	v	v			v
Sub Bagian C. Matriks studi klinik		v	v	v	v	v	v[g]		v
Sub Bagian D. Laporan studi klinik		v[i]	v[i]	v[i]	v[i]	v[i]	v[g]		v
1	Daftar isi laporan studi klinik	v[i]	v[i]	v[i]	v[i]	v[i]			v
2	Laporan studi klinik								
	2.1 Laporan studi biofarmasetika	v[i]	v[i]	v[i]	v[i]				v
	2.1.1. Laporan studi ketersediaan hayati/ *bioavailability* (BA)								
	2.1.2. Laporan studi perbandingan ketersediaan hayati/*bioavailability* (BA) dan bioekivalensi (BE)								
	2.1.3. Laporan studi korelasi *in vitro-in vivo*								
	2.1.4. Laporan metode bioanalisis dan analisis untuk studi pada manusia								
	2.2 Laporan studi terkait farmakokinetik menggunakan biomaterial manusia	v[i]	v[i]	v[i]	v[i]	v[i]			v
	2.2.1 Laporan studi ikatan protein plasma								
	2.2.2. Laporan studi metabolisme hati dan interaksi Obat								
	2.2.3. Laporan studi menggunakan biomaterial manusia lainnya								
	2.3 Laporan studi farmakokinetika (PK) pada manusia	v[i]	v[i]	v[i]	v[i]	v[i]			v
	2.3.1. Laporan studi PK pada subjek sehat dan tolerabilitas awal								
	2.3.2. Laporan studi PK pada subjek dan laporan tolerabilitas awal								
	2.3.3. Laporan studi PK pada populasi								
	2.4 Laporan studi farmakodinamika (PD) pada manusia	v[i]	v[i]	v[i]	v[i]	v[i]			v
	2.4.1. Laporan studi PD dan PK/PD pada subjek sehat								
	2.4.2. Laporan studi PD dan PK/PD pada subjek								
	2.5 Laporan studi khasiat dan keamanan	v[i]	v[i]	v[i]	v[i]	v[i]			v
	2.5.1. Laporan studi klinik berpembanding terkait klim indikasi					v			

No.		KATEGORI							
		1					2		3
		1.1	1.2	1.3	1.4	1.5	2.1	2.2	
	2.5.2. Laporan studi klinik tanpa pembanding								
	2.5.3. Laporan analisis data dari lebih dari satu studi, termasuk analisis formal terpadu, metaanalisis, dan *bridging analysis*.								
	2.5.4. Laporan studi klinik lain								
3	Laporan pengalaman pascapemasaran	v i)	v i)	v i)	v i)	v i)			v
4	Formulir laporan kasus dan daftar subjek individual (jika perlu)	v i)	v i)	v i)	v i)	v i)			v
Sub Bagian E. Daftar Pustaka		v i)	v i)	v i)	v i)	v i)	vg)		v

Keterangan :

v[a)] : jika Pendaftar bukan originator atau tidak mendapat penunjukan/Lisensi dari originator
v[b)] : untuk Obat Generik atau Produk Biosimilar pertama
v[c)] : jika sumber dan proses pembuatan Zat Aktif berbeda dari yang disetujui
v[d)] : untuk Zat Aktif nonkompendial
v[e)] : untuk rute pemberian baru
v[f)] : dipersyaratkan untuk komponen Obat yang belum pernah disetujui
v[g)] : untuk Obat Generik yang memerlukan uji klinik
v[h)] : diperlukan untuk Produk Biosimilar bila ada isu terkait mutu dan farmakotoksikologi Zat Aktif
v[i)] : tidak berlaku untuk Registrasi Obat dengan negara referensi

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LAMPIRAN XV
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KELENGKAPAN DOKUMEN
REGISTRASI OBAT KHUSUS EKSPOR

No.		KHUSUS EKSPOR	
		Obat Impor	Obat Produksi Dalam Negeri
1	Surat pengantar	v	v
2	Formulir Registrasi	v	v
3	Pernyataan Pendaftar	v	v
4	Sertifikat dan dokumen administratif sesuai Lampiran 6	v	v
	4.1 Izin Industri Farmasi	v	v
	4.2 Sertifikat CPOB Pendaftar	v	v
	4.3 Sertifikat CPOB atau dokumen lain yang setara dari produsen sesuai bentuk sediaan yang didaftarkan	v	-

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LAMPIRAN XVI
PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
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KRITERIA DAN TATA LAKSANA REGISTRASI OBAT

JENIS PERUBAHAN, PERSYARATAN DAN KELENGKAPAN DOKUMEN REGISTRASI VARIASI

A. Dokumen Administratif Registrasi Variasi

Dokumen administratif yang harus diserahkan pada saat pengajuan Registrasi Variasi meliputi:

1. Surat pengantar.
2. Formulir Registrasi.
3. Pernyataan Pendaftar.
4. Sertifikat dan dokumen administratif (sesuai dengan status produksi: Obat Produksi Dalam Negeri, kontrak, Lisensi, ekspor, impor) sesuai Lampiran 6.
5. Hasil praregistrasi (jika dipersyaratkan).
6. Kuitansi/bukti pembayaran.
7. Dokumen lain-lain.
   - 7.1. Surat pernyataan terkait pemenuhan persyaratan Registrasi Variasi (misal: surat pernyataan bahwa prosedur pengujian Zat Aktif tidak berubah untuk Registrasi Variasi pengetatan batas spesifikasi Zat Aktif).
   - 7.2. Izin Edar dan semua surat persetujuan Registrasi Variasi yang diterbitkan oleh Badan Pengawas Obat dan Makanan beserta lampirannya.
   - 7.3. Tabel sandingan perubahan yang diajukan, termasuk referensi perubahan.
   - 7.4. Justifikasi terhadap perubahan yang diajukan.

B. Dokumen Teknis Registrasi Variasi

Dokumen teknis diserahkan sesuai dengan Registrasi Variasi yang diajukan.

Khusus untuk vaksin, jenis perubahan, persyaratan dan kelengkapan dokumen mengacu pada pedoman WHO. Kategori perubahan pada pedoman WHO berbeda dengan kategori Registrasi di Indonesia, maka dilakukan penyesuaian kategori Registrasi sebagai berikut:

No	Kategori yang tercantum dalam pedoman WHO	Kategori Registrasi di Indonesia
1	*Major*	Registrasi Variasi Major
2	*Moderate*	Registrasi Variasi Minor
3	*Minor*	Registrasi Variasi Notifikasi

1. KATEGORI 4 : REGISTRASI VARIASI MAJOR

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG DISERAHKAN
A. Perubahan Informasi Produk yang mempengaruhi aspek khasiat keamanan yang memerlukan data uji klinik			
1.	Perubahan indikasi dan/atau posologi; penambahan indikasi dan/atau posologi baru.		A. Dokumen administratif, Informasi Produk, dan Label 1. Informasi Produk. B. Dokumen nonklinik (jika perlu) 1. Tinjauan studi nonklinik. 2. Ringkasan dan matriks studi nonklinik. C. Dokumen klinik 1. Tinjauan studi klinik. 2. Ringkasan studi klinik. 3. Matriks studi klinik untuk pengajuan perubahan atau penambahan indikasi dan/atau posologi. 4. Laporan studi klinik (sesuai yang tercantum dalam matriks studi klinik). 5. Laporan keamanan pasca pemasaran/PSUR sampai periode terbaru. 6. Referensi lain.
2.	Perubahan Informasi Produk yang mempengaruhi aspek keamanan.		A. Dokumen administratif, Informasi Produk, dan Label 1. Informasi Produk. B. Dokumen nonklinik (jika perlu) 1. Tinjauan studi nonklinik atau dokumen justifikasi perubahan/penambahan informasi nonklinik. 2. Ringkasan dan matriks studi nonklinik (sesuai perubahan yang diajukan). C. Dokumen klinik 1. Tinjauan studi klinik atau dokumen justifikasi perubahan/penambahan informasi klinik. 2. Daftar dokumen penunjang perubahan Informasi Produk yang diajukan. 3. Matriks studi klinik yang tersedia untuk pengajuan perubahan Informasi Produk. 4. Laporan studi klinik (sesuai yang tercantum dalam matriks studi klinik). 5. Laporan keamanan pasca pemasaran/PSUR sampai periode terbaru (jika perlu). 6. Referensi lain (jika perlu).
B. Perubahan Informasi Produk yang mempengaruhi aspek keamanan yang tidak memerlukan data uji klinik			
1.	Perubahan Informasi Produk yang mempengaruhi aspek keamanan.	1. Khusus Obat Baru dan Produk Biologi.	A. Dokumen administratif, Informasi Produk, dan Label 1. Informasi Produk. B. Dokumen klinik 1. Justifikasi dan/atau dokumen penunjang lainnya sesuai perubahan yang diajukan. 2. Laporan keamanan pascapemasaran/PSUR (jika perlu).

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG DISERAHKAN
			3. Referensi lain.
C. Perubahan terkait Zat Aktif dan/atau Formula yang mempengaruhi aspek khasiat-keamanan yang memerlukan data uji klinik			
1.	Perubahan terkait Zat Aktif dan/atau Formula yang memerlukan uji klinik.		A. Dokumen administratif, Informasi Produk, dan Label 1. Informasi Produk. B. Dokumen mutu 1. Dokumen mutu Zat Aktif lengkap (jika perlu). 2. Dokumen mutu Obat lengkap. 3. Data karakterisasi yang menggambarkan bahwa konformasi dan imunogenisitas antigen sebanding dengan bentuk sediaan dan/atau Formula baru (khusus vaksin). 4. Komitmen untuk melanjutkan studi stabilitas jangka panjang. C. Dokumen klinik 1. Tinjauan studi klinik atau dokumen justifikasi perubahan/penambahan informasi klinik. 2. Daftar dokumen penunjang perubahan Informasi Produk yang diajukan. 3. Matriks studi klinik yang tersedia untuk pengajuan perubahan Informasi Produk. 4. Laporan studi klinik (sesuai yang tercantum dalam matriks studi klinik). 5. Laporan keamanan pascapemasaran/PSUR sampai periode terbaru (jika perlu). 6. Referensi lain (jika perlu).
2.	Penggantian *Master Cell Bank (MCB)/ Master Seed Lot (MSL).*	1. Khusus Produk Biologi. 2. Untuk pembuatan *master cell/ seed lot* baru yang berasal dari *original or preapproved master cell/seed lot* atau *working cell/seed lot* dengan cara subkloning. 3. Tidak terkait dengan perubahan apapun pada *host cell line.*	A. Dokumen mutu 1. Sumber, riwayat dan jumlah pasase dari *master cell/seed* baru dengan dokumentasi semua *raw material* yang berasal dari hewan atau manusia yang digunakan dalam keseluruhan riwayat kultur. 2. Hasil semua uji identitas, termasuk karakteristik sitogenetik yang dapat digunakan untuk mengidentifikasi sel. 3. Informasi karakterisasi dan pengujian MCB/ *Working Cell Bank (WCB)* dan sel dari bagian akhir produksi atau bagian setelah produksi. 4. Hasil semua uji *adventitious agent* yang ada terhadap donor dan *master cell* baru. 5. Karakteristik pertumbuhan dan ekspresi bila substrat sel digunakan untuk memproduksi protein rekombinan. Termasuk evaluasi *copy number* dan stabilitas asam nukleat yang diintroduksi serta kuantitas dan kualitas *express protein* sampai pada tingkat pasase yang melebihi waktu siklus produksi yang diantisipasi. 6. Kualifikasi *cell bank* atau *seed lot* berdasarkan standar yang berlaku. 7. Stabilitas sel yang tervalidasi saat penyimpanan beku dan kondisi

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG DISERAHKAN
			penyimpanan menggunakan *data cell recovery* atau *viability*. 8. Untuk *viral master seed*, semua dokumen terkait semua manipulasi terhadap fenotipe virus misalnya atenuasi virulensi atau *genetic reassortment* atau rekombinan. Termasuk penetapan sekuen asam nukleat dan sumber bahan awal bersumber biologi. 9. Data uji sterilitas, mikoplasma, *adventitious virus* (jika perlu). 10. Komparabilitas Zat Aktif yang disetujui dan yang diajukan dalam hal karakterisasi fisikokimia, aktivitas biologi dan profil *impurity*. 11. Data analisis bets (dalam tabel) minimal tiga bets Zat Aktif yang berasal dari *cell/seed lot* baru dan lama. 12. Hasil studi stabilitas yang sesuai minimal tiga bets yang diproduksi menggunakan *cell/seed lot* baru sesuai pedoman stabilitas yang relevan; dan surat pernyataan akan melanjutkan studi stabilitas sampai *shelf life* yang disetujui, bila perlu, dan melaporkan ke Badan Pengawas Obat dan Makanan bila ada hasil uji yang tidak memenuhi syarat (dengan rencana aksi) atau bila diminta oleh Badan Pengawas Obat dan Makanan. 13. Komitmen untuk menyerahkan laporan studi stabilitas Obat sesuai perubahan yang diajukan. B. Dokumen klinik 1. Tinjauan studi klinik atau dokumen justifikasi perubahan. 2. Daftar dokumen penunjang perubahan. 3. Matriks studi klinik yang tersedia untuk pengajuan perubahan. 4. Laporan studi klinik (sesuai yang tercantum dalam matriks studi klinik). 5. Laporan keamanan pasca pemasaran/PSUR sampai periode terbaru (jika perlu). 6. Referensi lain (jika perlu).
3.	Perubahan kritis pada proses fermentasi (perubahan yang berpotensi memberikan dampak pada mutu Zat Aktif atau Produk Jadi).	Khusus produk rekombinan.	A. Dokumen mutu 1. Diagram alur (termasuk proses dan *in-process control (IPC)* dan deskripsi naratif proses produksi yang diajukan. 2. Informasi karakterisasi dan pengujian setelah produksi *cell bank* untuk produk rekombinan atau antigen untuk produk nonrekombinan, jika perubahan berdampak pada peningkatan hasil fermentasi atau subkultivasi. 3. Jika bersumber dari hewan disertai dengan informasi sumber hewan dan surat keterangan bebas *Bovine Spongiform Encephalopathy (BSE)/ Transmisible Spongiform Encephalophaties (TSE)*. 4. Laporan validasi proses.

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG DISERAHKAN
			5. Studi komparabilitas sebelum dan sesudah perubahan terkait sifat fisikokimia, aktivitas biologi, kemurnian, dan cemaran. 6. Studi nonklinik dan/atau klinik, jika data mutu tidak menunjukkan komparabilitas. 7. Sandingan hasil uji IPC dan *release* untuk setidaknya tiga bets berurutan Zat Aktif skala komersial, antara sebelum dan sesudah perubahan. 8. Perbandingan hasil uji stabilitas Zat Aktif jangka panjang, minimal tiga bets skala komersial yang diproduksi dengan perubahan yang diajukan (minimal tiga bulan pengujian kecuali dinyatakan lain). 9. Komitmen untuk melanjutkan studi stabilitas Zat Aktif jangka panjang.
4.	Perubahan kritis pada proses pemurnian Zat Aktif yang berpotensi mempunyai dampak pada proses kapasitas *viral clearance* atau profil cemaran Zat Aktif.	1. Khusus Produk Biologi.	A. Dokumen mutu 1. Diagram alur (termasuk proses dan IPC) dan deskripsi naratif proses produksi yang diajukan. 2. Laporan validasi proses. 3. Studi komparabilitas sebelum dan sesudah perubahan terkait sifat fisikokimia, aktivitas biologi, kemurnian, dan cemaran. 4. Studi nonklinik dan/atau klinik, jika data mutu tidak menunjukkan komparabilitas. 5. Sandingan hasil uji IPC dan *release* untuk setidaknya tiga bets berurutan Zat Aktif skala komersial, antara sebelum dan sesudah perubahan. 6. Perbandingan hasil uji stabilitas jangka panjang, minimal tiga bets skala komersial yang diproduksi dengan perubahan yang diajukan (minimal tiga bulan pengujian kecuali dinyatakan lain). 7. Komitmen untuk melanjutkan studi stabilitas Zat Aktif jangka panjang. 8. Informasi terkait risiko potensi kontaminasi dengan *adventitious agent* (contohnya, studi dampak pada *viral clearance*, risiko BSE/TSE).
D. Perubahan terkait mutu Zat Aktif			
1.	Perubahan WCB atau *Working Seed Lot (WSL)* baru.	1. *Cell bank* atau *seed lot* baru diperoleh dari MCB/MSL yang telah disetujui sebelumnya. 2. *Cell bank* baru berada pada tingkat pasase yang telah disetujui sebelumnya.	A. Dokumen administratif, Informasi Produk, dan Label 1. Revisi informasi terkait mutu dan kontrol bahan baku kritikal (contohnya *specific pathogen-free egg and chickens*) yang digunakan pada generasi baru WCB yang diajukan. B. Dokumen mutu terkini 1. Kualifikasi *cell bank* atau *seed lot.* 2. Informasi karakterisasi dan pengujian WCB dan sel yang dihasilkan setelah proses produksi. 3. Studi komparabilitas sebelum dan sesudah perubahan terkait sifat fisikokimia, aktivitas biologi, kemurnian, dan cemaran. 4. Studi nonklinik dan/atau klinik,

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG DISERAHKAN
			jika data mutu tidak menunjukkan komparabilitas. 5. Hasil uji kontrol kualitas berupa data kuantitatif dalam format tabel untuk *cell bank* baru yang diajukan. 6. Sandingan hasil uji IPC dan *release* untuk setidaknya tiga bets berurutan Zat Aktif skala komersial, antara sebelum dan sesudah perubahan. 7. Perbandingan hasil uji stabilitas Zat Aktif jangka panjang, minimal tiga bets skala komersial yang diproduksi dengan perubahan yang diajukan (minimal tiga bulan pengujian kecuali dinyatakan lain). 8. Komitmen untuk melanjutkan studi stabilitas Zat Aktif jangka panjang.
2.	Perubahan dan/atau penambahan produsen Zat Aktif atau fasilitas produksi untuk *bulk* Zat Aktif atau produk antara Zat Aktif.	1. Khusus untuk Obat Baru dan Obat yang memerlukan uji bioekivalensi (uji BE). 2. Spesifikasi Zat Aktif tidak berubah. 3. Spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah. 4. Uji stabilitas Obat sudah dilakukan sesuai protokol dengan minimal dua bets Zat Aktif skala pilot atau skala produksi dengan data minimal enam bulan memberikan hasil yang memenuhi spesifikasi.	A. Dokumen mutu 1. *Drug Master File (DMF)* dari produsen Zat Aktif untuk Zat Aktif yang belum pernah digunakan untuk produksi Obat yang disetujui di Indonesia. 2. Perbandingan data analisis bets Zat Aktif dari produsen lama dan baru (khusus Produk Biologi bets analisis dari minimal tiga bets Zat Aktif berurutan skala pilot/produksi). 3. Laporan stabilitas Zat Aktif (jika perlu). 4. Perbandingan data analisis bets Obat dari dua bets Obat (skala pilot/produksi) dari produsen Zat Aktif baru dan lama (khusus Produk Biologi bets analisis dari minimal tiga bets berurutan skala pilot/produksi). 5. Laporan stabilitas Obat dan komitmen stabilitas Obat jika laporan stabilitas Obat belum lengkap. 6. Data uji ekivalensi (*in vitro/in vivo*) (jika perlu).
3.	Perubahan dan/ atau penambahan fasilitas produksi Zat Aktif atau produk antara Zat Aktif.	1. Khusus Produk Biologi.	A. Dokumen mutu 1. Laporan hasil validasi proses pembuatan Zat Aktif. 2. Studi komparabilitas sebelum dan sesudah perubahan terkait sifat fisikokimia, aktivitas biologi, kemurnian, dan cemaran. 3. Studi nonklinik dan/atau klinik, jika data mutu tidak menunjukkan komparabilitas. 4. Sandingan hasil uji IPC dan *release* untuk setidaknya tiga bets berurutan Zat Aktif skala komersial, antara sebelum dan sesudah perubahan. 5. Perbandingan hasil uji stabilitas Zat Aktif jangka panjang, minimal tiga bets skala komersial yang diproduksi dengan perubahan yang diajukan (minimal tiga bulan pengujian kecuali dinyatakan lain). 6. Komitmen untuk melanjutkan studi stabilitas Zat Aktif jangka panjang.

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG DISERAHKAN
4.	Perubahan proses pembuatan Zat Aktif atau bahan awal/produk antara Zat Aktif.	1. Tidak termasuk Zat Aktif Produk Biologi. 2. Tidak termasuk Zat Aktif yang dipersyaratkan uji BE (misal : *pellet sustained release*). 3. Tidak menggunakan bahan baku yang bersumber manusia/hewan dimana memerlukan data keamanan viral. 4. Uji stabilitas Zat Aktif sudah dilakukan sesuai protokol dengan minimal dua bets skala pilot atau skala produksi dengan data minimal enam bulan memberikan hasil yang memenuhi spesifikasi.	A. Dokumen mutu 1. Uraian sintesis Zat Aktif. 2. Perbandingan data analisis bets Zat Aktif (dua skala pilot/produksi) dari proses pembuatan lama dan baru. 3. Laporan stabilitas Zat Aktif dengan proses pembuatan baru. 4. Perbandingan data analisis bets dari dua bets Obat (skala pilot/produksi) antara Zat Aktif dengan proses pembuatan lama dan baru.
5.	Introduksi tahap *reprocessing* Zat Aktif.	1. Kebutuhan *reprocessing* tidak disebabkan penyimpangan berulang dari proses yang sudah tervalidasi dan akar masalah penyebab *reprocessing* teridentifikasi.	A. Dokumen mutu 1. Sandingan hasil uji IPC dan *release* untuk setidaknya tiga bets berurutan Zat Aktif skala komersial, antara sebelum dan sesudah perubahan. 2. Perbandingan hasil uji stabilitas Zat Aktif, minimal tiga bets skala komersial yang diproduksi dengan perubahan yang diajukan dalam kondisi jangka panjang (minimum tiga bulan pengujian kecuali dinyatakan lain). 3. Komitmen untuk melanjutkan studi stabilitas Zat Aktif jangka panjang. 4. Data yang menggambarkan akar masalah penyebab *reprocessing*, termasuk data validasi untuk membantu mencegah *reprocessing* memberi dampak kepada Zat Aktif.
6.	Perubahan dan/ atau penambahan produsen/sumber bahan baku biologis.	1. Khusus Produk Biologi.	A. Dokumen mutu 1. Sertifikat BSE/TSE (bila menggunakan bahan yang berisiko BSE/TSE) atau informasi dan bukti bahwa material tidak berpotensi menimbulkan risiko BSE/TSE. 2. Sandingan hasil uji IPC dan *release* untuk setidaknya tiga bets berurutan Zat Aktif skala komersial, antara sebelum dan sesudah perubahan. 3. Informasi penilaian risiko terkait potensial kontaminasi dengan *adventitious agent.* 4. Informasi yang menggambarkan perbandingan bahan baku/pereaksi dari kedua sumber.
7.	Perubahan skala produksi pada tahap fermentasi, propagasi virus atau seluler.	1. Khusus Produk Biologi. 2. Tidak terdapat perubahan pada spesifikasi Zat Aktif diluar kadar yang telah ditentukan. 3. Tidak terdapat perubahan pada profil cemaran Zat Aktif diluar kadar yang telah ditentukan. 4. Perubahan tidak terjadi akibat kejadian berulang selama pembuatan atau	A. Dokumen mutu 1. Diagram alir (termasuk proses dan IPC) dan deskripsi naratif proses produksi yang diajukan. 2. Informasi karakterisasi dan pengujian setelah produksi *cell bank* untuk produk rekombinan atau antigen untuk produk nonrekombinan, jika perubahan berdampak pada peningkatan *population doublings* atau subkultivasi.

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG DISERAHKAN
		disebabkan masalah stabilitas. 5. Perubahan tidak mempunyai dampak pada proses pemurnian. 6. Perubahan tidak berdampak pada mutu, keamanan atau efikasi Produk Jadi. 7. Tidak terdapat perubahan dalam proporsionalitas bahan baku (dimana perubahan skala ini linear). 8. Perubahan skala menggunakan bioreaktor yang sama.	3. Laporan studi validasi proses. 4. Studi komparabilitas sebelum dan sesudah perubahan terkait sifat fisikokimia, aktivitas biologi, kemurnian, dan cemaran. 5. Jika data mutu tidak memadai untuk menggambarkan komparabilitas maka harus diserahkan studi nonklinik dan/atau klinik. 6. Sandingan hasil uji IPC dan *release* untuk setidaknya tiga bets berurutan Zat Aktif skala komersial, antara sebelum dan sesudah perubahan.
8.	Perubahan skala proses produksi pada tahap pemurnian.	1. Khusus Produk Biologi. 2. Tidak ada perubahan pada prinsip prosedur sterilisasi antigen. 3. Tidak terdapat perubahan pada spesifikasi antigen diluar kadar yang telah ditentukan. 4. Perubahan tidak harus terjadi dengan kejadian berulang selama pembuatan atau disebabkan pengamatan stabilitas. 5. Perubahan dalam skala linear dengan proporsionalitas parameter produksi dan material.	A. Dokumen mutu 1. Diagram alir (termasuk proses dan IPC) dan deskripsi naratif proses produksi yang diajukan. 2. Laporan studi validasi proses. 3. Studi komparabilitas sebelum dan sesudah perubahan terkait sifat fisikokimia, aktivitas biologi, kemurnian, dan cemaran. 4. Studi nonklinik dan/atau klinik, jika data mutu tidak menunjukkan komparabilitas. 5. Sandingan hasil uji IPC dan *release* untuk setidaknya tiga bets berurutan Zat Aktif skala komersial, antara sebelum dan sesudah perubahan. 6. Perbandingan hasil uji stabilitas Zat Aktif jangka panjang, minimal tiga bets skala komersial yang diproduksi dengan perubahan yang diajukan (minimal tiga bulan pengujian kecuali dinyatakan lain). 7. Komitmen untuk melanjutkan studi stabilitas Zat Aktif jangka panjang.
9.	Pelebaran batas *in-process* pembuatan Zat Aktif yang disetujui.	1. Khusus Produk Biologi.	A. Dokumen mutu 1. Data ilmiah dan/atau historis untuk mendukung alasan/ justifikasi perubahan yang diajukan. 2. Informasi IPC pada tahapan kritis dan produk antara Zat Aktif. 3. Salinan atau ringkasan prosedur analisis, jika prosedur analisis baru digunakan. 4. Laporan studi validasi, jika prosedur analisis baru digunakan. 5. Perbandingan IPC atau spesifikasi sebelum dan sesudah perubahan. 6. Sandingan hasil uji IPC dan *release* untuk setidaknya tiga bets berurutan Zat Aktif skala komersial, antara sebelum dan sesudah perubahan. 7. Justifikasi batas dan uji *in-process* baru. 8. Perbandingan hasil uji stabilitas Zat Aktif jangka panjang, minimal tiga bets skala komersial yang diproduksi dengan perubahan yang diajukan (minimal tiga bulan pengujian kecuali dinyatakan lain). 9. Komitmen untuk melanjutkan studi stabilitas Zat Aktif jangka panjang.

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG DISERAHKAN
			10. Sandingan perubahan spesifikasi Zat Aktif (jika perlu).
10.	Penghapusan uji *in-process* yang dapat menimbulkan efek signifikan pada kualitas Zat Aktif secara keseluruhan.	1. Khusus Produk Biologi.	A. Dokumen mutu 1. Data ilmiah dan/atau historis untuk mendukung alasan/justifikasi perubahan yang diajukan. 2. Informasi IPC pada tahapan kritis dan produk antara Zat Aktif. 3. Perbandingan IPC atau spesifikasi sebelum dan sesudah perubahan. 4. Sandingan hasil uji IPC dan *release* untuk setidaknya tiga bets berurutan Zat Aktif skala komersial, antara sebelum dan sesudah perubahan.
11.	Penambahan atau penggantian uji *in-process* akibat isu keamanan atau mutu.	1. Khusus Produk Biologi.	A. Dokumen mutu 1. Data ilmiah dan/atau historis untuk mendukung alasan/justifikasi perubahan yang diajukan. 2. Informasi IPC pada tahapan kritis dan produk antara Zat Aktif. 3. Salinan atau ringkasan prosedur analisis, jika prosedur analisis baru digunakan. 4. Laporan studi validasi, jika prosedur analisis baru digunakan. 5. Perbandingan IPC atau spesifikasi sebelum dan sesudah perubahan. 6. Sandingan hasil uji IPC dan *release* untuk setidaknya tiga bets berurutan Zat Aktif skala komersial, antara sebelum dan sesudah perubahan. 7. Sandingan perubahan spesifikasi Zat Aktif (jika perlu).
12.	Perubahan spesies hewan/*strain* untuk uji pelulusan Zat Aktif (contohnya, spesies/*strain* baru, hewan dari umur berbeda, produsen baru dimana *genotype* hewan tersebut tidak dapat dikonfirmasi).	1. Khusus Produk Biologi.	A. Dokumen mutu 1. Data yang menggambarkan bahwa perubahan yang diajukan pada hewan/*strain* yang diajukan memberikan hasil yang *comparable* dengan data yang telah disetujui. 2. Sertifikat kelayakan hewan untuk digunakan dalam uji.
13.	Perubahan spesifikasi Zat Aktif non-Farmakope.	1. Tidak termasuk Produk Biologi. 2. Uji stabilitas Zat Aktif sudah dilakukan sesuai protokol dengan minimal dua bets skala pilot atau skala produksi dengan data minimal enam bulan memberikan hasil yang memenuhi spesifikasi.	A. Dokumen mutu 1. Spesifikasi Zat Aktif yang baru. 2. Metode analisis Zat Aktif. 3. Laporan validasi metode analisis Zat Aktif. 4. Data analisis bets Zat Aktif untuk seluruh pengujian pada spesifikasi baru (dua skala pilot/produksi). 5. Laporan stabilitas Zat Aktif dan komitmen stabilitas Zat Aktif jika laporan stabilitas Zat Aktif belum lengkap.
14.	Pelebaran batas spesifikasi *starting material/ intermediate*, yang memiliki efek signifikan pada keseluruhan kualitas dari Zat Aktif dan/atau Obat.	1. Perubahan bukan konsekuensi dari komitmen penilaian sebelumnya untuk mengkaji batas spesifikasi. 2. Perubahan bukan hasil dari kejadian yang tidak diharapkan selama proses pembuatan Zat Aktif (misal cemaran baru; perubahan	A. Dokumen mutu 1. Perbandingan spesifikasi antara yang sudah disetujui dan yang diajukan. 2. Rincian metoda analisis dan data validasi metoda analisis yang baru, jika diperlukan. 3. Analisis bets dari dua bets produksi Zat Aktif (untuk Produk Biologi: tiga

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG DISERAHKAN
		batas cemaran total). 3. Prosedur uji sama, atau berubah minor. 4. Metode uji bukan metode *biological/immunological immunochemical* atau metode yang menggunakan *biological reagent* untuk Zat Aktif biologi (tidak termasuk metode standar mikrobiologi Farmakope). 5. Setiap bahan, perubahan bukan pada *genotoxic impurity*. Jika pada Zat Aktif akhir, *residual solvent* harus sesuai dengan batas *International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)/ International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH)*, kontrol *impurity* baru harus sesuai dengan Farmakope.	bets produksi, kecuali ditentukan lain) untuk semua parameter spesifikasi. 4. Perbandingan profil disolusi Obat minimum satu bets skala pilot yang mengandung Zat Aktif dengan spesifikasi yang sudah disetujui dan yang diajukan (jika perlu). 5. Justifikasi untuk parameter dan batas spesifikasi yang baru.
15.	Penghapusan parameter uji pelulusan Zat Aktif.	1. Khusus Produk Biologi.	A. Dokumen mutu 1. Spesifikasi Zat Aktif yang diajukan. 2. Data ilmiah dan/atau historis untuk mendukung alasan/justifikasi perubahan yang diajukan. 3. Bukti konsistensi kualitas dan proses produksi dipertahankan.
16.	Pelebaran kriteria penerimaan spesifikasi pelulusan Zat Aktif.	1. Khusus Produk Biologi.	A. Dokumen mutu 1. Data ilmiah dan/atau historis untuk mendukung alasan/justifikasi perubahan yang diajukan. 2. Spesifikasi Zat Aktif yang diajukan. 3. Bukti konsistensi mutu dan proses produksi dipertahankan.
17.	Perubahan spesifikasi *shelf life* Zat Aktif.	1. Khusus Produk Biologi. 2. Untuk perubahan apapun terhadap spesifikasi *shelf life* Zat Aktif. 3. Spesifikasi Obat tidak berubah.	A. Dokumen mutu 1. Data ilmiah dan/atau historis untuk mendukung alasan/justifikasi perubahan yang diajukan. 2. Perbandingan spesifikasi pelulusan dan/atau *shelf life*, antara yang sudah disetujui dan yang diajukan dengan perubahan yang diberi tanda. 3. Stabilitas Zat Aktif minimal tiga bets skala produksi dengan spesifikasi yang diajukan dan komitmen untuk melanjutkan studi stabilitas sampai *shelf life* yang disetujui.
18.	Perubahan Eksipien pada Zat Aktif Produk Biologi.	1. Untuk setiap perubahan kualitatif atau kuantitatif Eksipien pada Zat Aktif. 2. Perubahan Eksipien tidak mempengaruhi metode uji spesifikasi pelulusan dan *shelf life* Obat. 3. Formula bets dan spesifikasi Obat tidak berubah.	A. Dokumen mutu 1. Justifikasi perubahan, diberikan berupa pengembangan farmasetik yang sesuai (termasuk aspek stabilitas dan pengawetan dengan antimikroba bila sesuai). 2. Uraian dan *flowchart* proses pembuatan Zat Aktif. 3. Spesifikasi Eksipien lama dan baru. 4. CoA Eksipien baru. 5. Sandingan spesifikasi Zat Aktif

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG DISERAHKAN
			lama dan baru. 6. Informasi yang menunjukkan komparabilitas Eksipien antara yang disetujui dan yang diajukan dalam hal karakterisasi fisiko-kimia dan profil *impurity*. 7. Stabilitas Zat Aktif dengan Eksipien baru. 8. Untuk Eksipien yang berisiko TSE, bila perlu: - *Certificate of Suitability* untuk Eksipien. - Bukti terdokumentasi yang menunjukkan bahwa risiko TSE Eksipien telah dievaluasi. 9. Spesifikasi pelulusan dan *shelf life* Obat. 10. Data analisis bets komparatif (dalam bentuk tabel) minimal tiga bets Obat yang diproduksi menggunakan Zat Aktif dengan Eksipien yang baru dan yang diajukan. 11. Hasil studi stabilitas minimal tiga bets Obat yang diproduksi menggunakan Zat Aktif dengan Eksipien yang baru sesuai pedoman stabilitas yang relevan dan surat pernyataan melanjutkan studi stabilitas sampai *shelf life* (jika perlu) dan melaporkan ke Badan Pengawas Obat dan Makanan bila ada hasil yang tidak memenuhi syarat (dengan rencana aksi) atau bila diminta oleh Badan Pengawas Obat dan Makanan.
19.	Perubahan prosedur pengujian pada kontrol proses, pelulusan dan stabilitas Zat Aktif.	1. Khusus Produk Biologi. 2. Untuk setiap perubahan prosedur pengujian untuk pelulusan atau uji stabilitas Zat Aktif. 3. Spesifikasi Zat Aktif tidak berubah.	A. Dokumen mutu 1. Uraian metode uji yang diajukan. 2. Laporan studi validasi prosedur pengujian yang diajukan. 3. Hasil uji komparatif prosedur uji antara yang disetujui dan yang diajukan.
20.	Perubahan sistem kemasan Zat Aktif.	1. Khusus Produk Biologi. 2. Untuk setiap perubahan, termasuk tipe kemasan, komposisi kualitatif dan kuantitatif, bentuk dan dimensi sistem kemasan yang bersentuhan langsung dengan Zat Aktif. 3. Untuk setiap perubahan yang tidak termasuk kategori Variasi Minor.	A. Dokumen mutu 1. Informasi bahan konstruksi dan fitur desain sistem kemasan yang diajukan. 2. Laporan studi kompatibilitas, *leaching materials, leak test*, dan lain-lain untuk menunjukkan kesesuaian penggunaan sistem kemasan yang diajukan. 3. Laporan validasi proses produksi menggunakan sistem kemasan yang diajukan (bila perlu). 4. Spesifikasi pelulusan dan *shelf life* Zat Aktif. 5. Hasil studi stabilitas yang sesuai minimal tiga bets Zat Aktif yang diproduksi menggunakan sistem kemasan yang diajukan sesuai dengan studi stabilitas yang relevan dan surat pernyataan akan melanjutkan studi stabilitas sampai *shelf life*, jika perlu, dan melaporkan ke Badan Pengawas Obat dan Makanan bila ada hasil uji yang tidak memenuhi syarat (dengan rencana aksi) atau bila diminta oleh

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG DISERAHKAN
			Badan Pengawas Obat dan Makanan.
21.	Penambahan/*update*/perubahan pada *Plasma Master File (PMF).*	1. Variasi dilakukan terhadap produk darah yang telah terdaftar. 2. Perubahan memiliki pengaruh potensial pada mutu dan keamanan produk.	A. Dokumen administratif 1. Sertifikat CPOB fasilitas pengumpulan dan pemrosesan plasma dan/atau surat pernyataaan pemenuhan aspek CPOB dari fasilitas pengumpulan dan pemrosesan plasma dalam kasus *update*/perubahan sumber plasma. B. Dokumen mutu 1. Spesifikasi pelulusan dan *shelf life* Zat Aktif. 2. Spesifikasi pelulusan dan *shelf life* Obat. 3. Data analisis bets komparatif (dalam bentuk tabel) minimal tiga bets yang diproduksi menggunakan sumber plasma yang disetujui dan sumber plasma baru. 4. Hasil studi stabilitas yang sesuai minimal tiga bets yang diproduksi menggunakan sumber PMF baru dan/atau sumber plasma baru, sesuai pedoman stabilitas yang relevan. 5. Laporan *Adventitious Agents Safety Evaluation*, jika perlu. 6. *Expert statement* yang menyebutkan garis besar perubahan yang dilakukan terhadap PMF baru atau dokumen yang berisi evaluasi terhadap pengaruh potensial perubahan PMF terhadap Obat, termasuk penilaian risiko spesifik. 7. Untuk PMF baru/berubah, harus disertai: a. PMF baru/versi baru; b. Spesifikasi plasma dan data analisis bets *plasma pool;* c. Surat resertifikasi tahunan EMA, dan bila ada laporan hasil *assessment* resertifikasi; d. *Letter of Access* yang dikeluarkan oleh *PMF holder* ke pemilik produk; dan e. Informasi pada Bagian S.2.3 yang mencakup: • Sumber dan pengumpulan plasma. • Karakteristik donasi. • Data epidemiologi mengenai *blood transmissible infections.* • Kriteria seleksi/eksklusi. • Mutu dan keamanan plasma. • Kondisi penyimpanan dan transpor plasma. • Spesifikasi plasma dan data analisis bets *plasma pool.*
E. Perubahan terkait mutu Obat			
1.	Peningkatan ukuran bets Obat lebih dari sepuluh kali.	1. Tidak termasuk Produk Biologi. 2. Formula dan spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah. 3. Hasil validasi proses sesuai bets sebelumnya yang telah disetujui.	A. Dokumen mutu 1. Proses pembuatan dan kontrol proses. 2. Formula bets. 3. *Flowchart* proses produksi dari awal sampai pengemasan akhir. 4. Hasil validasi proses pembuatan Obat.

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG DISERAHKAN
		4. Perubahan tidak mempengaruhi reprodusibilitas dan/atau konsistensi Obat. 5. Uji stabilitas sudah dilakukan sesuai protokol dengan minimal dua bets skala pilot atau skala produksi dengan data minimal enam bulan memberikan hasil yang memenuhi spesifikasi.	5. Spesifikasi Obat. 6. Hasil analisis bets Obat. 7. Perbandingan data analisis bets antara bets produksi sebelumnya (tiga bets Obat skala produksi) dan yang saat ini diajukan (minimum dari dua bets Obat skala pilot atau skala produksi). 8. Komitmen menyerahkan bets analisis skala produksi yang baru (jika yang diserahkan bets analisis skala pilot). 9. Laporan stabilitas Obat dari skala pilot atau skala produksi yang baru dan komitmen stabilitas Obat jika laporan stabilitas Obat belum lengkap.
2.	Peningkatan ukuran bets Obat hingga sepuluh kali, untuk produk steril.	1. Tidak termasuk Produk Biologi. 2. Formula dan spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah. 3. Hasil validasi proses sesuai bets sebelumnya yang telah disetujui. 4. Perubahan tidak mempengaruhi reprodusibilitas dan/atau konsistensi Obat. 5. Uji stabilitas sudah dilakukan sesuai protokol dengan minimal dua bets skala produksi dengan data minimal enam bulan memberikan hasil yang memenuhi spesifikasi.	A. Dokumen mutu 1. Proses pembuatan dan kontrol proses. 2. Formula bets. 3. *Flowchart* proses produksi dari awal sampai pengemasan akhir. 4. Hasil validasi proses pembuatan Obat dan hasil validasi proses sterilisasi. 5. Spesifikasi Obat. 6. Hasil analisis bets Obat. 7. Perbandingan data analisis bets dari minimal dua bets Obat skala produksi yang lama dan baru. 8. Laporan stabilitas Obat dari skala produksi yang baru dan komitmen stabilitas Obat jika laporan stabilitas Obat belum lengkap.
3.	Penurunan ukuran bets Obat hingga sepuluh kali, untuk produk steril.	1. Tidak termasuk Produk Biologi. 2. Formula dan spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah. 3. Hasil validasi proses sesuai bets sebelumnya yang telah disetujui. 4. Perubahan tidak mempengaruhi reprodusibilitas dan/atau konsistensi Obat. 5. Perubahan bukan karena pengaruh pada proses pembuatan Obat atau masalah stabilitas. 6. Uji stabilitas sudah dilakukan sesuai protokol dengan minimal dua bets skala produksi dengan data minimal enam bulan memberikan hasil yang memenuhi spesifikasi.	A. Dokumen mutu 1. Proses pembuatan dan kontrol proses. 2. Formula bets. 3. *Flowchart* proses produksi dari awal sampai pengemasan akhir. 4. Laporan hasil validasi proses pembuatan Obat. 5. Spesifikasi Obat. 6. Hasil analisis bets Obat. 7. Perbandingan data analisis bets dari minimal dua bets Obat skala produksi yang lama dan baru. 8. Laporan stabilitas Obat dari skala produksi yang baru dan komitmen stabilitas Obat jika laporan stabilitas Obat belum lengkap.
4.	*Scale up* proses produksi pada tahap formulasi/pengisian.	1. Khusus Produk Biologi. 2. Skala yang diajukan menggunakan peralatan yang sejenis/*comparable* dengan yang sudah disetujui. Catatan: perubahan ukuran peralatan dianggap tidak sejenis/*comparable*.	A. Dokumen mutu 1. Uraian proses produksi, jika berbeda dari proses yang disetujui dan informasi IPC tahap kritis dan pada produk antara Produk Jadi yang diajukan. 2. Informasi pengujian IPC, sesuai yang diajukan. 3. Laporan studi validasi proses

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG DISERAHKAN
		3. Perubahan lain terkait proses produksi dan/atau pada IPC hanya yang disebabkan oleh perubahan ukuran bets (contohnya, formulasi, uji dan *Standard Operating Procedure (SOP)* sama). 4. Perubahan tidak boleh disebabkan kejadian berulang selama produksi atau masalah stabilitas. 5. Tidak terdapat perubahan pada prinsip prosedur sterilisasi Produk Jadi.	(contohnya, *media fill*), sesuai yang diajukan. 4. Sandingan hasil uji pelulusan untuk setidaknya tiga bets berurutan Obat skala komersial, antara sebelum dan sesudah perubahan. 5. Perbandingan hasil uji stabilitas Obat jangka panjang, minimal tiga bets skala komersial yang diproduksi dengan perubahan yang diajukan (minimal tiga bulan pengujian kecuali dinyatakan lain). 6. Komitmen untuk melanjutkan studi stabilitas jangka panjang untuk mendukung *shelf life/holdtime* lengkap dalam kondisi penyimpanan normal dan melaporkan kepada Badan Pengawas Obat dan Makanan kegagalan apa saja yang terjadi selama studi stabilitas jangka panjang. 7. Informasi *leachables* dan *extractables*, sesuai yang diajukan.
5.	Perubahan berat penyalut tablet atau berat cangkang kapsul sediaan *gastroresistant*, modifikasinya atau sediaan lepas lambat.	1. Formula Obat (kualitatif) tidak berubah. 2. Komposisi penyalut dan cangkang kapsul tidak berubah. 3. Profil disolusi Obat tidak berubah untuk bentuk sediaan padat (bila diperlukan). 4. Spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah kecuali berat penyalut. 5. Uji stabilitas sudah dilakukan sesuai protokol dengan minimal dua bets skala pilot atau skala produksi dengan data minimal enam bulan memberikan hasil yang memenuhi spesifikasi.	A. Dokumen mutu 1. Formula bets. 2. Hasil analisis bets Obat. 3. Perbandingan data analisis bets Obat dari minimal dua bets Obat (skala pilot/produksi) dari penyalut tablet atau cangkang kapsul yang lama dan baru. 4. Hasil analisis bets Obat. 5. Laporan stabilitas Obat dua bets skala pilot dengan Formula baru dan komitmen stabilitas Obat jika laporan stabilitas Obat belum lengkap. 6. Data uji ekivalensi (*in vitro/in vivo*) (jika perlu). 7. Justifikasi tidak melakukan uji BE baru.
6.	Perubahan kuantitatif dan/atau kualitatif Eksipien.	1. Tidak termasuk Produk Biologi. 2. Tidak untuk perubahan yang memerlukan data uji klinik (khasiat dan keamanan). 3. Uji stabilitas sudah dilakukan sesuai protokol dengan minimal dua bets skala pilot atau skala produksi dengan data minimal enam bulan memberikan hasil yang memenuhi spesifikasi.	A. Dokumen mutu 1. Pengembangan farmasetika. 2. Formula bets. 3. *Flowchart* proses produksi dari awal sampai pengemasan akhir. 4. Laporan hasil validasi proses pembuatan Obat. 5. Spesifikasi dan metode pengujian Eksipien. 6. Spesifikasi Obat. 7. Prosedur analisis Obat. 8. Laporan hasil validasi metode analisis Obat. 9. Hasil analisis bets Obat. 10. Perbandingan data analisis bets Obat dari minimal dua bets (skala pilot/produksi) dari Formula lama dan baru. 11. Hasil uji keseragaman kadar (untuk *scoring* atau *breakline*). 12. Laporan stabilitas Obat dan komitmen stabilitas Obat jika laporan stabilitas Obat belum lengkap. 13. Data uji ekivalensi (*in vitro/in vivo*)

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG DISERAHKAN
			(jika perlu). 14. Justifikasi tidak melakukan uji BE.
7.	Perubahan Eksipien Produk Biologi.	1. Untuk setiap perubahan kualitatif atau kuantitatif formulasi Eksipien pada Obat. 2. Perubahan Eksipien tidak mempengaruhi metode uji spesifikasi pelulusan dan *shelf life* Obat.	A. Dokumen mutu 1. Sandingan Formula bets dan per unit dosis Obat yang disetujui dan diajukan. 2. Justifikasi perubahan harus diberikan berupa pengembangan farmasetik yang sesuai (termasuk aspek stabilitas dan pengawetan dengan antimikroba bila sesuai). 3. Informasi yang menujukkan komparabilitas Eksipien antara yang disetujui dan yang diajukan dalam hal karakterisasi fisiko-kimia dan profil *impurity*. 4. Untuk Eksipien yang berisiko TSE, bila perlu: - *Certificate of Suitability* untuk Eksipien. - Bukti terdokumentasi yang menunjukkan bahwa risiko TSE Eksipien telah dievaluasi. 5. Sandingan spesifikasi pelulusan dan *shelf life* Obat yang disetujui dan yang diajukan. 6. Perbandingan data analisis bets (dalam bentuk tabel) minimal tiga bets Obat yang diproduksi sesuai formulasi yang disetujui dan yang diajukan. 7. Hasil studi stabilitas minimal tiga bets Obat yang diproduksi dengan Formula yang diajukan sesuai pedoman stabilitas yang relevan dan surat pernyataan melanjutkan studi stabilitas sampai *shelf life*, jika perlu, dan melaporkan ke Badan Pengawas Obat dan Makanan bila ada hasil yang tidak memenuhi syarat (dengan rencana aksi) atau bila diminta oleh Badan Pengawas Obat dan Makanan.
8.	Perubahan proses produksi Obat yang dapat mempengaruhi stabilitas.	1. Tidak termasuk Produk Biologi. 2. Tidak mempengaruhi efikasi keamanan produk. 3. Validasi proses/konsistensi produksi sudah dilakukan. 4. Formula dan spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah. 5. Uji stabilitas sudah dilakukan sesuai protokol dengan minimal dua bets skala pilot atau skala produksi dengan data minimal enam bulan memberikan hasil yang memenuhi spesifikasi.	A. Dokumen mutu 1. Pengembangan farmasetika. 2. Proses pembuatan dan kontrol proses. 3. *Flowchart* proses produksi dari awal sampai pengemasan akhir. 4. Laporan hasil validasi proses pembuatan Obat. 5. Hasil analisis bets Obat. 6. Perbandingan data analisis bets antara proses produksi sebelumnya (tiga bets Obat skala produksi) dan yang saat ini diajukan (minimum dari dua bets Obat skala produksi atau satu bets Obat skala produksi dan dua bets Obat skala pilot). 7. Laporan stabilitas Obat dari dua bets Obat skala pilot dan komitmen stabilitas Obat jika laporan stabilitas Obat belum lengkap dan komitmen stabilitas Obat satu bets skala produksi.
9.	Perubahan proses pembuatan Obat di produsen Obat yang	1. Khusus Produk Biologi. 2. Untuk perubahan apapun dalam proses pembuatan	A. Dokumen mutu 1. Laporan dan ringkasan studi validasi proses pembuatan yang

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG DISERAHKAN
	sama.	dan/atau perubahan skala produksi pada setiap tahap proses pembuatan Obat. 3. Untuk perubahan apapun yang tidak terdapat dalam Variasi Minor.	diajukan. 2. Spesifikasi pelulusan dan *shelf life* Obat. 3. Data analisis bets komparatif (dalam bentuk tabel) menggunakan minimal tiga bets Obat yang diproduksi menggunakan proses yang disetujui dan yang diajukan. 4. Laporan studi stabilitas minimal tiga bets Obat yang diproduksi menggunakan proses yang diajukan sesuai pedoman stabilitas yang relevan dan surat pernyataan akan melanjutkan studi stabilitas sampai *shelf life*, jika perlu, dan melaporkan ke Badan Pengawas Obat dan Makanan bila ada hasil uji yang tidak memenuhi syarat (dengan rencana aksi) atau bila diminta oleh Badan Pengawas Obat dan Makanan. 5. Surat berisi pernyataan bahwa: a. Tidak ada perubahan dalam hal profil *impurity* kualitatif dan kuantitatif atau sifat fisikokimia; b. Perubahan tidak memberikan perubahan negatif pada reprodusibilitas proses; c. Perubahan yang dilakukan bukan akibat dari kejadian yang tidak diharapkan ketika produksi atau karena masalah stabilitas; d. Spesifikasi Obat tidak berubah.
10.	Perubahan atau penambahan tempat sebagian atau keseluruhan tahapan produksi Obat.	1. Hasil evaluasi SMF/ inspeksi (bila diperlukan) memenuhi syarat. 2. Hasil inspeksi CPOB dua tahun terakhir memuaskan. 3. Tidak ada perubahan Formula, sumber bahan baku Zat Aktif dan Eksipien, proses produksi, spesifikasi Obat, dan spesifikasi bahan kemasan. 4. Validasi proses pembuatan Obat sudah dilakukan sesuai protokol dari tiga bets Obat skala produksi, atau minimum satu bets Obat skala pilot dan komitmen validasi proses tiga bets produksi pertama dengan prediksi waktu penyerahannya. (Untuk Produk Biologi: Laporan validasi proses minimal tiga bets skala produksi). 5. Transfer metode analisis dari tempat lama ke tempat baru sudah memenuhi syarat. 6. Uji stabilitas sudah dilakukan sesuai protokol dengan minimal dua bets skala pilot atau skala produksi dengan data minimal enam bulan memberikan hasil yang memenuhi spesifikasi (Untuk Produk Biologi:	A. Dokumen administratif, Informasi Produk, dan Label 1. Informasi Produk (jika perlu). 2. Label pada kemasan (jika perlu). B. Dokumen mutu 1. Proses pembuatan dan kontrol proses. 2. *Flowchart* proses produksi dari awal sampai pengemasan akhir. 3. Laporan hasil validasi proses pembuatan Obat pada tempat baru. 4. Laporan hasil validasi/verifikasi metode analisis yang merupakan transfer metode dari tempat lama ke tempat baru. 5. Hasil analisis bets Obat. 6. Perbandingan data analisis bets antara tempat produksi sebelumnya (tiga bets Obat skala produksi) dan yang saat ini diajukan (minimum dari dua bets Obat skala produksi atau satu bets Obat skala produksi dan dua bets Obat skala pilot). 7. Perbandingan data profil disolusi antara Obat dari tempat produksi lama dan baru (jika perlu). 8. Laporan stabilitas Obat dan komitmen stabilitas Obat jika laporan stabilitas Obat belum lengkap. (Untuk Produk Biologi: laporan studi stabilitas Obat yang diproduksi di tempat baru minimal tiga bets skala produksi). 9. Data uji ekivalensi (*in vitro/in vivo*)

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG DISERAHKAN
		laporan studi stabilitas Obat di tempat baru minimal tiga bets skala produksi).	(jika perlu).
11.	Perubahan tempat pengemasan primer Obat.	1. Tidak untuk produk steril. 2. Hasil inspeksi CPOB dua tahun terakhir memuaskan. 3. Tidak ada perubahan Formula, sumber bahan baku Zat Aktif dan Eksipien, proses produksi, spesifikasi Obat, dan spesifikasi bahan kemasan. 4. Validasi proses pengemasan primer Obat sudah dilakukan sesuai protokol dari tiga bets Obat skala produksi, atau minimum satu bets Obat skala pilot dan komitmen validasi proses tiga bets produksi pertama dengan prediksi waktu penyerahannya. 5. Uji stabilitas sudah dilakukan sesuai protokol dengan minimal dua bets skala pilot atau skala produksi dengan data minimal enam bulan memberikan hasil yang memenuhi spesifikasi.	A. Dokumen administratif, Informasi Produk, dan Label 1. Informasi Produk (jika perlu). 2. Label pada kemasan (jika perlu). B. Dokumen mutu 1. *Flowchart* proses produksi dari awal sampai pengemasan akhir dan informasi lokasi tiap tahap produksi sampai pengemasan akhir. 2. Laporan hasil validasi proses pengemasan primer di tempat baru. 3. Hasil analisis bets Obat. 4. Perbandingan data analisis bets antara tempat produksi sebelumnya (tiga bets Obat skala produksi) dan yang saat ini diajukan (minimum dari dua bets Obat skala produksi atau satu bets Obat skala produksi dan dua bets Obat skala pilot). 5. Studi *bulk holding time* (jika perlu). 6. Laporan stabilitas Obat dan komitmen stabilitas Obat jika laporan stabilitas Obat belum lengkap.
12.	Perubahan spesifikasi Obat non-Farmakope.	1. Metode analisis Obat tidak berubah. 2. Uji stabilitas sudah dilakukan sesuai protokol dengan minimal dua bets skala pilot atau skala produksi dengan data minimal enam bulan memberikan hasil yang memenuhi spesifikasi.	A. Dokumen mutu 1. Spesifikasi Obat yang baru. 2. Data analisis bets Obat untuk seluruh pengujian pada spesifikasi baru (dua skala pilot/produksi). 3. Laporan stabilitas Obat dan komitmen stabilitas Obat jika laporan stabilitas Obat belum lengkap.
13.	Perubahan bentuk dan/atau dimensi kemasan primer (untuk sediaan steril).	1. Tidak ada perubahan spesifikasi bahan kemasan primer. 2. Bukan merupakan bagian penting dari bahan kemasan yang mempengaruhi distribusi, penggunaan, keamanan, atau stabilitas Obat. 3. Khusus untuk Obat dengan metode sterilisasi akhir: Validasi proses pembuatan Obat sudah dilakukan sesuai protokol dari tiga bets Obat skala produksi, atau minimum satu bets Obat skala pilot dan komitmen validasi proses tiga bets produksi pertama dengan prediksi waktu penyerahannya. 4. Untuk perubahan *"head space"* atau perubahan *"surface/ volume ratio"* : • Uji stabilitas sudah dilakukan sesuai protokol dengan minimal dua bets skala pilot atau	A. Dokumen administratif, Informasi Produk, dan Label 1. Contoh kemasan primer dalam bentuk foto atau gambar sesuai aslinya *(mock up/dummy).* B. Dokumen mutu 1. Spesifikasi dan metode pengujian bahan kemasan. 2. Laporan hasil validasi proses pembuatan Obat untuk Obat dengan proses sterilisasi akhir. 3. Laporan stabilitas Obat dan komitmen stabilitas Obat jika laporan stabilitas Obat belum lengkap.

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG DISERAHKAN
		skala produksi dengan data minimal enam bulan memberikan hasil yang memenuhi spesifikasi.	
14.	Perubahan spesifikasi pelulusan dan *shelf life* Obat.	1. Khusus Produk Biologi. 2. Untuk perubahan apapun terhadap spesifikasi pelulusan dan *shelf life* Obat.	A. Dokumen mutu 1. Justifikasi perubahan disertai data ilmiah dan/atau historis untuk mendukung perubahan yang diajukan. 2. Perbandingan spesifikasi pelulusan dan/atau *shelf life* Obat, antara yang sudah disetujui dan yang diajukan dengan perubahan yang diberi tanda. 3. Analisis bets Obat untuk semua uji dalam spesifikasi yang diajukan (minimal tiga bets). 4. Untuk setiap perubahan pada *stability-indicating parameter* dalam spesifikasi: – Hasil studi stabilitas yang sesuai minimal tiga bets Obat yang diuji sesuai spesifikasi yang diajukan sesuai pedoman stabilitas yang relevan; dan – Surat pernyataan akan melanjutkan studi stabilitas sampai *shelf life* yang disetujui, bila perlu, dan melaporkan ke Badan Pengawas Obat dan Makanan bila ada hasil uji yang tidak memenuhi syarat (dengan rencana aksi) dan bila diperlukan.
15.	Perubahan spesifikasi pada kontrol proses dalam proses pembuatan Obat.	1. Untuk perubahan apapun terhadap spesifikasi pada kontrol proses dalam proses pembuatan Produk Biologi.	A. Dokumen mutu 1. Justifikasi perubahan disertai data ilmiah dan/atau historis untuk mendukung perubahan yang diajukan. 2. Perbandingan spesifikasi pada kontrol proses antara yang sudah disetujui dan yang diajukan dengan perubahan yang diberi tanda. 3. Analisis bets untuk semua uji dalam kontrol proses yang diajukan minimal tiga bets.
16.	Pelebaran batas *in-process* yang disetujui dalam proses pembuatan Obat.	1. Khusus Produk Biologi.	A. Dokumen mutu 1. Informasi kontrol proses produksi tahap kritis dan pada produk antara antigen yang diajukan. 2. Perbaruan spesifikasi Produk Jadi jika berubah. 3. Salinan atau ringkasan prosedur analisis, jika prosedur analisis baru digunakan. 4. Laporan studi validasi, jika prosedur analisis digunakan. 5. Tabel sandingan atau deskripsi, sesuai perubahan, antara yang disetujui dan diajukan. 6. Perbandingan data analisis bets setidaknya tiga bets berurutan Obat skala komersial, antara sebelum dan sesudah perubahan. 7. Justifikasi untuk uji dan batas *in-process* baru. 8. Perbandingan hasil uji stabilitas Obat jangka panjang, minimal tiga

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG DISERAHKAN
			bets skala komersial yang diproduksi dengan perubahan yang diajukan (minimal tiga bulan pengujian kecuali dinyatakan lain).
17.	Perubahan prosedur pengujian Eksipien pada Obat.	1. Khusus Produk Biologi. 2. Untuk setiap perubahan prosedur pengujian Eksipien pada Zat Aktif. 3. Spesifikasi Zat Aktif dan Obat tidak berubah.	A. Dokumen mutu 1. Uraian metode uji yang diajukan. 2. Laporan studi validasi prosedur pengujian yang diajukan. 3. Hasil uji komparatif prosedur uji antara yang disetujui dan yang diajukan. 4. Spesifikasi Eksipien.
18.	Perubahan pada produksi Eksipien biologi (tidak termasuk *adjuvant* biologi).	1. Khusus Produk Biologi.	A. Dokumen mutu 1. Informasi rinci sumber Eksipien (contohnya, spesies hewan, negara asal) dan tahap yang dilakukan selama proses untuk meminimalkan risiko paparan TSE. 2. Perbandingan sifat fisikokimia dan profil cemaran Eksipien yang diajukan dan yang disetujui. 3. Informasi proses produksi dan pengawasan tahap kritis pada proses produksi dan pada produk antara Eksipien yang diajukan. 4. Perbandingan data analisis bets setidaknya tiga bets berurutan Eksipien skala komersial, antara sebelum dan sesudah perubahan. 5. Perbandingan hasil uji stabilitas Obat jangka panjang, minimal tiga bets skala komersial yang diproduksi dengan perubahan yang diajukan (minimal tiga bulan pengujian kecuali dinyatakan lain). 6. Komitmen untuk melanjutkan studi stabilitas Obat jangka panjang. 7. Informasi penilaian risiko mengenai potensi kontaminasi dengan *adventitious agent* (contohnya, dampak pada studi *viral clearance* atau risiko BSE/TSE) termasuk dokumentasi keamanan virus yang dibutuhkan.
19.	Perubahan produsen Eksipien bersumber plasma.	1. Khusus Produk Biologi.	A. Dokumen mutu 1. Perbandingan sifat fisikokimia dan profil cemaran Eksipien yang diajukan dan yang disetujui. 2. Informasi proses produksi dan pengawasan tahap kritis pada proses produksi dan pada produk antara Eksipien yang diajukan. 3. Perbandingan data analisis bets setidaknya tiga bets berurutan Eksipien skala komersial, antara sebelum dan sesudah perubahan. 4. Perbandingan hasil uji stabilitas Obat jangka panjang, minimal tiga bets skala komersial yang diproduksi dengan perubahan yang diajukan (minimal tiga bulan pengujian kecuali dinyatakan lain). 5. Komitmen untuk melanjutkan studi stabilitas Obat jangka panjang. 6. Informasi penilaian risiko mengenai potensi kontaminasi dengan *adventitious agent.* 7. Data lengkap produksi dan

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG DISERAHKAN
			keamanan klinik untuk mendukung penggunaan Eksipien turunan plasma manusia yang diajukan.
20.	Perubahan prosedur pengujian pada kontrol proses dalam proses pembuatan Obat.	1. Khusus Produk Biologi. 2. Untuk setiap perubahan prosedur pengujian untuk pelulusan atau uji stabilitas Obat. 3. Spesifikasi Zat Aktif dan Obat tidak berubah.	A. Dokumen mutu 1. Uraian metode uji yang diajukan. 2. Laporan studi validasi prosedur pengujian yang diajukan. 3. Hasil uji komparatif prosedur uji antara yang disetujui dan yang diajukan.
21.	Perubahan prosedur pengujian Obat untuk pelulusan/studi stabilitas.	1. Khusus Produk Biologi. 2. Untuk setiap perubahan prosedur pengujian untuk pelulusan atau uji stabilitas Obat. 3. Spesifikasi Zat Aktif dan Obat tidak berubah.	A. Dokumen mutu 1. Spesifikasi pelulusan dan *shelf life* Obat. 2. Uraian metode uji yang diajukan. 3. Laporan studi validasi prosedur pengujian yang diajukan. 4. Hasil uji komparatif prosedur uji antara yang disetujui dan yang diajukan.
22.	Perubahan sistem kemasan Obat.	1. Khusus Produk Biologi dan sediaan steril. 2. Untuk setiap perubahan, termasuk tipe kemasan, komposisi kualitatif dan kuantitatif, bentuk dan dimensi sistem kemasan yang bersentuhan langsung dengan Obat. 3. Untuk setiap perubahan yang tidak termasuk kategori Variasi Minor.	A. Dokumen mutu 1. Informasi bahan konstruksi dan fitur desain sistem kemasan yang diajukan. 2. Laporan studi kompatibilitas, *leaching materials, leak test*, dan lain-lain untuk menunjukkan kesesuaian penggunaan sistem kemasan yang diajukan. 3. Laporan validasi proses produksi menggunakan sistem kemasan yang diajukan (bila perlu). 4. Spesifikasi pelulusan dan *shelf life* Obat. 5. Perbandingan hasil uji stabilitas Obat jangka panjang, minimal tiga bets skala komersial yang diproduksi dengan perubahan yang diajukan (minimal tiga bulan pengujian kecuali dinyatakan lain). 6. Komitmen untuk melanjutkan studi stabilitas Obat jangka panjang.
23.	Perubahan sistem kemasan pelarut.	1. Khusus Produk Biologi. 2. Untuk setiap perubahan, termasuk tipe kemasan, komposisi kualitatif dan kuantitatif, bentuk dan dimensi sistem kemasan yang bersentuhan langsung dengan pelarut yang digunakan untuk rekonstitusi. 3. Untuk setiap perubahan yang tidak termasuk kategori Variasi Minor.	A. Dokumen mutu 1. Informasi bahan konstruksi dan fitur desain sistem kemasan yang diajukan. 2. Laporan studi kompatibilitas, *leaching materials*, *leak test*, dan lain-lain untuk menunjukkan kesesuaian penggunaan sistem kemasan yang diajukan. 3. Laporan validasi proses produksi menggunakan sistem kemasan yang diajukan (jika perlu). 4. Spesifikasi pelulusan dan *shelf life* pelarut. 5. Hasil studi stabilitas yang sesuai minimal tiga bets pelarut yang diproduksi menggunakan sistem kemasan yang diajukan sesuai dengan studi stabilitas yang relevan.
24.	Perubahan ukuran kemasan/besar volume dan/atau perubahan bentuk atau dimensi kemasan sediaan steril padat dan	1. Obat dengan kemasan baru konsisten dengan posologi dan lamanya pengobatan. 2. Spesifikasi Obat tidak berubah. 3. Spesifikasi bahan kemasan tidak berubah.	A. Informasi Produk dan Label 1. Informasi Produk. 2. Label pada kemasan primer dan sekunder. B. Dokumen mutu 1. Justifikasi yang menyatakan bahwa

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG DISERAHKAN
	cairan.	4. Uji stabilitas sudah dilakukan sesuai protokol dengan minimal dua bets skala pilot atau skala produksi dengan data minimal enam bulan memberikan hasil yang memenuhi spesifikasi.	besar volume sediaan yang diajukan konsisten dengan regimen dosis yang telah disetujui. 2. Laporan validasi proses, sterilisasi, dan sistem kemasan (jika perlu). 3. Sertifikat analisis bets (minimal dua bets Obat). 4. Laporan stabilitas Obat dan komitmen stabilitas Obat jika data stabilitas Obat belum lengkap.

2. KATEGORI 5 : REGISTRASI VARIASI MINOR

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG HARUS DISERAHKAN
A. Perubahan terkait Infomasi Produk dan/atau Label			
1.	Perubahan Informasi Produk.	1. Khusus Obat Generik. 2. Informasi Produk (klim yang diajukan) harus sesuai dengan yang sudah disetujui di Indonesia.	A. Informasi Produk dan Label 1. Informasi Produk. 2. Label kemasan (jika perlu). 3. Dokumen penunjang perubahan Informasi Produk yang diajukan.
2.	Perubahan nama Pendaftar/Industri Farmasi/pemberi lisensi/industri farmasi sebagai sumber impor Obat.	1. Pemilik Izin Edar tidak berubah. 2. Lokasi Pendaftar/Industri Farmasi/pemberi lisensi Obat tidak berubah.	A. Informasi Produk dan Label 1. Surat keterangan berubah nama. 2. Informasi Produk. 3. Label kemasan.
3.	Perubahan nama dagang Obat.	1. Nama Obat sesuai dengan ketentuan yang berlaku. 2. Informasi Produk, Label dan desain kemasan tidak berubah.	A. Informasi Produk dan Label 1. Informasi Produk. 2. Label kemasan primer dan sekunder.
4.	Penambahan besar kemasan.	1. Klim Informasi Produk tidak berubah. 2. Spesifikasi kemasan tidak berubah.	A. Informasi Produk dan Label 1. Informasi Produk. 2. Label kemasan sekunder.
5.	Penambahan Informasi Produk dalam bahasa Inggris/Indonesia.	1. Informasi Produk sesuai dengan yang disetujui terakhir.	A. Informasi Produk dan Label 1. Informasi Produk. 2. Label kemasan (jika perlu).
6.	Pengetatan klim yang berkaitan dengan keamanan.		A. Informasi Produk dan Label 1. Informasi Produk. B. Dokumen klinik 1. Justifikasi dan/atau dokumen penunjang lainnya sesuai perubahan yang diajukan. 2. Laporan keamanan pasca pemasaran/PSUR (jika perlu). 3. Referensi lain.
B. Perubahan terkait mutu Zat Aktif			
1.	Perubahan atau penambahan fasilitas produksi untuk *bulk* Zat Aktif atau produk antara Zat Aktif.	1. Fasilitas produksi yang diajukan merupakan lokasi produksi antigen yang telah disetujui. 2. Perubahan apapun pada proses produksi dan/atau kontrol dianggap sebagai kategori Variasi Minor atau Variasi Notifikasi. 3. Fasilitas di tempat yang baru berada dalam pengawasan pemastian mutu/kontrol kualitas yang sama. 4. Perubahan yang diajukan tidak melibatkan persyaratan *containment* tambahan.	A. Dokumen mutu 1. Justifikasi bahwa perubahan yang diajukan masuk kategori Variasi Minor. 2. Studi komparabilitas sebelum dan sesudah perubahan terkait: - sifat fisikokimia, - aktivitas biologi, - kemurnian, - cemaran, dan - kontaminan, sesuai perubahan yang diajukan. 3. Sandingan hasil uji IPC dan *release* untuk setidaknya tiga bets berurutan Zat Aktif skala komersial, antara sebelum dan sesudah perubahan. 4. Perbandingan hasil uji stabilitas Zat Aktif, minimal tiga bets skala komersial yang diproduksi dengan perubahan yang diajukan dalam kondisi jangka panjang (minimum tiga bulan pengujian kecuali dinyatakan lain). 5. Komitmen untuk melanjutkan studi stabilitas jangka panjang untuk mendukung *shelf life/hold time*

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG HARUS DISERAHKAN
			lengkap dalam kondisi penyimpanan normal dan melaporkan kepada Badan Pengawas Obat dan Makanan kegagalan apa saja yang terjadi selama studi stabilitas jangka panjang.
2.	Perubahan minor pada proses pembuatan Zat Aktif.	1. Tidak termasuk Zat Aktif biologi. 2. Tidak ada perubahan kualitatif dan kuantitatif dari profil *impurity*/fisika kimia. 3. Rute sintesis tetap sama (misal: senyawa antara tidak berubah). 4. Spesifikasi dan stabilitas Zat Aktif atau produk antara tidak berubah. 5. Proses pembuatan Zat Aktif tidak menggunakan bahan baku yang bersumber manusia/hewan dimana memerlukan keamanan viral.	A. Dokumen mutu 1. Karakterisasi Zat Aktif. 2. Uraian sintesis Zat Aktif. 3. Hasil analisis Zat Aktif. 4. Perbandingan data analisis bets Zat Aktif minimal dua bets (skala pilot/produksi) yang diproduksi menurut proses pembuatan Zat Aktif lama dan baru. 5. Untuk Zat Aktif steril, laporan hasil validasi proses produksi (jika perlu).
3.	Perubahan minor pada proses pembuatan Zat Aktif.	1. Khusus Produk Biologi. 2. Berlaku untuk setiap perubahan minor dalam prosedur dan/atau skala produksi pada tahap manapun produksi Zat Aktif. 3. Terkait perubahan proses yang tidak kritis, seperti perubahan prosedur *harvesting* dan/atau *pooling* tanpa perubahan metode produksi, perolehan kembali, kondisi penyimpanan atau skala produksi; duplikasi *fermentation strain*, penambahan bioreaktor yang identik atau similar/ *comparable*. 4. Tidak ada perubahan bersifat prinsip pada prosedur sterilisasi. 5. Tidak ada perubahan spesifikasi diluar yang sudah disetujui. 6. Tidak ada perubahan dalam profil *impurity* Zat Aktif diluar batas yang telah disetujui. 7. Perubahan tidak disebabkan karena kejadian berulang yang terjadi selama proses pembuatan atau karena masalah stabilitas. 8. Perubahan tidak berdampak pada data *viral clearance* atau sifat kimia *inactivating agent*.	A. Dokumen mutu 1. Justifikasi perubahan. 2. Justifikasi kategori perubahan yang berkaitan dengan dampaknya terhadap mutu antigen. 3. Ringkasan perubahan proses dikaitkan dengan proses yang disetujui dalam bentuk tabel. 4. Diagram alir (termasuk proses dan IPC) dan deskripsi naratif proses produksi yang diajukan. 5. Sertifikat BSE/TSE (bila menggunakan bahan yang berisiko BSE/TSE) contohnya *ruminant origin*, atau informasi dan bukti bahwa material tidak berpotensi menimbulkan risiko BSE/TSE. 6. Validasi perubahan proses (bila perlu). 7. Untuk perubahan proses pembuatan Zat Aktif, komparabilitas Zat Aktif dalam hal karakterisasi fisikokimia, aktivitas biologi dan profil *impurity*. 8. Data analisis bets komparatif (dalam bentuk tabel) minimal tiga bets yang diproduksi menggunakan proses yang disetujui dan yang diajukan. 9. Studi stabilitas menggunakan minimal tiga bets Zat Aktif (skala pilot atau skala produksi) sesuai pedoman stabilitas yang relevan atau komitmen untuk melakukan studi stabilitas yang sesuai dan melaporkan ke Badan Pengawas Obat dan Makanan bila ada hasil uji yang tidak memenuhi syarat atau bila diminta oleh Badan Pengawas Obat dan Makanan. 10. Komitmen untuk menyerahkan laporan studi stabilitas Obat sesuai perubahan yang diajukan.

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG HARUS DISERAHKAN
4.	Pelebaran batas spesifikasi *in process* Zat Aktif.	1. Tidak ada perubahan spesifikasi Zat Aktif. 2. Tidak ada perubahan profil cemaran Zat Aktif diluar batas yang disetujui. 3. Perubahan bukan karena kejadian berulang selama produksi atau masalah stabilitas.	A. Dokumen mutu 1. Informasi kontrol yang dilakukan pada tahap kritis produksi dan pada produk antara Zat Aktif yang diajukan. 2. Sandingan uji/kriteria penerimaan IPC antara yang disetujui dan diajukan. 3. Sandingan hasil uji IPC dan *release* untuk setidaknya tiga bets Zat Aktif skala komersial, antara sebelum dan sesudah perubahan. 4. Justifikasi batas dan uji *in-process* baru. 5. Perbandingan hasil uji stabilitas Zat Aktif, minimal tiga bets skala komersial yang diproduksi dengan perubahan yang diajukan dalam kondisi jangka panjang (minimum tiga bulan pengujian kecuali dinyatakan lain). 6. Komitmen untuk melanjutkan studi stabilitas jangka panjang untuk mendukung *shelf life/hold time* lengkap dalam kondisi penyimpanan normal dan melaporkan kepada Badan Pengawas Obat dan Makanan kegagalan apa saja yang terjadi selama studi stabilitas jangka panjang.
5.	Penambahan atau penggantian peralatan dalam proses pembuatan Obat (contohnya, *formulation tank, filter housing, filling line and head*, dan *lyophilizer*).	1. Khusus Produk Biologi.	A. Dokumen mutu 1. Uraian proses produksi, jika berbeda dari proses yang disetujui dan informasi pengawasan proses produksi tahap kritis dan produk antara Produk Jadi yang diajukan. 2. Informasi pengujian IPC, sesuai yang diajukan. 3. Laporan studi validasi proses sesuai yang diajukan. 4. Data analisis bets (dalam tabel) minimal tiga bets Obat sebelum dan sesudah perubahan. 5. Perbandingan hasil uji stabilitas Obat jangka panjang, minimal tiga bets skala komersial yang diproduksi dengan perubahan yang diajukan (minimal tiga bulan pengujian kecuali dinyatakan lain). 6. Komitmen untuk melanjutkan studi stabilitas Obat jangka panjang. 7. Informasi *leachables* dan *extractables*, sesuai yang diajukan. 8. Informasi peralatan baru dan perbandingan kesamaan dan perbedaan prinsip operasional dan spesifikasi antara yang disetujui dan yang diajukan.
6.	Perubahan metode analisis Zat Aktif (nonkompendial).	1. Tidak termasuk Produk Biologi. 2. Spesifikasi Zat Aktif tidak berubah. 3. Spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah.	A. Dokumen mutu 1. Metode analisis Zat Aktif. 2. Laporan hasil validasi metode analisis yang lama dan baru. 3. Laporan hasil uji kesesuaian metode analisis lama dan baru.
7.	Perubahan spesifikasi IPC dalam proses pembuatan	1. Perubahan bukan konsekuensi dari komitmen penilaian sebelumnya untuk	A. Dokumen mutu 1. Tabel sandingan uji *in-process* yang disetujui dan yang diajukan.

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG HARUS DISERAHKAN
	Zat Aktif.	mengkaji batas spesifikasi. 2. Perubahan bukan hasil dari kejadian yang tidak diharapkan selama proses pembuatan Zat Aktif, contohnya cemaran baru; perubahan batas cemaran total. 3. Perubahan harus dalam rentang batas yang telah disetujui. 4. Prosedur uji sama atau berubah minor. 5. Metode uji baru tidak melibatkan teknik nonstandar baru atau teknik standar yang digunakan secara baru.	2. Rincian metode analisis non-Farmakope dan data validasi yang baru, jika perlu. 3. Analisis bets dari dua bets produksi Zat Aktif (khusus Produk Biologi tiga bets produksi, kecuali ditentukan lain) untuk semua parameter spesifikasi.
8.	Perpanjangan periode *retest*/penyimpanan Zat Aktif.	1. Perubahan bukan karena kejadian yang tidak diharapkan saat proses pembuatan atau karena stabilitas. 2. Perubahan tidak berhubungan dengan pelebaran kriteria penerimaan dari parameter yang diuji, penghilangan parameter stabilitas atau pengurangan frekuensi pengujian.	A. Dokumen mutu 1. Data uji stabilitas Zat Aktif. 2. Spesifikasi Zat Aktif.
9.	Peningkatan ukuran bets Zat Aktif/*intermediate* lebih dari sepuluh kali.	1. Zat Aktif tidak termasuk Produk Biologi/zat imunologi atau steril. 2. Perubahan tidak mempengaruhi reprodusibilitas proses. 3. Perubahan bukan karena kejadian yang tidak diharapkan saat proses pembuatan atau karena stabilitas. 4. Spesifikasi Zat Aktif/*intermediate* tidak berubah. 5. Hasil analisis dari minimal dua bets sesuai dengan spesifikasi harus tersedia untuk besar bets yang diajukan. 6. Perubahan pada metode pembuatan yang mengharuskan untuk melakukan *scale up*, contohnya penggunaan peralatan/mesin yang berbeda ukuran.	A. Dokumen mutu 1. Spesifikasi Zat Aktif/*intermediate*. 2. Perbandingan data analisis bets (dalam bentuk tabel) Zat Aktif/*intermediate* produksi sebelumnya dan yang saat ini diajukan (minimum dari satu bets skala produksi). Data dari dua bets skala produksi berikutnya harus tersedia dan dilaporkan apabila diluar spesifikasi.
10.	Penambahan atau perubahan tempat pengujian Zat Aktif termasuk pengujian untuk studi stabilitas dan kontrol proses.	1. Khusus Produk Biologi. 2. Prosedur pengujian tidak berubah. 3. Spesifikasi Zat Aktif tidak berubah. 4. Hasil validasi memenuhi syarat. 5. Transfer metode analisis telah memenuhi syarat.	A. Dokumen mutu 1. Ringkasan studi validasi pengujian di tempat pengujian baru. 2. Data hasil pengujian minimal tiga bets yang diuji di tempat yang sudah disetujui dan yang diajukan. 3. Informasi dan spesifikasi baku pembanding. 4. Khusus untuk perubahan tempat uji stabilitas, laporan uji stabilitas di

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			tempat pengujian baru.
11.	Penambahan atau perubahan kondisi penyimpanan Zat Aktif (contohnya, perluasan atau penyempitan kriteria suhu).	1. Khusus Produk Biologi.	A. Dokumen mutu 1. Kondisi penyimpanan dan *shelf life* yang diajukan. 2. Hasil uji stabilitas (berupa, data stabilitas jangka panjang lengkap selama *shelf life* yang diajukan pada setidaknya tiga bets skala komersial.
12.	Pengurangan atau penghilangan *overage*.	1. Perubahan merupakan *overage* bahan aktif yang sebelumnya telah disetujui. 2. Spesifikasi pelulusan dan *shelf life* dari produk Obat tidak berubah.	A. Dokumen mutu 1. Justifikasi dari perubahan yang diajukan. 2. Tabel sandingan dari Formula yang diajukan dan Formula yang disetujui. 3. Hasil pengujian (*Certificate of Analysis/CoA*) dari dua bets produk Obat. 4. Laporan stabilitas Obat dan komitmen stabilitas Obat jika data stabilitas Obat belum lengkap.
C. Perubahan terkait mutu Obat			
1.	Perubahan industri penanggung jawab pelulusan bets (tidak termasuk pengujian Obat).	1. Khusus Obat impor. 2. Berlaku untuk satu *mother company*.	A. Informasi Produk dan Label 1. Informasi Produk. 2. Label pada kemasan.
2.	Perubahan industri penanggung jawab pelulusan bets (termasuk pengujian Obat).	1. Tidak termasuk Produk Biologi. 2. Khusus Obat impor. 3. Berlaku untuk satu *mother company*. 4. Transfer metode analisis dari tempat lama ke tempat baru sudah memenuhi syarat.	A. Informasi Produk dan Label 1. Informasi Produk. 2. Label pada kemasan. B. Dokumen mutu 1. Laporan hasil validasi/verifikasi metode analisis yang merupakan transfer dari tempat lama ke tempat baru. 2. Data analisis bets (minimal dua bets Obat skala pilot) di tempat pengujian yang baru dan lama.
3.	Perubahan atau penambahan tempat pengujian Obat.	1. Pemilik produk dan tempat pelulusan bets tetap sama. 2. Tempat pengujian sudah terdaftar. 3. Transfer metode analisis Obat dari tempat lama ke tempat baru sudah memenuhi syarat. 4. Spesifikasi Obat tidak berubah.	A. Dokumen mutu 1. Hasil analisis bets Obat yang baru. 2. Spesifikasi Obat. 3. Baku pembanding. 4. Hasil analisis bets Obat. 5. Laporan transfer metode analisis Obat.
4.	Peningkatan dan/atau penurunan ukuran bets Obat hingga sepuluh kali, untuk bentuk sediaan tablet biasa dan cairan oral.	1. Tidak termasuk Produk Biologi. 2. Perubahan tidak mempengaruhi spesifikasi Obat; harus melaporkan setiap perubahan cara pembuatan dan/atau kontrol proses yang dilakukan terhadap perubahan yang terkait dengan ukuran bets misalnya penggunaan alat dengan besar berbeda. 3. Hasil validasi proses sesuai bets sebelumnya yang telah disetujui. 4. Perubahan tidak mempengaruhi	A. Dokumen mutu 1. Proses pembuatan dan kontrol proses. 2. Formula bets. 3. Spesifikasi Obat. 4. Hasil analisis bets Obat. 5. Perbandingan data analisis bets minimal dua bets Obat (skala produksi) dari bets lama dan baru. 6. Laporan stabilitas Obat dari skala produksi yang baru dan komitmen stabilitas Obat jika laporan stabilitas Obat belum lengkap.

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG HARUS DISERAHKAN
		reprodusibilitas dan/atau konsistensi Obat. 5. Perubahan bukan karena pengaruh pada proses pembuatan Obat atau masalah stabilitas.	
5.	Perubahan satu komponen Eksipien dengan Eksipien lain dengan karakteristik fungsional yang sama.	1. Tidak termasuk sediaan lepas termodifikasi dan sediaan steril. 2. Tidak termasuk sediaan yang memerlukan uji klinik, termasuk uji bioekivalensi. 3. Validasi proses pembuatan Obat sudah dilakukan sesuai protokol dari tiga bets Obat skala produksi, atau minimum satu bets Obat skala pilot dan komitmen validasi proses tiga bets produksi pertama dengan prediksi waktu penyerahannya. 4. Spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah. 5. Uji stabilitas sudah dilakukan sesuai protokol dengan minimal dua bets skala pilot atau skala produksi dengan data minimal tiga bulan memberikan hasil yang memenuhi spesifikasi.	A. Dokumen mutu 1. Jika bersumber dari hewan disertai dengan informasi sumber hewan dan surat keterangan bebas BSE/TSE. 2. Laporan hasil validasi proses pembuatan Obat. 3. Data uji disolusi terbanding Formula lama dan baru. 4. Laporan stabilitas Obat dan komitmen stabilitas Obat jika laporan stabilitas Obat belum lengkap. 5. Justifikasi tidak melakukan uji BE.
6.	Perubahan Eksipien untuk Obat yang termasuk indeks terapi sempit atau *Biopharmaceutics Classification System (BCS)* Kelas 4 yang tidak memerlukan uji BE.	1. Profil disolusi Obat Formula baru sebanding dengan Formula lama. 2. Validasi proses pembuatan Obat sudah dilakukan sesuai protokol dari tiga bets Obat skala produksi, atau minimum satu bets Obat skala pilot dan komitmen validasi proses tiga bets produksi pertama dengan prediksi waktu penyerahannya. 3. Spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah. 4. Uji stabilitas sudah dilakukan sesuai protokol dengan minimal dua bets skala pilot atau skala produksi dengan data minimal tiga bulan memberikan hasil yang memenuhi spesifikasi.	A. Dokumen mutu 1. Data uji disolusi terbanding Formula lama dan baru. 2. Laporan hasil validasi proses pembuatan Obat. 3. Perbandingan data analisis bets antara bets produksi sebelumnya (dua bets Obat skala produksi) dan yang saat ini diajukan (minimum dari dua bets Obat skala produksi atau satu bets skala produksi dan dua bets pilot). 4. Komitmen menyerahkan bets analisis skala produksi yang baru (jika yang diserahkan bets analisis skala pilot). 5. Laporan stabilitas Obat dan komitmen stabilitas Obat jika laporan stabilitas Obat belum lengkap. 6. Justifikasi tidak melakukan uji BE.
7.	Perubahan produsen cangkang kapsul.	1. Spesifikasi Obat tidak berubah. 2. Formula dan proses produksi Obat tidak berubah. 3. Uji stabilitas sudah dilakukan sesuai protokol dengan minimal dua bets skala pilot atau skala produksi dengan data minimal enam bulan	A. Dokumen mutu 1. Spesifikasi cangkang kapsul. 2. Sertifikat analisis cangkang kapsul. 3. Informasi sumber gelatin sebagai bahan baku cangkang kapsul. 4. Sertifikat bebas BSE/TSE. 5. Data uji disolusi terbanding minimal satu bets skala pilot antara Obat dengan produsen cangkang kapsul yang diajukan dengan yang disetujui (jika perlu).

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG HARUS DISERAHKAN
		memberikan hasil yang memenuhi spesifikasi. 4. Tidak berlaku untuk perubahan dari kapsul keras ke kapsul lunak.	6. Hasil analisis bets Obat.
8.	Perubahan ukuran cangkang kapsul.	1. Formula Obat, spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah (kecuali pemerian). 2. Material cangkang kapsul sama dengan material dari cangkang kapsul sebelumnya. 3. Hanya untuk kapsul lepas cepat.	A. Dokumen mutu 1. Pemerian dan Formula. 2. Hasil analisis bets Obat. 3. Perbandingan data analisis bets Obat minimal dua bets Obat skala produksi dari cangkang kapsul lama dan baru. 4. Spesifikasi kapsul. 5. Komposisi cangkang kapsul. 6. Informasi sumber gelatin sebagai bahan baku cangkang kapsul. 7. Sertifikat analisis cangkang kapsul. 8. Sertifikat bebas BSE/TSE. 9. Data uji disolusi terbanding minimal satu bets skala pilot antara Obat dengan cangkang kapsul yang diajukan dan disetujui (jika perlu).
9.	Bentuk atau dimensi tablet *gastroresistant*, tablet lepas lambat, dan *scored tablet.*	1. Spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah (kecuali dimensi). 2. Profil disolusi Obat dimensi baru sebanding dengan Obat sebelumnya (bila dipersyaratkan dalam monografi). 3. Formula secara kualitatif dan kuantitatif dan berat rata-rata tidak berubah.	A. Dokumen mutu 1. Spesifikasi Obat (termasuk gambar dan uraian dimensi yang disetujui dan diajukan). 2. Perbandingan profil disolusi baru dan lama (jika perlu). 3. Informasi Produk (jika perlu). 4. Hasil analisis bets Obat. 5. Perbandingan data analisis bets Obat minimal dua bets Obat (skala pilot/produksi) dari bentuk atau dimensi lama dan baru. 6. Hasil uji keseragaman kadar (untuk *scoring* atau *breakline tablet*). 7. Jusitifikasi tidak melakukan uji BE.
10.	Bentuk atau dimensi tablet lepas cepat, kapsul, supositoria atau pesari.	1. Tidak berlaku untuk *scored tablet.* 2. Spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah (kecuali dimensi). 3. Profil disolusi Obat dimensi baru sebanding dengan Obat sebelumnya (bila dipersyaratkan dalam monografi). 4. Formula secara kualitatif dan kuantitatif dan berat rata-rata tidak berubah.	A. Informasi Produk dan Label 1. Informasi Produk (jika perlu). 2. Label pada kemasan (jika perlu). B. Dokumen mutu 1. Spesifikasi Obat (termasuk gambar dan uraian dimensi yang disetujui dan diajukan). 2. Perbandingan data profil disolusi baru dan lama (jika perlu). 3. Hasil analisis bets Obat. 4. Perbandingan data analisis bets Obat minimal dua bets Obat skala produksi dari bentuk atau dimensi lama dan baru.
11.	Perubahan minor pada proses pembuatan Obat.	1. Khusus Produk Biologi. 2. Berlaku untuk setiap perubahan minor dalam prosedur dan/atau skala produksi pada tahap manapun produksi Obat. 3. Terkait perubahan proses yang tidak kritis, seperti: perubahan tanpa perubahan metode produksi, kondisi penyimpanan atau skala produksi. 4. Peningkatan skala produksi aseptik untuk Obat tanpa	A. Dokumen mutu 1. Ringkasan perubahan proses dikaitkan dengan proses yang disetujui dalam bentuk tabel. 2. Justifikasi perubahan. 3. Validasi perubahan proses (jika perlu). 4. Data analisis bets komparatif (dalam bentuk tabel) minimal tiga bets yang diproduksi menggunakan proses yang disetujui dan yang diajukan. 5. Studi stabilitas menggunakan minimal tiga bets Zat Aktif (skala pilot atau skala produksi) sesuai pedoman stabilitas yang relevan

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG HARUS DISERAHKAN
		perubahan peralatan, misalnya perubahan dalam jumlah vial yang diisi. 5. Tidak ada perubahan bersifat prinsip pada prosedur sterilisasi. 6. Tidak ada perubahan spesifikasi diluar yang sudah disetujui. 7. Perubahan tidak disebabkan karena kejadian berulang yang terjadi selama proses pembuatan atau karena masalah stabilitas.	atau komitmen untuk melakukan studi stabilitas yang sesuai dan melaporkan ke Badan Pengawas Obat dan Makanan bila ada hasil uji yang tidak memenuhi syarat atau bila diminta oleh Badan Pengawas Obat dan Makanan.
12.	Penambahan tahap baru dalam proses pembuatan Obat.	1. Khusus Produk Biologi. 2. Perubahan tidak boleh disebabkan kejadian berulang selama produksi atau masalah stabilitas.	A. Dokumen mutu 1. Uraian proses produksi, jika berbeda dari proses yang disetujui dan informasi pengawasan proses produksi tahap kritis dan produk antara Produk Jadi yang diajukan. 2. Informasi pengujian IPC, sesuai yang diajukan. 3. Laporan studi validasi proses (contohnya, *media fill*), sesuai yang diajukan. 4. Sandingan hasil uji *release* untuk setidaknya tiga bets berurutan Obat skala komersial, antara sebelum dan sesudah perubahan. 5. Perbandingan hasil uji stabilitas Obat, minimal tiga bets skala komersial yang diproduksi dengan perubahan yang diajukan dalam kondisi jangka panjang (minimum tiga bulan pengujian kecuali dinyatakan lain). 6. Informasi *leachables* dan *extractables*, sesuai yang diajukan.
13.	Penambahan atau penggantian uji *in-process* karena isu keamanan atau kualitas.	1. Khusus Produk Biologi. 2. Spesifikasi Obat tidak berubah.	A. Dokumen mutu 1. Justifikasi perubahan disertai data ilmiah dan/atau historis untuk mendukung perubahan yang diajukan. 2. Informasi pengawasan proses produksi tahap kritis dan pada produk antara antigen yang diajukan. 3. Prosedur analisis, jika digunakan prosedur analisis baru. 4. Laporan studi validasi, jika digunakan prosedur analisis. 5. Tabel sandingan atau deskripsi, sesuai perubahan, antara yang disetujui dan yang diajukan. 6. Sandingan hasil uji pelulusan untuk setidaknya tiga bets berurutan Obat skala komersial, antara sebelum dan sesudah perubahan.
14.	Penghilangan pelarut untuk produk Obat.	1. Perubahan yang diajukan tidak mengakibatkan perubahan pada bentuk sediaan, dosis, indikasi dan cara pemberian Obat.	A. Dokumen mutu 1. Informasi Produk dan Label yang telah mencantumkan perubahan yang diajukan (jika perlu). 2. Justifikasi penghilangan pelarut, termasuk pernyataan yang menunjukan cara alternatif untuk mendapatkan pelarut.

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG HARUS DISERAHKAN
15.	Perubahan metode analisis Obat.	1. Tidak termasuk Produk Biologi. 2. Spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah.	A. Dokumen mutu 1. Metode analisis Obat. 2. Laporan hasil validasi metode analisis Obat yang baru. 3. Laporan hasil uji kesesuaian metode analisis Obat lama dan baru.
16.	Perubahan sistem kemasan Obat.	1. Tidak termasuk Produk Biologi dan sediaan steril. 2. Untuk setiap perubahan jenis kemasan yang bersentuhan langsung dengan Obat. 3. Uji stabilitas sudah dilakukan sesuai protokol dengan minimal dua bets skala pilot atau skala produksi dengan data minimal tiga bulan memberikan hasil yang memenuhi spesifikasi.	A. Dokumen mutu 1. Spesifikasi dan metode pengujian bahan kemasan. 2. Laporan studi kompatibilitas, *leak test* untuk menunjukkan kesesuaian penggunaan sistem kemasan yang diajukan. 3. Spesifikasi pelulusan dan *shelf life* Obat. 4. Laporan stabilitas Obat dan komitmen stabilitas Obat jika laporan stabilitas Obat belum lengkap.
17.	Perubahan bentuk dan/atau dimensi kemasan primer (untuk sediaan nonsteril).	1. Tidak ada perubahan spesifikasi bahan kemasan primer. 2. Bukan merupakan bagian penting dari bahan kemasan yang mempengaruhi distribusi, penggunaan, keamanan, atau stabilitas Obat. 3. Untuk perubahan *"head space"* atau perubahan *"surface/volume ratio"*: • Uji stabilitas sudah dilakukan sesuai protokol dengan minimal dua bets skala pilot atau skala produksi dengan data minimal enam bulan memberikan hasil yang memenuhi spesifikasi.	A. Informasi Produk dan Label 1. Label kemasan primer, termasuk *mock up.* B. Dokumen mutu 1. Spesifikasi dan metode pengujian bahan kemasan. 2. Laporan stabilitas Obat dan komitmen stabilitas Obat jika laporan stabilitas Obat belum lengkap.
18.	Perubahan besar volume sediaan nonparenteral multi dosis.	1. Klim Informasi Produk tidak berubah. 2. Obat dengan kemasan baru konsisten dengan posologi dan lamanya pengobatan. 3. Spesifikasi Obat tidak berubah. 4. Spesifikasi bahan kemasan tidak berubah. 5. Uji stabilitas sudah dilakukan sesuai protokol dengan minimal dua bets skala pilot atau skala produksi dengan data minimal tiga bulan memberikan hasil yang memenuhi spesifikasi.	A. Informasi Produk dan Label 1. Informasi Produk. 2. Label pada kemasan primer dan sekunder. B. Dokumen mutu 1. Justifikasi yang menyatakan bahwa besar volume sediaan yang diajukan konsisten dengan regimen dosis yang telah disetujui. 2. Laporan stabilitas Obat dan komitmen stabilitas Obat jika data stabilitas Obat belum lengkap.
19.	Penambahan tempat pengujian stabilitas.	1. Spesifikasi *shelf life* dan metode pengujian Obat tidak berubah.	A. Dokumen mutu 1. Spesifikasi dan metode pengujian terhadap Obat. 2. Laporan validasi/verifikasi metode analisis Obat. 3. Spesifikasi Obat. 4. Baku pembanding. 5. Laporan stabilitas Obat di tempat pengujian baru.

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG HARUS DISERAHKAN
20.	Perubahan kondisi penyimpanan Obat, termasuk produk yang direkonstitusi.	1. Spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah. 2. Uji stabilitas telah dilakukan sesuai protokol yang disetujui, dan memenuhi syarat spesifikasi. 3. Perubahan bukan karena pengaruh pada proses pembuatan Obat atau karena masalah stabilitas.	A. Informasi Produk dan Label 1. Informasi Produk. 2. Label pada kemasan. B. Dokumen mutu 1. Spesifikasi Obat. 2. Laporan stabilitas Obat sesuai kondisi penyimpanan Obat yang diajukan.
21.	Perpanjangan batas kedaluwarsa Obat: Kemasan belum dibuka.	1. Spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah. 2. Uji stabilitas telah dilakukan sesuai protokol yang disetujui, dan memenuhi syarat spesifikasi. 3. Perubahan bukan karena pengaruh pada proses pembuatan Obat atau karena masalah stabilitas. 4. Batas kedaluwarsa tidak boleh lebih dari lima tahun.	A. Informasi Produk dan Label 1. Informasi Produk (jika perlu). B. Dokumen mutu 1. Spesifikasi Obat. 2. Laporan stabilitas Obat sesuai batas kedaluwarsa yang diajukan.
22.	Perpanjangan batas kedaluwarsa Obat: Setelah kemasan dibuka atau setelah rekonstitusi.	1. Spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah. 2. Uji stabilitas telah dilakukan sesuai protokol yang disetujui, dan memenuhi syarat spesifikasi.	A. Informasi Produk dan label 1. Informasi Produk. B. Dokumen mutu 1. Spesifikasi Obat. 2. Laporan stabilitas Obat setelah kemasan dibuka atau setelah rekonstitusi sesuai batas kedaluwarsa yang diajukan.

3. KATEGORI 6 : REGISTRASI VARIASI NOTIFIKASI

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG HARUS DISERAHKAN
A. Perubahan terkait Informasi Produk dan/atau Label			
1.	Perubahan atau penambahan logo (termasuk logo perusahaan).	1. Klim Informasi Produk tidak berubah. 2. Spesifikasi kemasan tidak berubah.	A. Informasi Produk dan Label 1. Foto kemasan primer dan sekunder dari semua sisi dan contoh kemasan siap edar (termasuk Informasi Produk).
2.	Penambahan klim efek samping dan/atau kontraindikasi pada Informasi Produk.		A. Informasi Produk dan Label 1. Foto kemasan primer dan sekunder dari semua sisi dan contoh kemasan siap edar (termasuk Informasi Produk). B. Dokumen klinik 1. Justifikasi dan/atau dokumen penunjang lainnya sesuai perubahan yang diajukan. 2. Laporan keamanan pasca pemasaran/PSUR (jika perlu). 3. Referensi lain.
3.	Pengurangan tempat produksi (termasuk Zat Aktif, produk antara atau Obat, lokasi pengemasan, tempat pelulusan bets).	1. Masih terdapat tempat produksi dengan fungsi/ peruntukan yang sama (termasuk Zat Aktif, produk antara atau Obat, lokasi pengemasan, tempat pelulusan bets) yang telah disetujui. 2. Pengurangan tempat produksi bukan karena faktor kritis terkait proses produksi.	A. Informasi Produk dan Label 1. Sertifikat Izin Edar Obat (asli) atau surat persetujuan Registrasi Variasi sesuai perubahan terkait.
4.	Perubahan nama Zat Aktif.	1. Zat Aktif tidak berubah. 2. Nama baru Zat Aktif harus sesuai dengan *International Nonproprietary Names Modified (INNM).*	A. Dokumen administratif, Informasi Produk dan Label 1. Bukti perubahan nama Zat Aktif. 2. Foto kemasan primer dan sekunder dari semua sisi dan contoh kemasan siap edar (termasuk Informasi Produk).
5.	Perubahan pada bagian dari kemasan primer yang tidak kontak dengan Obat (seperti warna *flip-off caps*, warna *ring* pada ampul, perubahan pada pelindung jarum (digunakan plastik yang berbeda).	1. Bukan merupakan bagian penting dari bahan kemasan yang mempengaruhi distribusi, penggunaan, keamanan, atau stabilitas Obat. 2. Spesifikasi bahan kemasan primer yang kontak dengan Obat tidak berubah.	A. Dokumen mutu 1. Spesifikasi dan metode pengujian bahan kemasan.
6.	Penghilangan bahasa asing dari Label Obat.	1. Klim Informasi Produk tidak berubah.	A. Informasi Produk dan Label 1. Foto kemasan primer dan sekunder dari semua sisi dan contoh kemasan siap edar (termasuk Informasi Produk).
7.	Perubahan bentuk dan/atau dimensi kemasan sekunder.	1. Tidak ada perubahan spesifikasi bahan kemasan kecuali bentuk dan/atau dimensi. 2. Klim Informasi Produk tidak berubah.	A. Informasi Produk dan Label 1. Foto kemasan sekunder dari semua sisi dan contoh kemasan siap edar. B. Dokumen mutu 1. Spesifikasi bahan kemasan.
8.	Perubahan desain kemasan.	1. Klim Informasi Produk dan klim Label tidak berubah. 2. Hanya berlaku untuk	A. Informasi Produk dan Label 1. Foto kemasan primer dan sekunder dari semua sisi dan contoh kemasan

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		perubahan letak teks dan gambar, warna, dan garis. 3. Tidak termasuk perubahan gambar. 4. Tidak mengandung kalimat/informasi yang bersifat promotif.	siap edar (termasuk Informasi Produk).
9.	Perubahan alamat (redaksional) Pendaftar/Industri Farmasi/pemberi lisensi.	1. Lokasi Pendaftar/Industri Farmasi/pemberi lisensi tidak berubah. 2. Tidak termasuk perubahan nama kota/kabupaten.	A. Dokumen administratif, Informasi Produk dan Label 1. Surat keterangan berubah alamat. 2. Foto kemasan primer dan sekunder dari semua sisi dan contoh kemasan siap edar (termasuk Informasi Produk).
10.	Perubahan sistem penomoran bets.		A. Informasi Produk dan Label 1. Penjelasan sistem penomoran bets yang baru.
11.	Perubahan Informasi Produk dan/atau Label berdasarkan keputusan pemerintah.	1. Informasi Produk dan/atau Label sesuai keputusan pemerintah.	A. Informasi Produk dan Label 1. Foto kemasan primer dan sekunder dari semua sisi dan contoh kemasan siap edar (termasuk Informasi Produk).
12.	Pencantuman nama distributor.	1. Klim Informasi Produk dan Label tidak berubah kecuali nama distributor.	A. Dokumen administrasi, Informasi Produk dan Label 1. Izin Pedagang Besar Farmasi (PBF). 2. Surat penunjukan. 3. Foto kemasan primer dan sekunder dari semua sisi dan contoh kemasan siap edar (termasuk Informasi Produk).
B. Perubahan terkait mutu Zat Aktif			
1.	Perubahan dan/atau penambahan produsen Zat Aktif.	1. Tidak termasuk Obat Baru, Produk Biologi dan Obat yang memerlukan uji bioekivalensi. 2. Produsen Zat Aktif sudah tercantum pada *database* AeRO/Web Registrasi Badan Pengawas Obat dan Makanan. 3. Spesifikasi Zat Aktif tidak berubah. 4. Spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah. 5. *Shelf life* Obat untuk produsen Zat Aktif baru paling lama 24 bulan, dikecualikan jika didukung oleh data yang memenuhi syarat.	A. Dokumen mutu 1. Sertifikat CPOB produsen yang masih berlaku. 2. Sertifikat analisis Zat Aktif. 3. Perbandingan data analisis bets Zat Aktif dari produsen Zat Aktif lama dan baru (khusus Produk Biologi bets analisis dari minimal tiga bets berurutan skala pilot/produksi). 4. Perbandingan data analisis bets Obat dari dua bets Obat (skala pilot/ produksi) dari produsen Zat Aktif baru dan lama (khusus Produk Biologi bets analisis dari minimal tiga bets berurutan skala pilot/produksi). 5. Laporan hasil uji stabilitas yang telah dilakukan dan komitmen untuk melanjutkan uji stabilitas sampai *shelf life* yang diajukan.
2.	Penambahan uji pada spesifikasi pelulusan Zat Aktif.	1. Perubahan tidak disebabkan kejadian tak diinginkan selama produksi (contohnya, cemaran baru yang tidak memenuhi syarat atau perubahan pada jumlah batas cemaran). 2. Penambahan parameter tidak ditujukan untuk menguji cemaran baru.	A. Dokumen mutu 1. Spesifikasi Zat Aktif. 2. Metode analisis Zat Aktif. 3. Laporan validasi metode analisis.
3.	Perubahan produsen *starting material/reagent/ intermediate* yang	1. Zat Aktif tidak termasuk Produk Biologi/zat imunologi atau steril. 2. Untuk spesifikasi *starting*	A. Dokumen mutu 1. Jika bersumber dari hewan disertai dengan informasi sumber hewan dan surat keterangan bebas BSE/TSE.

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	digunakan dalam proses pembuatan Zat Aktif atau perubahan produsen Zat Aktif (termasuk tempat uji kontrol mutu).	*material/reagent/intermediate* (termasuk dalam kontrol proses, metode analisis semua bahan) sama dengan yang telah disetujui. 3. Untuk metode penyiapan dan rute sintesis produk *intermediate* dan Zat Aktif (termasuk ukuran bets) sama dengan yang telah disetujui. 4. Spesifikasi ukuran partikel Zat Aktif dan metode analisis tetap sama.	2. Perbandingan data analisis bets Zat Aktif dari produsen lama dan baru (minimal dua bets skala pilot/produksi).
4.	Perubahan nama dan/atau alamat produsen Zat Aktif.	1. Lokasi produsen Zat Aktif tidak berubah.	A. Informasi Produk dan Label 1. Dokumen penunjang perubahan nama dan/atau alamat produsen Zat Aktif.
5.	*Update Ph. Eur. Certificate of Suitability (CEP).*	1. Tidak termasuk Produk Biologi. 2. Spesifikasi Obat (pelulusan dan *shelf life*) tidak berubah. 3. Spesifikasi untuk *impurity* tidak berubah. 4. Proses pembuatan Zat Aktif tidak menggunakan bahan yang bersumber manusia/ hewan dimana memerlukan data keamanan viral.	A. Dokumen mutu 1. *Certificate of Suitability (Ph. Eur)* yang baru.
6.	Penyempitan batas spesifikasi untuk bahan baku/produk antara.	1. Perubahan spesifikasi bahan baku/produk antara dalam batas yang disetujui. 2. Tidak terdapat perubahan spesifikasi Zat Aktif diluar batas yang disetujui. 3. Tidak terdapat perubahan pada profil cemaran Zat Aktif diluar batas yang disetujui.	A. Dokumen mutu 1. Informasi mutu dan pengujian material/produk antara yang diajukan. 2. Ringkasan prosedur analisis, jika digunakan prosedur analisis baru.
7.	Perubahan pencantuman edisi Farmakope untuk Zat Aktif.	1. Metode pengujian Zat Aktif tidak berubah. 2. Spesifikasi Zat Aktif dan Obat tidak berubah.	A. Dokumen mutu 1. Referensi Farmakope terkait.
8.	Pengetatan batas spesifikasi Zat Aktif.	1. Perubahan masih dalam batas standar yang berlaku. 2. Prosedur pengujian tidak berubah.	A. Dokumen mutu 1. Spesifikasi Zat Aktif yang baru. 2. Sertifikat analisis Zat Aktif dengan spesifikasi yang baru.
9.	Perubahan spesifikasi Zat Aktif untuk memenuhi persyaratan Farmakope terbaru.	1. Spesifikasi Obat (pelulusan dan *shelf life*) tidak berubah. 2. Spesifikasi *impurity* dan Zat Aktif tidak berubah (profil ukuran partikel, bentuk *polimorfisme*). 3. Validasi tambahan dari metode Farmakope yang baru atau yang berubah tidak diperlukan.	A. Dokumen mutu 1. Spesifikasi dan metode pengujian Zat Aktif. 2. Sertifikat analisis Zat Aktif. 3. Hasil analisis bets dari dua bets skala produksi Zat Aktif untuk semua pengujian pada spesifikasi baru. 4. Referensi Farmakope terkait.
10.	Perubahan spesifikasi Zat Aktif non-Farmakope untuk memenuhi persyaratan Farmakope.	1. Telah melakukan verifikasi metode pengujian. 2. Spesifikasi *impurity* dan Zat Aktif tidak berubah (profil ukuran partikel, bentuk *polimorfisme*).	A. Dokumen mutu 1. Spesifikasi dan metode pengujian Zat Aktif. 2. Sertifikat analisis Zat Aktif. 3. Hasil analisis bets dari dua bets skala produksi Zat Aktif untuk

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		3. Tidak ada perubahan signifikan pada komposisi kualitatif dan kuantitatif kecuali pengetatan spesifikasi. 4. Validasi tambahan dari metode Farmakope yang baru atau yang berubah tidak diperlukan.	semua pengujian pada spesifikasi baru. 4. Hasil analisis bets dari dua bets Obat skala produksi dengan Zat Aktif yang telah memenuhi spesifikasi terkini dan yang diajukan (jika perlu). 5. Data profil disolusi Obat minimal satu bets skala pilot (jika perlu). 6. Referensi Farmakope terkait.
11.	Penambahan parameter pengujian dan batas spesifikasi pada kontrol proses dalam proses pembuatan Zat Aktif.	1. Perubahan bukan karena pengaruh pada proses pembuatan Obat. 2. Spesifikasi Zat Aktif tidak berubah. 3. Telah dilakukan validasi metode pengujian.	A. Dokumen mutu 1. Prosedur pembuatan. 2. Sandingan uji *in-process* selama pembuatan Zat Aktif yang baru dan lama. 3. Rincian metode analisis dan data validasi metode analisis baru. 4. Data analisis bets menggunakan dua bets Zat Aktif (tiga bets Zat Aktif untuk Produk Biologi) untuk semua uji dalam spesifikasi yang baru.
12.	Perubahan minor pada prosedur analisis Zat Aktif.	1. Metode analisis tidak berubah (misalnya perubahan pada panjang kolom atau temperatur, tetapi metode dan jenis kolom tetap sama). 2. Studi revalidasi sudah dilakukan sesuai protokol. 3. Hasil validasi metode menunjukkan bahwa prosedur analisis yang baru sama/ekivalen dengan prosedur sebelumnya. 4. Spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah. 5. Tidak berlaku untuk penambahan prosedur pengujian.	A. Dokumen mutu 1. Spesifikasi dan metode pengujian Zat Aktif. 2. Sertifikat analisis Zat Aktif. 3. Perbandingan hasil validasi atau perbandingan hasil analisis yang menunjukkan bahwa prosedur pengujian yang baru dan prosedur sebelumnya sama/ekivalen.
13.	Perubahan metode analisis penetapan kadar Zat Aktif sesuai dengan monografi Farmakope.	1. Spesifikasi Zat Aktif tidak berubah. 2. Spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah.	A. Dokumen mutu 1. Metode analisis Zat Aktif. 2. Verifikasi prosedur analisis Zat Aktif. 3. Sertifikat analisis Zat Aktif. 4. Baku pembanding.
14.	Perubahan kondisi penyimpanan Zat Aktif.	1. Hasil uji stabilitas masih memenuhi persyaratan spesifikasi yang disetujui sebelumnya. 2. Perubahan bukan karena pengaruh pada proses pembuatan Zat Aktif atau masalah stabilitas. 3. Tidak ada perubahan periode uji ulang Zat Aktif.	A. Dokumen mutu 1. Laporan stabilitas Zat Aktif. 2. Spesifikasi Zat Aktif.
15.	Peningkatan/penurunan ukuran bets (termasuk rentang ukuran bets) Zat Aktif atau zat antara (*intermediates*) yang digunakan pada proses pembuatan Zat Aktif hingga sepuluh kali.	1. Tidak termasuk Produk Biologi. 2. Perubahan tidak mempengaruhi spesifikasi Zat Aktif/*intermediates*; harus melaporkan setiap perubahan cara pembuatan dan/atau kontrol proses yang dilakukan terhadap perubahan yang terkait dengan ukuran bets misal	A. Dokumen mutu 1. Perbandingan analisis bets lama dan baru. 2. Surat berisi pernyataan bahwa: a. Perubahan tidak memberikan perubahan negatif pada reprodusibilitas proses; b. Perubahan yang dilakukan bukan akibat dari kejadian yang tidak diharapkan ketika produksi atau karena masalah stabilitas;

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		penggunaan alat dengan besar berbeda. 3. Hasil validasi proses sesuai bets sebelumnya yang telah disetujui. 4. Perubahan tidak mempengaruhi reproducibilitas dan/atau konsistensi Zat Aktif atau *intermediates*. 5. Perubahan bukan karena pengaruh pada proses pembuatan Obat atau masalah stabilitas.	c. Spesifikasi Zat Aktif tidak berubah.
16.	Pembuatan WCB baru.	1. *Cell bank* baru diperoleh dari MCB/MSL yang sebelumnya telah disetujui. 2. *Cell bank* baru berada pada tingkat pasase yang sebelumnya telah disetujui. 3. *Cell bank* baru dikeluarkan berdasarkan protokol/proses yang sebelumnya telah disetujui.	A. Dokumen mutu 1. Kualifikasi *cell bank* atau *seed lot* berdasarkan prosedur yang sudah disetujui Badan Pengawas Obat dan Makanan. 2. Informasi karakterisasi dan pengujian MCB/WCB dan sel yang dihasilkan pada bagian akhir produksi (*end of production*) atau pascaproduksi (*postproduction passage*).
17.	Perubahan *seed lot*: generasi baru WSL.	1. *Seed lot* baru diperoleh dari MSL yang sebelumnya telah disetujui. 2. *Seed lot* baru berada pada tingkat pelulusan yang sebelumnya telah disetujui. 3. *Seed lot* baru dikeluarkan berdasarkan protokol/proses yang sebelumnya telah disetujui atau seperti yang digambarkan pada lisensi asli.	A. Dokumen mutu 1. Komparabilitas Zat Aktif yang disetujui dan yang diajukan dalam hal karakterisasi fisikokimia, aktivitas biologi dan profil *impurity*. 2. Hasil uji kontrol kualitas sebagai data kuantitatif dalam format tabel untuk *seed lot* baru yang diajukan. 3. Komitmen untuk menyerahkan studi stabilitas Zat Aktif yang diproduksi menggunakan *seed* yang diajukan dan melaporkan ke Badan Pengawas Obat dan Makanan apabila terdapat hasil yang tidak memenuhi syarat.
18.	Pengurangan batas kedaluwarsa Zat Aktif.	1. Perubahan tidak disebabkan karena kejadian berulang yang terjadi selama proses pembuatan atau karena masalah stabilitas. 2. Spesifikasi (pelulusan dan *shelf life*) Zat Aktif tidak berubah.	A. Dokumen mutu 1. Laporan stabilitas Zat Aktif.
19.	Penghilangan uji *in-process* dalam produksi Zat Aktif yang tidak signifikan.	1. Parameter yang dihilangkan bukan merupakan parameter yang kritis termasuk tetapi tidak terbatas pada kadar, cemaran, dan ukuran partikel. 2. Perubahan bukan karena kejadian berulang selama produksi atau disebabkan masalah stabilitas. 3. Uji tidak terkait parameter kritis (sebagai contoh, komposisi, cemaran, karakteristik kritis fisik lain atau kemurnian mikroba).	A. Dokumen mutu 1. Informasi kontrol yang dilakukan pada tahap kritis produksi dan pada produk antara Zat Aktif yang diajukan. 2. Justifikasi/penilaian risiko bahwa atribut bersifat tidak signifikan.

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C. Perubahan terkait mutu Obat			
1.	Perubahan minor pada pembuatan Obat.	1. Tidak termasuk Produk Biologi dan sediaan steril. 2. Prinsip pembuatan secara keseluruhan tetap sama. 3. Proses baru menghasilkan produk yang sama dari aspek kualitas (sudah divalidasi), spesifikasi Obat, keamanan, dan khasiat. 4. Tidak ada perubahan kualitatif dan kuantitatif dari profil *impurity* atau sifat fisikokimia. 5. Spesifikasi Obat maupun produk antara tidak berubah. 6. Tidak ada perubahan batas spesifikasi pada kontrol proses dalam pembuatan Obat. 7. Uji stabilitas Obat telah dilakukan minimal tiga bulan dari satu bets skala pilot atau skala produksi. 8. Lokasi produksi tidak berubah. 9. Perubahan tidak menyebabkan dampak buruk terhadap mutu, efikasi, dan keamanan Obat. 10. Profil disolusi tidak berubah.	A. Dokumen mutu 1. Prosedur pembuatan Obat. 2. Data analisis bets Obat. 3. Untuk bentuk sediaan padat, data profil disolusi terbanding dari satu bets produksi representatif dan data perbandingan dari tiga bets produksi terakhir dari proses pembuatan Obat sebelumnya. 4. Laporan stabilitas Obat dan komitmen stabilitas Obat jika laporan stabilitas Obat belum lengkap. 5. Justifikasi tidak melakukan uji BE.
2.	Pengetatan batas spesifikasi pelulusan Obat.	1. Perubahan masih dalam kisaran batas spesifikasi yang disetujui. 2. Prosedur pengujian tidak berubah atau perubahan pada prosedur pengujian hanya bersifat minor.	A. Dokumen mutu 1. Sandingan spesifikasi pelulusan Obat yang baru dan lama. 2. Sertifikat analisis Obat yang baru.
3.	Perubahan spesifikasi (pelulusan dan *shelf life)* Obat untuk memenuhi persyaratan Farmakope.	1. Perubahan bukan akibat dari penilaian sebelumnya. 2. Perubahan bukan karena pengaruh pada proses pembuatan Obat. 3. Perubahan masih dalam kisaran batas spesifikasi yang disetujui. 4. Prosedur pengujian tidak berubah, atau perubahan pada prosedur pengujian hanya bersifat minor. 5. Tidak ada perubahan kualitatif dan kuantitatif dari profil *impurity*/sifat fisikokimia atau disolusi.	A. Dokumen mutu 1. Spesifikasi (pelulusan dan *shelf life*) Obat yang baru. 2. Sandingan spesifikasi (pelulusan dan *shelf life*) Obat yang baru dan lama. 3. Data analisis bets Obat untuk seluruh pengujian pada spesifikasi baru (dua bets).
4.	Penambahan parameter pengujian pada kontrol proses dalam proses pembuatan Obat.	1. Perubahan bukan karena pengaruh pada proses pembuatan Obat. 2. Spesifikasi Obat tidak berubah. 3. Telah dilakukan validasi metode pengujian.	A. Dokumen mutu 1. Prosedur pembuatan. 2. Rincian metode analisis dan data validasi metode analisis baru. 3. Data analisis bets dari tiga bets Obat untuk semua uji dalam spesifikasi yang baru.
5.	Pengetatan batas spesifikasi *in-process* selama pembuatan	1. Perubahan bukan akibat dari penilaian sebelumnya. 2. Tidak terdapat perubahan	A. Dokumen mutu 1. Spesifikasi *in-process* selama pembuatan Obat yang baru.

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	Obat.	profil cemaran Produk Jadi diluar batas yang disetujui. 3. Perubahan bukan karena pengaruh pada proses pembuatan Obat atau masalah stabilitas. 4. Spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah. 5. Perubahan masih dalam batas standar yang berlaku. 6. Prosedur pengujian tidak berubah atau perubahan hanya bersifat minor.	2. Sandingan spesifikasi *in-process* selama pembuatan Obat yang baru dan lama.
6.	Penghilangan uji *in-process* yang tidak signifikan.	1. Tidak terdapat perubahan pada profil cemaran Produk Jadi diluar batas yang disetujui. 2. Perubahan bukan karena kejadian berulang selama produksi atau disebabkan masalah stabilitas. 3. Uji tidak terkait hal kritis (seperti: kadar, volume, cemaran, karakteristik fisika kritis lain atau kemurnian mikrobial).	A. Dokumen mutu 1. Justifikasi/penilaian risiko menunjukkan bahwa hal tersebut tidak signifikan.
7.	Perubahan tempat pengujian IPC.	1. Tidak terdapat perubahan spesifikasi Produk Jadi diluar batas yang disetujui. 2. Tidak terdapat perubahan pada profil cemaran Produk Jadi diluar batas yang disetujui. 3. Perubahan yang terjadi tidak disebabkan kejadian berulang selama produksi atau disebabkan masalah stabilitas. 4. Prosedur analisis yang diajukan harus tetap atau memperketat presisi, akurasi, spesifisitas dan sensitivitas, jika dilakukan. 5. Tidak terdapat perubahan pada batas IPC diluar batas yang disetujui.	A. Dokumen administratif 1. Sertifikat CPOB. B. Dokumen mutu 1. Data analisis bets dari tiga bets Obat. 2. Laporan transfer metode analisis.
8.	Penambahan parameter pengujian Obat.	1. Perubahan bukan karena pengaruh pada proses pembuatan Obat. 2. Spesifikasi Obat selain parameter pengujian yang ditambahkan tidak berubah.	A. Dokumen mutu 1. Spesifikasi Obat. 2. Prosedur analisis Obat. 3. Hasil analisis bets Obat (dua bets). 4. Laporan validasi prosedur analisis Obat (jika perlu).
9.	Perubahan prosedur analisis Obat sesuai dengan monografi Farmakope.	1. Tidak termasuk Produk Biologi. 2. Tidak ada perubahan kualitatif dan kuantitatif dari profil *impurity*/fisikokimia. 3. Metode analisis Obat tidak berubah.	A. Dokumen mutu 1. Spesifikasi dan metode pengujian Obat. 2. Data analisis bets Obat dengan prosedur analisis lama dan yang saat ini diajukan. 3. Hasil validasi/verifikasi metode analisis.
10.	Perubahan dan/atau penambahan produsen Zat Tambahan	1. Tidak termasuk Produk Biologi. 2. Spesifikasi Eksipien tidak berubah. 3. Spesifikasi (pelulusan dan	A. Dokumen mutu 1. Sertifikat analisis Eksipien

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		shelf life) Obat tidak berubah. 4. Bahan baku yang digunakan memenuhi kriteria *pharmaceutical grade* atau *food grade.*	
11.	Pengetatan batas spesifikasi Eksipien.	1. Perubahan bukan akibat dari hasil penilaian sebelumnya. 2. Perubahan bukan karena pengaruh pada proses pembuatan Obat. 3. Perubahan masih dalam batas standar yang berlaku. 4. Prosedur pengujian tidak berubah. 5. Kriteria penerimaan untuk residu pelarut masih dalam batas yang disetujui (contohnya, dalam batas ICH untuk pelarut residual kelas tiga atau persyaratan Farmakope).	A. Dokumen mutu 1. Spesifikasi Eksipien yang baru. 2. Sertifikat analisis Eksipien dengan spesifikasi yang baru.
12.	Perubahan minor pada prosedur analisis Eksipien.	1. Metode analisis tidak berubah (misalnya, perubahan pada panjang kolom atau temperatur, tetapi metode dan jenis kolom tidak berbeda). 2. Prosedur analisis bukan merupakan prosedur analisis secara biologi/imunologi/ imunokimia atau prosedur analisis dengan menggunakan pereaksi biologi.	A. Dokumen mutu 1. Spesifikasi dan metode analisis Eksipien. 2. Sertifikat analisis Eksipien.
13.	Perubahan prosedur analisis Eksipien sesuai dengan monografi Farmakope atau yang relevan.	1. Spesifikasi Eksipien tidak berubah (misalnya, ukuran partikel, bentuk *polimorfisme*).	A. Dokumen mutu 1. Spesifikasi Eksipien. 2. Prosedur analisis Eksipien. 3. Sertifikat analisis Eksipien. 4. Referensi Farmakope atau dokumen penunjang terkait.
14.	Penambahan parameter uji pada spesifikasi Eksipien.	1. Tidak termasuk Eksipien *adjuvant* untuk Produk Biologi. 2. Perubahan bukan karena pengaruh pada proses pembuatan Obat.	A. Dokumen mutu 1. Spesifikasi dan metode pengujian Eksipien. 2. Data analisis bets dari Eksipien dengan spesifikasi lama dan yang saat ini diajukan.
15.	Perubahan pada prosedur analisis Eksipien, termasuk penggantian metode pengujian.	1. Studi revalidasi sudah dilakukan sesuai protokol. 2. Hasil validasi metode menunjukkan bahwa prosedur analisis yang baru sama/ekivalen dengan prosedur sebelumnya. 3. Spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah.	A. Dokumen mutu 1. Spesifikasi dan metode pengujian Eksipien. 2. Revisi spesifikasi *impurity* (jika ada). 3. Hasil validasi terbanding yang menunjukkan bahwa prosedur pengujian baru dengan lama ekivalen.
16.	Perubahan spesifikasi Eksipien untuk memenuhi persyaratan Farmakope.	1. Telah melakukan verifikasi metode pengujian terbaru dengan hasil memenuhi syarat spesifikasi. 2. Spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah.	A. Dokumen mutu 1. Spesifikasi dan metode pengujian Eksipien. 2. Sertifikat analisis Eksipien. 3. Spesifikasi Obat. 4. Hasil analisis bets Obat dari dua bets Obat skala produksi.

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG HARUS DISERAHKAN
			5. Referensi Farmakope terkait.
17.	Perubahan sumber Eksipien atau reagen yang berisiko BSE/TSE.	1. Spesifikasi pelulusan Eksipien dan Obat serta spesifikasi *shelf life* tidak berubah. 2. Tidak untuk Eksipien atau reagen yang digunakan dalam produksi Produk Biologi atau Obat yang mengandung Zat Aktif biologi.	A. Dokumen mutu 1. Pernyataan dari produsen Eksipien atau reagen bahwa zat tersebut bersumber nabati atau hewani atau sintetis. 2. Sertifikat bebas BSE/TSE. 3. Sertifikat analisis Eksipien.
18.	Perubahan berat penyalut tablet atau berat cangkang kapsul pada bentuk sediaan *oral immediate release.*	1. Profil disolusi Obat dengan berat penyalut tablet atau berat cangkang kapsul baru (minimal dua bets skala pilot) sebanding dengan Obat sebelumnya. 2. Spesifikasi Obat hanya mengubah berat dan dimensi. 3. Uji stabilitas sudah dilakukan sesuai protokol dengan minimal dua bets skala pilot atau skala produksi dengan data minimal tiga bulan memberikan hasil yang memenuhi spesifikasi. 4. Penyalut bukan merupakan faktor kritis untuk mekanisme pelepasan Obat.	A. Dokumen mutu 1. Pemerian dan Formula. 2. Spesifikasi Obat. 3. Hasil analisis bets dari Obat dengan berat penyalut tablet/cangkang kapsul lama dan baru. 4. Data uji disolusi terbanding minimal satu bets skala pilot antara Obat dengan Formula yang diajukan dengan yang telah disetujui, jika dipersyaratkan. 5. Laporan stabilitas Obat dan komitmen stabilitas Obat jika laporan stabilitas Obat belum lengkap.
19.	Peningkatan, penambahan, penghilangan atau penggantian zat warna dan/atau pengaroma.	1. Tidak ada perubahan spesifikasi (pelulusan dan *shelf life*) Obat kecuali warna dan/atau aroma. 2. Tidak ada perubahan karakteristik fungsional dari Obat (misalnya, waktu hancur, profil disolusi). 3. Zat warna dan/atau pengaroma yang baru bukan termasuk yang dilarang untuk penggunaan farmasetik. 4. Zat warna dan/atau pengaroma baru tidak bersumber manusia/hewan dimana memerlukan keamanan viral. 5. Perubahan bukan karena masalah stabilitas atau produksi. 6. Uji stabilitas sudah dilakukan sesuai protokol dengan minimal dua bets skala pilot atau skala produksi dengan data minimal tiga bulan memberikan hasil yang memenuhi spesifikasi.	A. Dokumen mutu 1. Pemerian dan Formula. 2. Formula bets. 3. Proses pembuatan dan kontrol proses. 4. Spesifikasi zat warna dan/atau pengaroma yang baru. 5. Prosedur pengujian zat warna dan/atau pengaroma yang baru. 6. Sertifikat analisis zat warna dan/atau pengaroma yang baru. 7. Spesifikasi Obat. 8. Hasil analisis Obat. 9. Perbandingan data analisis bets Obat dari dua bets Obat skala produksi dari Obat dengan Formula lama dan baru. 10. Sertifikat bebas BSE/TSE (jika perlu). 11. Laporan stabilitas Obat dan komitmen stabilitas Obat jika laporan stabilitas Obat belum lengkap.
20.	Pengurangan atau penghilangan satu atau lebih komponen dari zat warna dan/atau zat pengaroma.	1. Tidak ada perubahan spesifikasi Obat kecuali warna dan/atau pengaroma. 2. Uji stabilitas sudah dilakukan sesuai protokol dengan minimal dua bets	A. Dokumen mutu 1. Pemerian dan Formula. 2. Formula bets. 3. Prosedur pembuatan Obat. 4. Spesifikasi Obat. 5. Data analisis bets Obat dari dua bets Obat skala produksi.

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG HARUS DISERAHKAN
		skala pilot atau skala produksi dengan data minimal enam bulan memberikan hasil yang memenuhi spesifikasi.	6. Laporan stabilitas Obat dan komitmen stabilitas Obat jika laporan stabilitas Obat belum lengkap.
21.	Perubahan atau penambahan *imprint, bossing* atau tanda lain (kecuali garis bagi) pada tablet atau *printing* pada kapsul, termasuk penggantian atau penambahan tinta yang digunakan untuk Label produk.	1. Spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah (kecuali pemerian). 2. Tinta yang digunakan harus memenuhi syarat peraturan kefarmasian. 3. Pemerian baru tidak menyebabkan kerancuan dengan Obat yang sudah terdaftar.	A. Informasi Produk dan Label 1. Informasi Produk (jika perlu). B. Dokumen mutu 1. Spesifikasi Obat. 2. Sertifikat analisis tinta/bahan *printing*. 3. Data analisis bets Obat dari dua bets Obat skala produksi.
22.	Perubahan warna cangkang kapsul.	1. Tidak ada perubahan spesifikasi cangkang kapsul kecuali warna. 2. Tidak ada perubahan spesifikasi (pelulusan dan *shelf life*) Obat kecuali warna cangkang kapsul. 3. Tidak ada perubahan karakteristik fungsional dari cangkang kapsul (misalnya, waktu hancur, profil disolusi). 4. Perubahan bukan karena masalah stabilitas atau produksi. 5. Uji stabilitas sudah dilakukan sesuai protokol dengan minimal dua bets skala pilot atau skala produksi dengan data minimal tiga bulan memberikan hasil yang memenuhi spesifikasi.	A. Dokumen mutu 1. Pemerian. 2. Spesifikasi Obat. 3. Sertifikat bebas BSE/TSE. 4. Informasi sumber gelatin sebagai bahan baku cangkang kapsul. 5. Spesifikasi cangkang kapsul. 6. Sertifikat analisis cangkang kapsul. 7. Hasil analisis bets dari Obat dengan cangkang kapsul lama dan baru. 8. Laporan stabilitas Obat dan komitmen stabilitas Obat jika laporan stabilitas Obat belum lengkap.
23.	Perubahan sintesis Eksipien (non-Farmakope).	1. Tidak termasuk Eksipien Produk Biologi. 2. Tidak termasuk zat *adjuvant*. 3. Tidak berpengaruh terhadap spesifikasi Eksipien. 4. Tidak ada perubahan kualitatif dan kuantitatif pada profil *impurity* atau sifat fisikokimia. 5. Rute sintesis dan spesifikasi Eksipien identik dan tidak ada perubahan profil *impurity* secara kualitatif dan kuantitatif.	A. Dokumen mutu 1. Perbandingan data analisis bets Eksipien minimal dua bets skala pilot yang diproduksi menurut proses pembuatan Eksipien lama dan baru. 2. Perbandingan data profil disolusi Obat minimal dua bets skala pilot.
24.	Perubahan spesifikasi Eksipien non-Farmakope untuk memenuhi persyaratan Farmakope.	1. Spesifikasi Eksipien tidak berubah (untuk: ukuran partikel dan bentuk *polimorfisme*). 2. Spesifikasi Obat tidak berubah.	A. Dokumen mutu 1. Spesifikasi dan metode pengujian Eksipien. 2. Hasil analisis Eksipien. 3. Referensi Farmakope terkait.
25.	Penggantian atau penambahan tempat pengemasan sekunder Obat.	1. Hasil inspeksi dua tahun terakhir memuaskan.	A. Dokumen administratif, Informasi Produk dan Label 1. Sertifikat CPOB tempat pengemasan sekunder. 2. Foto kemasan sekunder dari semua sisi dan contoh Informasi Produk

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG HARUS DISERAHKAN
			siap edar (jika perlu).
26.	Pengetatan batas spesifikasi kemasan primer Obat.	1. Perubahan bukan akibat dari hasil penilaian sebelumnya. 2. Perubahan masih dalam batas standar yang berlaku. 3. Prosedur pengujian tidak berubah atau perubahan pada prosedur pengujian hanya bersifat minor.	A. Dokumen mutu 1. Spesifikasi kemasan. 2. Sertifikat analisis kemasan.
27.	Perubahan komposisi secara kualitatif dan/atau kuantitatif dari bahan kemasan primer Obat (untuk semua bentuk sediaan).	1. Tidak termasuk Produk Biologi dan produk steril. 2. Perubahan hanya pada jenis dan bahan kemasan yang sama. 3. Bahan kemasan yang diajukan sama/ekivalen dengan yang telah disetujui. 4. Uji stabilitas sudah dilakukan sesuai protokol dengan minimal dua bets skala pilot atau skala produksi dengan data minimal enam bulan memberikan hasil yang memenuhi spesifikasi.	A. Dokumen mutu 1. Spesifikasi dan metode pengujian bahan kemasan. 2. Sertifikat analisis kemasan. 3. Laporan stabilitas Obat dan komitmen stabilitas Obat jika laporan stabilitas Obat belum lengkap. 4. Untuk sediaan cair dan semisolid, bukti tidak terdapat interaksi antara Obat dengan jenis/bahan kemasan yang diajukan.
28.	Penambahan atau penggantian alat takar yang bukan merupakan bagian dari kemasan primer (tidak termasuk *spacer device* untuk *metered dose inhaler*).	1. Alat takar yang diajukan harus mencakup dosis tepat yang dibutuhkan sesuai posologi yang telah disetujui dan ditunjang dengan data uji yang sesuai. 2. Alat takar yang baru kompatibel dengan Obat. 3. Perubahan tidak menyebabkan perubahan pada informasi Obat.	A. Informasi Produk dan Label 1. Foto alat takar, kemasan primer dan sekunder dari semua sisi dan contoh kemasan siap edar yang mencantumkan Label baru termasuk Informasi Produk (jika perlu). B. Dokumen mutu 1. Spesifikasi dan metode pengujian alat takar. 2. Data hasil kalibrasi alat takar.
29.	Perubahan minor pada prosedur analisis kemasan primer Obat.	1. Hasil validasi metode menunjukkan bahwa prosedur analisis yang baru sama/ekivalen dengan prosedur sebelumnya. 2. Metode pengujian tidak berubah (misalnya, perubahan panjang kolom atau temperatur tetapi tidak terdapat perubahan jenis kolom).	A. Dokumen mutu 1. Spesifikasi dan prosedur analisis bahan kemasan.
30.	Perubahan prosedur pengujian bahan kemasan primer Obat, termasuk penggantian atau penambahan prosedur pengujian.	1. Hasil validasi metode menunjukkan bahwa prosedur pengujian yang baru sama/ekivalen dengan prosedur sebelumnya. 2. Metode analisis yang baru tidak menggunakan teknik nonstandar yang baru atau teknik standar yang digunakan dengan metode yang baru.	A. Dokumen mutu 1. Spesifikasi dan metode pengujian bahan kemasan.
31.	Perubahan atau penambahan produsen komponen kemasan atau alat kesehatan yang menyertai Obat, tidak termasuk	1. Spesifikasi bahan kemasan atau alat kesehatan tidak berubah.	A. Informasi Produk dan Label 1. Surat keterangan penggantian atau penambahan produsen. B. Dokumen mutu 1. Izin edar alat kesehatan. 2. Spesifikasi bahan kemasan.

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG HARUS DISERAHKAN
	produsen *spacer devices* untuk *metered dose inhaler.*		3. Sertifikat analisis alat kesehatan. 4. Khusus Produk Biologi dilengkapi juga dengan perbandingan hasil uji (*control*) komponen kemasan atau alat kesehatan yang menyertai Obat antara produsen baru dengan produsen yang telah disetujui.
32.	Pengurangan produsen komponen kemasan atau alat kesehatan yang menyertai Obat, tidak termasuk produsen *spacer devices* untuk *metered dose inhaler.*	1. Tidak ada penghilangan komponen kemasan atau alat kesehatan yang menyertai Obat.	A. Informasi Produk dan Label 1. Surat keterangan pengurangan produsen.
33.	Penambahan parameter pengujian kemasan primer Obat.	1. Perubahan bukan karena pengaruh pada proses pembuatan Obat.	A. Dokumen mutu 1. Spesifikasi dan metode pengujian bahan kemasan. 2. Hasil pengujian kemasan primer memenuhi syarat.
34.	Perubahan bahan kemasan sekunder.	1. Label tidak berubah.	A. Dokumen mutu 1. Spesifikasi dan prosedur analisis bahan kemasan sekunder.
35.	Perubahan klim penyimpanan Obat (redaksional).	1. Spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah. 2. Perubahan bukan karena pengaruh pada proses pembuatan Obat atau karena masalah stabilitas.	A. Informasi Produk dan Label 1. Foto kemasan primer dan sekunder dari semua sisi dan contoh kemasan siap edar (termasuk Informasi Produk).
36.	Pengurangan batas kedaluwarsa Obat: kemasan belum dibuka.	1. Spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah. 2. Uji stabilitas telah dilakukan sesuai protokol yang disetujui dan memenuhi syarat spesifikasi.	A. Informasi Produk dan Label 1. Foto dan contoh Informasi Produk siap edar (jika perlu). B. Dokumen mutu 1. Spesifikasi Obat. 2. Laporan stabilitas Obat.
37.	Pengurangan batas kedaluwarsa Obat: setelah kemasan dibuka atau setelah rekonstitusi.	1. Spesifikasi (pelulusan dan *shelf life*) Obat tidak berubah. 2. Uji stabilitas telah dilakukan sesuai protokol yang disetujui dan memenuhi syarat spesifikasi.	A. Informasi Produk dan Label 1. Foto dan contoh Informasi Produk siap edar (jika perlu). B. Dokumen mutu 1. Spesifikasi Obat. 2. Laporan stabilitas Obat setelah kemasan dibuka atau setelah rekonstitusi.

KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA,

ttd.

PENNY K. LUKITO

LAMPIRAN XVII
PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA
NOMOR 24 TAHUN 2017
TENTANG
KRITERIA DAN TATA LAKSANA REGISTRASI OBAT

KELENGKAPAN DOKUMEN REGISTRASI ULANG

1. Surat pengantar.
2. Pernyataan Pendaftar.
3. Izin Edar dan semua surat Persetujuan Registrasi Variasi yang diterbitkan oleh Badan POM beserta lampirannya.
4. Formulir Registrasi.
5. Obat Produksi Dalam Negeri
   a. Surat izin Industri Farmasi Pendaftar yang masih berlaku.
   b. Sertifikat CPOB produsen Obat yang masih berlaku sesuai dengan bentuk sediaan yang diajukan.
   c. Sertifikat CPOB produsen Zat Aktif.
   d. Surat perjanjian kontrak (khusus Obat Kontrak) yang masih berlaku.
   e. Surat Keterangan dari pemberi lisensi yang menyatakan bahwa masih ada kerja sama antara pemberi lisensi dan penerima lisensi (Khusus Obat Lisensi).
   f. Dokumen mutu terkini sebagai berikut:
      - Sertifikat analisis Zat Aktif.
      - Catatan bets Obat produksi terakhir disertai dengan sertifikat analisis Obat (maksimal dua tahun terakhir).
      - Laporan hasil uji bioekivalensi (BE) atau uji disolusi terbanding (UDT) untuk Zat Aktif yang dipersyaratkan uji BE/UDT.
      - Klarifikasi sumber bahan baku tertentu yang berasal dari hewan atau tumbuhan.
      - Surat pernyataan bahwa dalam proses pembuatan menggunakan atau tidak menggunakan bahan tertentu yang berasal dari babi.
      - Pemenuhan komitmen dari Registrasi sebelumnya.
   g. Dokumen Informasi Produk dan Label, dilengkapi dengan foto Obat beserta kemasan yang beredar (*hard copy* dan *soft copy*).

6. Obat Impor
   a. Surat izin Industri Farmasi Pendaftar.
   b. Sertifikat CPOB atau dokumen lain yang setara dari produsen Obat dan/atau tempat pelulusan bets yang masih berlaku sesuai dengan bentuk sediaan yang diajukan.
   c. Sertifikat CPOB produsen Zat Aktif.
   d. Bukti pemasukan paling lama dua tahun terakhir.
   e. Justifikasi impor.
   f. CPP atau dokumen lain yang setara dari negara produsen dan/atau negara dimana diterbitkan sertifikat pelulusan bets.
   g. Dokumen mutu terkini sebagai berikut:
      - Sertifikat analisis Zat Aktif dan Obat.
      - Laporan hasil uji bioekivalensi (BE) atau uji disolusi terbanding (UDT) untuk Zat Aktif yang dipersyaratkan uji BE/UDT.
      - Pemenuhan komitmen dari Registrasi sebelumnya.
   h. Dokumen Informasi Produk dan Label, dilengkapi dengan foto Obat beserta kemasan yang beredar (*hard copy* dan *soft copy*).
   i. Surat persetujuan tertulis terakhir dari industri farmasi atau pemilik produk di luar negeri dikecualikan untuk Pendaftar yang merupakan afiliasi dari perusahaan induk

7. Untuk Registrasi Ulang yang disertai dengan perubahan, kelengkapan dokumen mutu lainnya sesuai dengan jenis perubahan yang diajukan.

KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA,

ttd.

PENNY K. LUKITO

LAMPIRAN XVIII
PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA
NOMOR 24 TAHUN 2017
TENTANG
KRITERIA DAN TATA LAKSANA REGISTRASI OBAT

TATA CARA PENILAIAN KEMBALI

1. Kepala Badan memberitahukan secara tertulis kepada Pendaftar tentang Obat yang perlu dilakukan penilaian kembali.

2. Pendaftar yang Obatnya dinilai kembali diberikan kesempatan untuk menyerahkan data dan informasi yang terkini dan autentik guna menunjang Izin Edar Obat yang dinilai kembali.

3. Data sebagaimana dimaksud pada angka 2 harus diserahkan paling lambat enam bulan terhitung mulai tanggal pemberitahuan.

4. Apabila melewati batas waktu yang telah ditentukan pada angka 3, data dan informasi yang diserahkan Pendaftar tidak akan dipertimbangkan dan Izin Edar akan dibatalkan.

5. Terhadap data yang diserahkan Pendaftar, akan dilakukan penilaian kembali berdasarkan kriteria khasiat, keamanan, dan mutu yang telah ditetapkan.

KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA,

ttd.

PENNY K. LUKITO

Number of reviewers	New Drugs							New Generic (NG)	Generic (G)	Biologics		
	NCE	NI	NCO	ND	NR	NDOS	NS			NB	BF	B
CMC	2	-	2	2	2	2	2	2	2	2	2	2
Clinical	2	2	2	2	2	2	2	2(BA/BE)	-	2	1	
Non-clinical	2	2*	1*	1*	1*	-	1*	(labelling,efficacy&safety	(labelling,efficacy&safety	2	1	1(labelling,efficacy&safety)

* If applicable

NCE = New Chemical Entity,
NI = New Indication,
NCO = New Combination,
ND = New Delivery system,
NR = New Route of administration,
NDOS = New Dosage form of Approved New Drug,
NS = New Strength of Approved New Drug
NB = New Biological drug
BF = New Generic of Biological drug

BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA

PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA
NOMOR 3 TAHUN 2013
TENTANG
PERUBAHAN ATAS PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN NOMOR HK.03.1.23.10.11.08481 TAHUN 2011 TENTANG KRITERIA DAN TATA LAKSANA REGISTRASI OBAT

DENGAN RAHMAT TUHAN YANG MAHA ESA

KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA,

Menimbang : a. bahwa pengaturan registrasi obat sebagaimana telah diatur dalam Peraturan Kepala Badan Pengawas Obat dan Makanan Nomor HK.03.1.23.10.11.08481 Tahun 2011 tentang Kriteria dan Tata Laksana Registrasi Obat perlu disesuaikan dengan kondisi terkini terkait dengan registrasi obat generik;

b. bahwa berdasarkan pertimbangan sebagaimana dimaksud dalam huruf a perlu menetapkan Peraturan Kepala Badan Pengawas Obat dan Makanan tentang Perubahan Atas Peraturan Kepala Badan Pengawas Obat dan Makanan Nomor HK.03.1.23.10.11.08481 Tahun 2011 tentang Kriteria dan Tata Laksana Registrasi Obat;

Mengingat : 1. Ordonansi Obat Keras (*Sterkwerkende Geneesmiddelen Ordonnantie, Staatsblad* 1949:419);

2. Undang-Undang Nomor 5 Tahun 1997 tentang Psikotropika (Lembaran Negara Republik Indonesia Tahun 1997 Nomor 10, Tambahan Lembaran Negara Republik Indonesia Nomor 3671);

3. Undang-Undang Nomor 8 Tahun 1999 tentang Perlindungan Konsumen (Lembaran Negara Republik Indonesia Tahun 1999 Nomor 42, Tambahan Lembaran Negara Republik Indonesia Nomor 3821);

4. Undang-Undang Nomor 35 Tahun 2009 tentang Narkotika (Lembaran Negara Republik Indonesia Tahun 2009 Nomor 143, Tambahan Lembaran Negara Republik Indonesia Nomor 5062);
5. Undang-Undang Nomor 36 Tahun 2009 tentang Kesehatan (Lembaran Negara Republik Indonesia Tahun 2009 Nomor 144, Tambahan Lembaran Negara Republik Indonesia Nomor 5063);
6. Keputusan Presiden Nomor 103 Tahun 2001 tentang Kedudukan, Tugas, Fungsi, Kewenangan, Susunan Organisasi, dan Tata Kerja Lembaga Pemerintah Non Departemen sebagaimana telah beberapa kali diubah terakhir dengan Peraturan Presiden Nomor 3 Tahun 2013;
7. Keputusan Presiden Nomor 110 Tahun 2001 tentang Unit Organisasi dan Tugas Eselon I Lembaga Pemerintah Non Departemen sebagaimana telah beberapa kali diubah terakhir dengan Peraturan Presiden Republik Indonesia Nomor 4 Tahun 2013;
8. Peraturan Menteri Kesehatan Nomor 1010/Menkes/Per/XI/2008 tentang Registrasi Obat sebagaimana telah diubah dengan Peraturan Menteri Kesehatan Nomor 1120/Menkes/Per/XII/2008;
9. Keputusan Kepala Badan Pengawas Obat dan Makanan Nomor 02001/SK/KBPOM Tahun 2001 tentang Organisasi dan Tata Kerja Badan Pengawas Obat dan Makanan sebagaimana telah diubah dengan Keputusan Kepala Badan Pengawas Obat dan Makanan Nomor HK.00.05.21.4231 Tahun 2004;
10. Peraturan Kepala Badan Pengawas Obat dan Makanan Nomor HK.03.1.23.10.11.08481 Tahun 2011 tentang Kriteria dan Tata Laksana Registrasi Obat (Berita Negara Republik Indonesia Tahun 2011 Nomor 634);
11. Peraturan Kepala Badan Pengawas Obat dan Makanan Nomor HK.03.01.23.12.11.10217 Tahun 2011 tentang Obat Wajib Uji Ekivalensi (Berita Negara Republik Indonesia Tahun 2012 Nomor 120);

12. Peraturan Kepala Badan Pengawas Obat dan Makanan Nomor HK.03.1.34.11.12.7542 Tahun 2012 tentang Pedoman Teknis Cara Distribusi Obat Yang Baik (Berita Negara Republik Indonesia Tahun 2012 Nomor 1268);
13. Peraturan Kepala Badan Pengawas Obat dan Makanan Nomor HK.03.1.33.12.12.8195 Tahun 2012 tentang Penerapan Pedoman Cara Pembuatan Obat yang Baik (Berita Negara Republik Indonesia Tahun 2013 Nomor 122);

MEMUTUSKAN:

Menetapkan : PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN TENTANG PERUBAHAN ATAS PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN NOMOR HK.03.1.23.10.11.08481 TAHUN 2011 TENTANG KRITERIA DAN TATA LAKSANA REGISTRASI OBAT.

Pasal I

Beberapa ketentuan dalam Peraturan Kepala Badan Pengawas Obat dan Makanan Nomor HK.03.1.23.10.11.08481 Tahun 2011 tentang Kriteria dan Tata Laksana Registrasi Obat diubah sebagai berikut:

1. Setelah Pasal 21 ditambah Bagian Kesepuluh Pasal 21A yang berbunyi sebagai berikut:

Bagian Kesepuluh

Registrasi Obat dengan Nama Generik

Pasal 21A

(1) Obat yang diregistrasi dengan nama generik harus mempunyai spesifikasi dan mutu yang sama dengan obat dengan nama dagang atau sebaliknya yang dibuat oleh industri farmasi yang sama.

(2) Spesifikasi sebagaimana dimaksud pada ayat (1) meliputi:

a. ukuran;

b. bentuk;

c. warna;

d. aroma; dan

e. rasa.

2. Diantara Pasal 24 dan Pasal 25 disisipkan 1 (satu) pasal, yakni Pasal 24A yang berbunyi sebagai berikut:

Pasal 24A

(1) Untuk menjamin kestabilan obat dalam bentuk sediaan oral padat, registrasi obat dengan kemasan botol berisi paling banyak 100 (seratus) sediaan.

(2) Registrasi obat dengan kemasan botol sebagaimana dimaksud pada ayat (1) hanya dapat dilakukan untuk obat dengan zat aktif yang stabil.

(3) Jika industri farmasi melakukan registrasi obat yang memiliki lebih dari 1 (satu) kekuatan zat aktif, maka harus memiliki perbedaan paling sedikit salah satu spesifikasi sebagaimana dimaksud dalam Pasal 21A ayat (2).

(4) Khusus registrasi obat dengan nama generik, dokumen penandaan sebagaimana dimaksud dalam Pasal 24 ayat (3) harus mencantumkan:

a. harga eceran tertinggi sesuai dengan ketentuan peraturan perundang-undangan; dan

b. logo generik yang berwarna hijau sebagai contoh berikut:

(5) Logo generik sebagaimana dimaksud pada ayat (4) dicantumkan secara proporsional sesuai dengan ukuran kemasan.

(6) Jika industri farmasi melakukan registrasi obat dengan nama generik lebih dari 1 (satu) kekuatan zat aktif, maka pada kemasan harus mencantumkan kekuatan zat aktif setelah bentuk sediaan dengan ukuran huruf sesuai ukuran huruf nama generik.

3. Mengubah ketentuan Pasal 46 ayat (1) dan antara ayat (2) dan ayat (3) disisipkan 1 (satu) ayat yakni ayat (2a) sehingga berbunyi sebagai berikut:

Pasal 46

(1) Persetujuan sebagaimana dimaksud dalam Pasal 45 ayat (3) diberitahukan kepada Pendaftar secara tertulis berupa:

a. pemberitahuan persetujuan (*approvable letter*);

b. persetujuan Izin Edar;

c. persetujuan impor dalam bentuk ruahan;

d. persetujuan impor Khusus Ekspor;

e. persetujuan Khusus Ekspor.

(2) Persetujuan Registrasi Variasi berupa persetujuan Izin Edar atau surat persetujuan perubahan yang merupakan adendum dari persetujuan Izin Edar yang telah diterbitkan.

(2a) Pemberitahuan persetujuan sebagaimana dimaksud pada ayat (1) huruf a merupakan surat pemberitahuan persetujuan untuk melakukan persiapan pembuatan obat dengan skala komersial atau persiapan pelaksanaan importasi obat sebelum diterbitkan persetujuan Izin Edar.

(3) Persetujuan sebagaimana dimaksud pada ayat (1) huruf b menggunakan format sesuai Lampiran XVII yang merupakan bagian yang tidak terpisahkan dari Peraturan ini.

4. Diantara Pasal 46 dan Pasal 47 disisipkan 1 (satu) pasal, yakni Pasal 46A yang berbunyi sebagai berikut:

Pasal 46A

(1) Pemberitahuan persetujuan (*approvable letter*) sebagaimana dimaksud dalam Pasal 46 ayat (1) huruf a bukan sebagai pengganti Persetujuan Izin Edar.

(2) Pemberitahuan persetujuan sebagaimana dimaksud dalam Pasal 46 ayat (1) huruf a berlaku 2 (dua) tahun sejak tanggal surat diterbitkan.

(3) Persetujuan Izin Edar sebagaimana dimaksud dalam Pasal 46 ayat (1) huruf b diterbitkan apabila hasil pembuatan obat skala komersial memenuhi persyaratan atau telah menyerahkan bukti importasi obat.

Pasal II

Peraturan ini mulai berlaku pada tanggal diundangkan.

Agar setiap orang mengetahuinya, memerintahkan pengundangan Peraturan ini dengan penempatannya dalam Berita Negara Republik Indonesia.

Ditetapkan di Jakarta
pada tanggal 26 Maret 2013
KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA,

ttd.

LUCKY S. SLAMET

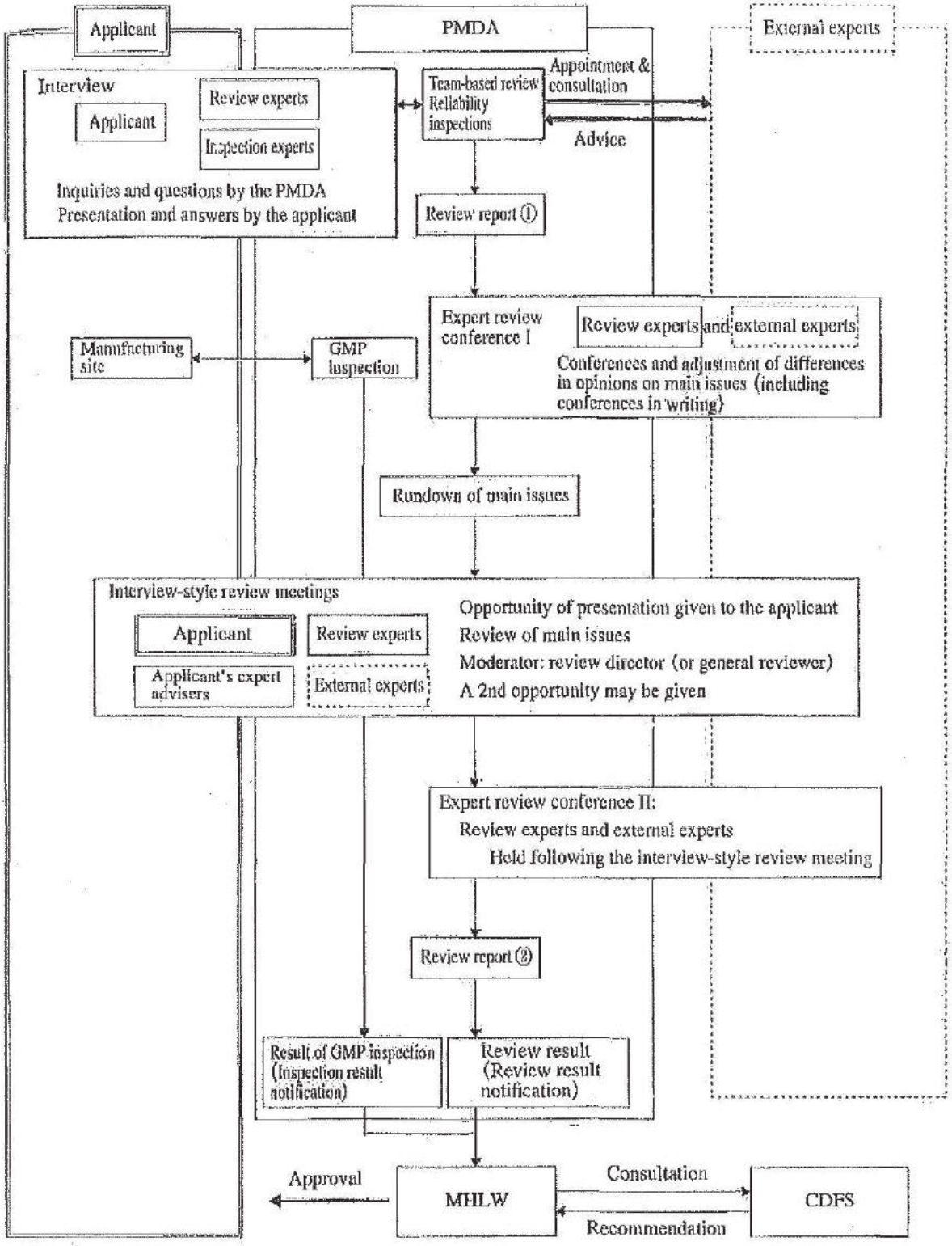
Diundangkan di Jakarta
pada tanggal 4 April 2013
MENTERI HUKUM DAN HAK ASASI MANUSIA
REPUBLIK INDONESIA,

ttd.

AMIR SYAMSUDIN

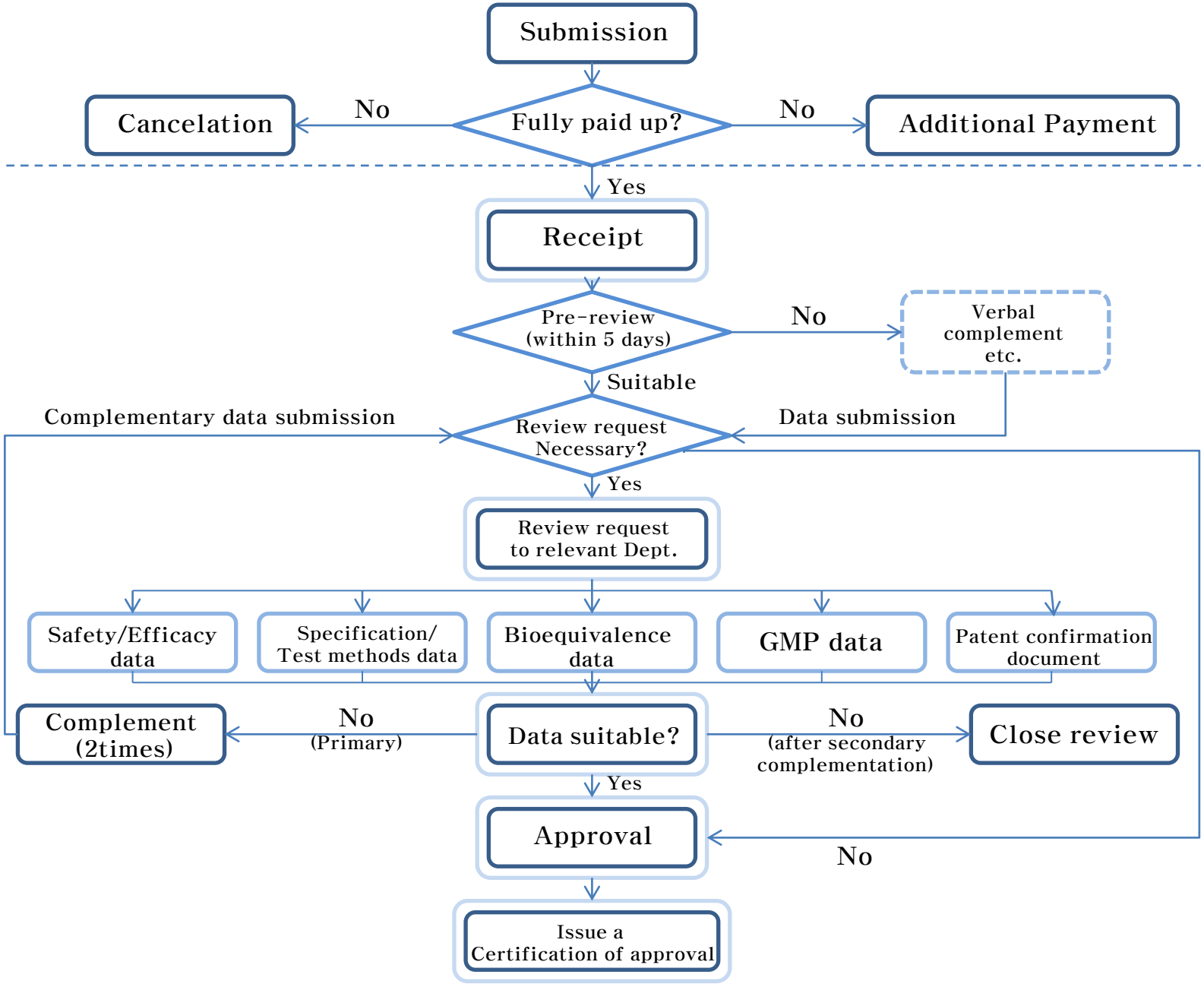
BERITA NEGARA REPUBLIK INDONESIA TAHUN 2013 NOMOR 540

Application Review Process

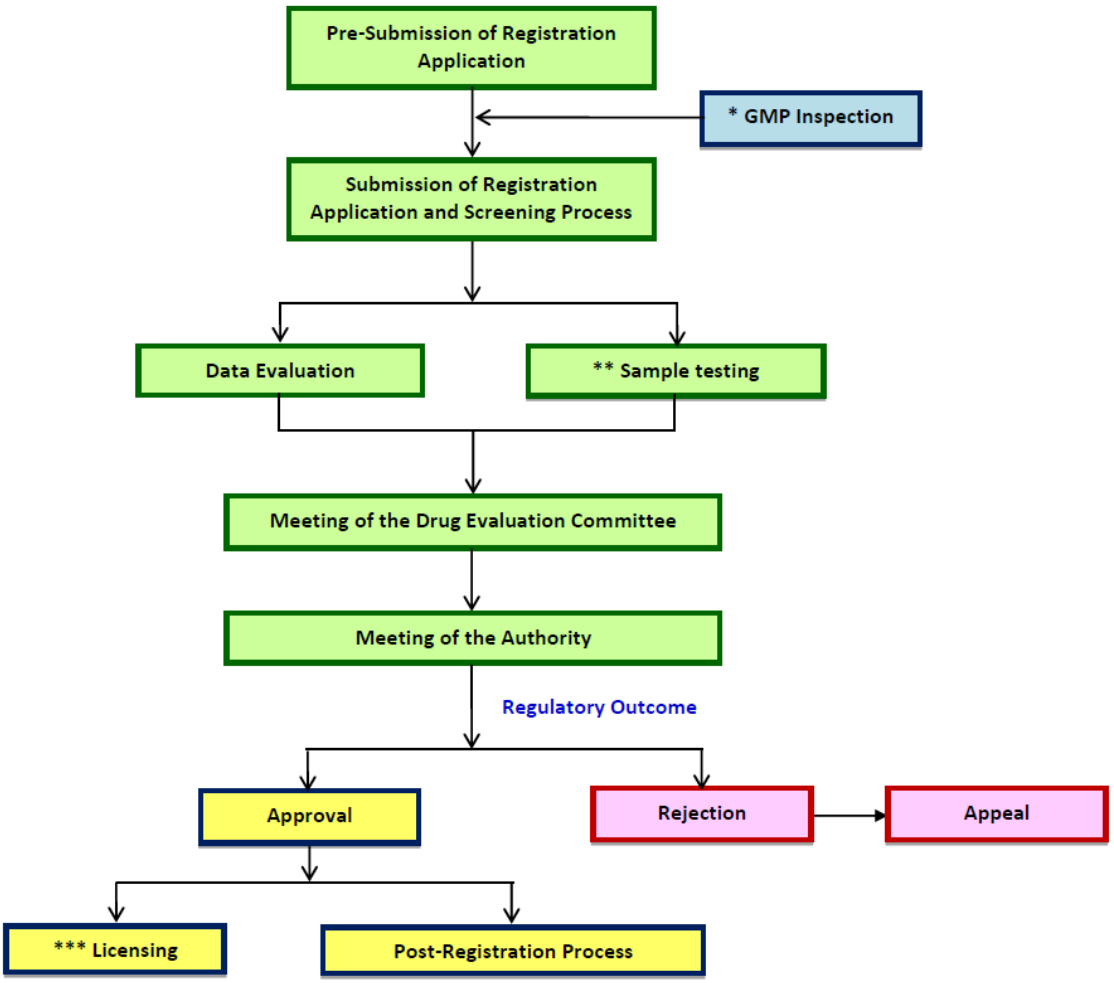


(Source: Jiho. Drug Approval Licensing Procedures in Japan 2010. Tokyo. Jiho, Inc, 2011; P. 489.)

Flow of Application process



Registration process includes quality control, inspection & licensing as well as post-registration process of medicinal products is illustrated in **Figure 2** below:



* Good Manufacturing Practice (GMP) Certification
** For natural products only
*** Application for Manufacturer, Import and/or Wholesale License

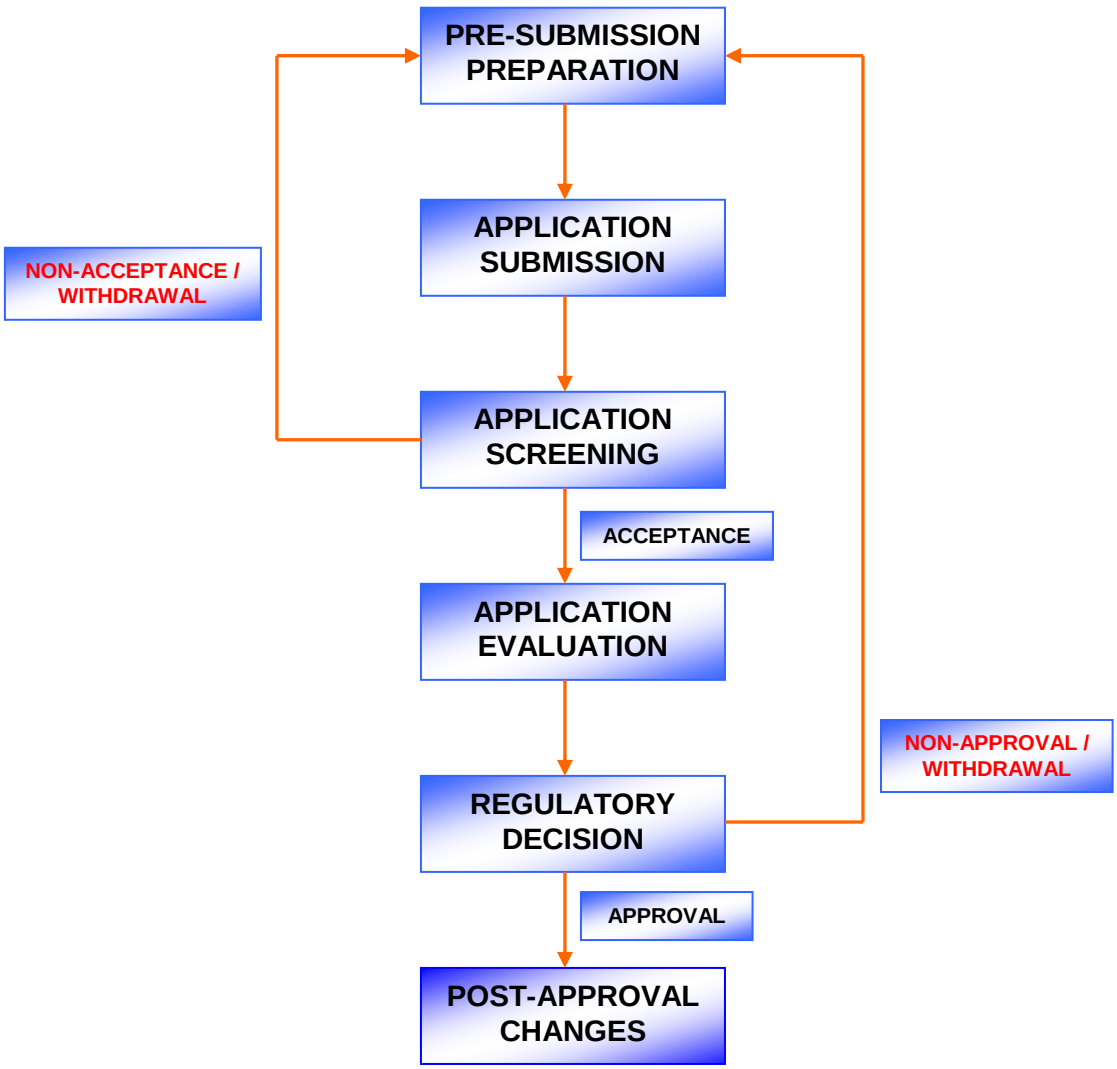
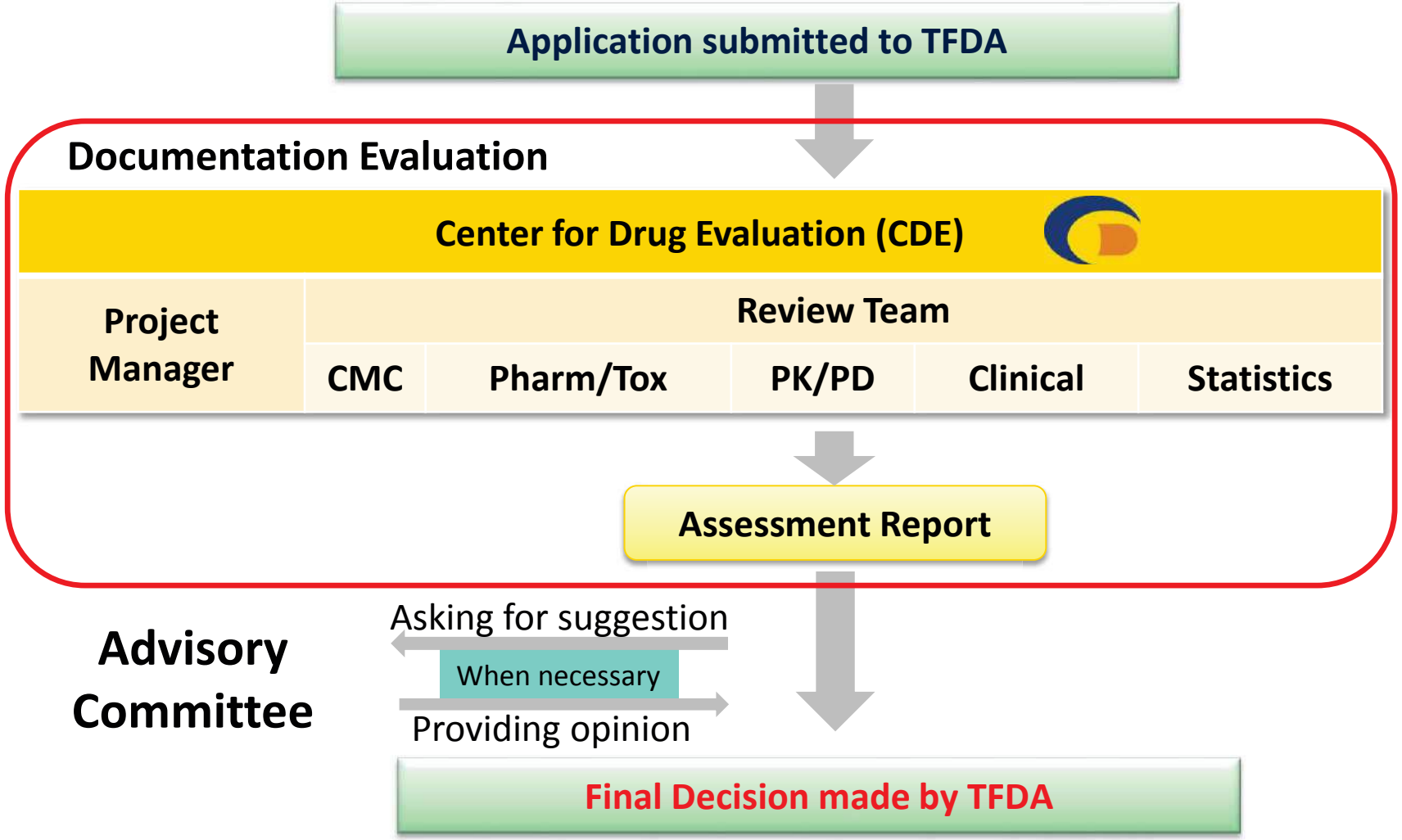


Figure 1 Registration Process for a Therapeutic Product

Source : GUIDANCE ON MEDICINAL PRODUCT REGISTRATION IN SINGAPORE, HSA

Review Process



NATIONAL AGENCY OF DRUG AND FOOD CONTROL
OF THE REPUBLIC OF INDONESIA

REGULATION OF THE HEAD OF THE NATIONAL AGENCY OF DRUG AND FOOD CONTROL OF THE REPUBLIC OF INDONESIA NUMBER 17 IN 2016
CONCERNING
THE SECOND AMENDMENT TO THE REGULATION OF THE HEAD OF THE NATIONAL AGENCY OF DRUG AND FOOD CONTROL NUMBER HK.03.1.23.10.11.08481 IN 2011 ON THE CRITERIA AND PROCEDURES OF DRUG REGISTRATION

WITH THE BLESSING OF GOD ALMIGHTY

THE HEAD OF THE NATIONAL AGENCY OF DRUG AND FOOD CONTROL OF THE REPUBLIC OF INDONESIA,

Considering: a. that in order to improve public service in drug and food monitoring, especially in drug registration process, it is necessary to change several stipulations in the Regulation of the Head of the National Agency of Drug and Food Control Number HK.03.1.23.10.11.08481 in 2011 on the Criteria and Procedures of Drug Registration which has been amended with the Regulation of the Head of the National Agency of Drug and Food Control Number 3 in 2013;

b. that based on the considerations stated in letter a, it is necessary to stipulate a Regulation of the Head of the National Agency of Drug and Food Control concerning the Second Amendment to the Regulation of the Head of the National Agency of Drug and Food Control Number HK.03.1.23.10.11.08481 in 2011 on the Criteria and Procedures of Drug Registration;

In view of:

1. Ordinance on Hard Drugs (*Sterkwerkende Geneesmiddelen Ordonnantie, Staatsblad* 1949:419);
2. Law Number 5 in 1997 on Psychotropic Drugs (State Gazette of the Republic of Indonesia in 1997 Number 10, Supplement to the State Gazette of the Republic of Indonesia Number 3671);
3. Law Number 8 in 1999 on Consumer Protection (State Gazette of the Republic of Indonesia in 1999 Number 42, Supplement to the State Gazette of the Republic of Indonesia Number 3821);
4. Law Number 35 in 2009 on Narcotics (State Gazette of the Republic of Indonesia in 2009 Number 143, Supplement to the State Gazette of the Republic of Indonesia Number 5062);
5. Law Number 36 in 2009 on Health (State Gazette of the Republic of Indonesia in 2009 Number 144, Supplement to the State Gazette of the Republic of Indonesia Number 5063);
6. Presidential Decree Number 103 in 2001 on the Position, Tasks, Function, Authority, Organizational Structure, and Work Procedures of Non-Departmental Government Agencies which has been amended several times, the last of which was with the Presidential Regulation Number 145 in 2015 on the Eighth Amendment to the Presidential Decree Number 103 in 2001 on the Position, Tasks, Function, Authority, Organizational Structure, and Work Procedures of Non-Ministerial Government Agencies (State Gazette of the Republic of Indonesia in 2015 Number 322);
7. Presidential Decree Number 110 in 2001 on Organizational Units and Tasks of Echelon I Non-Departmental Government Agencies which has been amended several times, the last of which was with the Presidential Regulation Number 4 in 2013 on the Eighth Amendment to the Presidential Decree Number 110 in 2001 on Organizational Units and Tasks of Echelon I Non-Ministerial Government Agencies (State Gazette of the Republic of Indonesia in 2013 Number

11);

8. Health Ministerial Regulation Number 1010/Menkes/Per/XI/2008 on Drug Registration which has been amended with the Health Ministerial Regulation Number 1120/Menkes/Per/XII/2008;
9. Decree of the Head of the National Agency of Drug and Food Control Number 02001/SK/KBPOM in 2001 on the Organization and Working Procedures of the National Agency of Drug and Food Control which has been amended with the Decree of the Head of the National Agency of Drug and Food Control Number HK.00.05.21.4231 in 2004 concerning the Amendment to the Decree of the Head of the National Agency of Drug and Food Control Number 02001/SK/KBPOM in 2001 on the Organization and Working Procedures of the National Agency of Drug and Food Control;
10. Regulation of the Head of the National Agency of Drug and Food Control Number HK.03.1.23.10.11.08481 in 2011 on the Criteria and Procedures of Drug Registration which has been amended with the Regulation of the Head of the National Agency of Drug and Food Control Number 3 in 2013 concerning the Amendment to the Regulation of the Head of the National Agency of Drug and Food Control Number HK.03.1.23.10.11.08481 in 2011 on the Criteria and Procedures of Drug Registration (Official Gazette of the Republic of Indonesia in 2013 Number 540);
11. Regulation of the Head of the National Agency of Drug and Food Control Number HK.03.01.23.12.11.10217 in 2011 on Equivalence Testing-Mandatory Drugs (Official Gazette of the Republic of Indonesia in 2012 Number 120);
12. Regulation of the Head of the National Agency of Drug and Food Control Number HK.03.1.34.11.12.7542 in 2012 on the Technical Guide of Proper Drug Distribution Methods (Official Gazette of the Republic of Indonesia in 2012 Number 1268);
13. Regulation of the Head of the National Agency of Drug and Food Control Number HK.03.1.33.12.12.8195 in 2012 on

the Implementation of Proper Drug Manufacturing Methods (Official Gazette of the Republic of Indonesia in 2013 Number 122);

DECIDED:

To enact: REGULATION OF THE HEAD OF THE NATIONAL AGENCY OF DRUG AND FOOD CONTROL CONCERNING THE SECOND AMENDMENT TO THE FOOD AND DRUG MONITORING AGENCY HEAD REGULATION NUMBER HK.03.1.23.10.11.08481 IN 2011 ON THE CRITERIA AND PROCEDURES OF DRUG REGISTRATION.

Article I

Several stipulations in the Regulation of the Head of the National Agency of Drug and Food Control Number HK.03.1.23.10.11.08481 in 2011 on the Criteria and Procedures of Drug Registration which has been amended with the Regulation of the Head of the National Agency of Drug and Food Control Number 3 in 2013 are amended as follows:

1. Article 30 is changed into the following:

Article 30

(1) Excluded from the terms stipulated in Article 28 are Registration of Variation for category 4, category 5, and category 6 drugs as stipulated in Article 5 verse (3) letter a, letter b, and letter c, as well as Re-Registration of category 7 as stipulated in Article 5 verse (4).

(2) Registration of Variation for category 4 drugs as stipulated in verse (1) only applies to registration of variation in relation to drug quality which does not require clinical testing.

2. Article 31 is changed into the following:

Article 31

The evaluation tracks as stipulated in Article 28 verse (1) consist of:

1. The 7 (seven)-day track covering registration application for export-only drugs

2. The 10 (ten)-day track covering re-registration without any changes
3. The 40 (forty)-day track covering registration of minor variation which requires approval;
4. The 100 (one hundred)-day track covering:
   a. New Registration of New Drugs and Biological Products indicated to be used to treat diseases that are life-threatening, and/or highly communicable, and/or do not yet have or lack other options of safe and effective treatments;
   b. New Registration of New Drugs and Biological Products which based on justification are indicated to be used for serious and rare diseases (orphan drugs);
   c. New Registration of New Drugs, Biological Products and Copy of Generic Drugs intended for public health programs that are equipped with documents supporting the programs' needs or data supporting the drugs as essential drugs;
   d. New Registration of New Drugs and Biological Products which have undergone a process of new drug development by the Pharmaceutical Industry or a research institution in Indonesia with all stages of clinical testing performed in Indonesia;
   e. Registration of major variation of new indication/new posology for the intended drugs as stipulated in letter a, letter b, letter c, and letter d;
   f. Registration of major variation which is not included in letter e.
5. The 150 (one hundred and fifty)-day track covering:
   a. New Registration of New Drugs and Biological Products, and registration of major variation of new indication/new posology which have been approved in countries that have applied a harmonized evaluation system and in countries with a well-known evaluation system;

b. New Registration of New Drugs and Biological Products, and registration of major variation of new indication/new posology which have been approved in at least 3 (three) countries with a well-known evaluation system;

c. New Registration of Copy Drugs.

6. The 300 (three hundred)-day track covering New Registration of New Drugs, Biological Products and Similar Biological Products, or registration of major variation of new indication/new posology which are not included in evaluation tracks stipulated in numbers 4 and 5.

3. Article 35 is changed into the following:

Article 35

(1) Registration of variation for category 6 as stipulated in Article 5 verse (3) letter c is applied for by filling in a form, an example of which is included in Appendix I, and enclosing a Registration of Variation document as stipulated in Article 34 verse (3).

(2) The applicant may make the changes stated in verse (1) and report to the National Agency of Drug and Food Control every 6 (six) months cumulatively for all of the changes.

(3) Implementation of the changes stated in verse (2) is done through a mechanism of change control.

(4) If the reported changes are not in accordance with the type of changes stipulated in Appendix XV letter B number 3, then the registration shall be processed according to the determined registration of variation category.

(5) Appendix XV letter B number 3 is changed into that which is included in the amendment to Appendix XV letter B number 3, which forms an inseparable part of this Agency Head Regulation.

Article II

This Agency Head Regulation takes effect at the time it is stipulated.

So that everyone is aware of it, this Agency Head Regulation is published in the Official Gazette of the Republic of Indonesia.

Enacted di Jakarta

on May 24, 2016

HEAD OF THE NATIONAL AGENCY OF DRUG AND FOOD CONTROL OF THE REPUBLIC OF INDONESIA,

signed

ROY A. SPARRINGA

Stipulated in Jakarta
on August 4, 2016

DIRECTOR GENERAL OF REGULATORY LAW
JUSTICE AND HUMAN RIGHTS MINISTRY
OF THE REPUBLIC OF INDONESIA,

signed

WIDODO EKATJAHJANA

OFFICIAL GAZETTE OF THE REPUBLIC OF INDONESIA IN 2016 NUMBER 1140

ATTACHMENT
DECREE OF THE HEAD OF NATIONAL AGENCY OF DRUG AND FOOD CONTROL
NUMBER 17 YEAR 2016
ON SECOND CHANGES TO
HEAD OF NATIONAL AGENCY OF DRUG AND FOOD CONTROL REGULATION
NO: HK. 03.1.23.10.11.08481 OF 2011
ON THE CRITERIA AND PROCEDURE OF DRUG REGISTRATION

Category 6: Registration of Drug Minor Variation which
Need an Approval (VaMi-A)

No	Type of Modification	Criteria	Submit Documents
Modification of relevant product information and/or labelling			
1	Modification or adding of trademark (logo) (including trademark/logo of the company)	1. Claims in product information are unmodified 2. Specification of the packaging is unmodified	Picture of primary and/or secondary packaging to be marketed from all angles (including product information).
2	A stringent additional claims of side effects and/or contraindication in the product information		Picture of primary and/or secondary packaging to be marketed from all angles (including product information).
3	Decreasing of manufacturing location/space (including active ingredient, intermediate product or finished drug, packaging location, batch released location	1. Manufacturing location still available with the same usage/function (including: active ingredient, intermediate product or finished drug, packaging location, batch released location) has been approved 2. Decreasing of manufacturing location is not due to the critical factor relevant to manufacturing procedure	
4	Modification of the	1. Active ingredient is	Picture of primary and/or

	name of active ingredient	unmodified 2. The new name of active ingredient should be in lined with INN/Pharmacopoeia	secondary packaging to be marketed from all angles (including product information).
5	Modification of the primary packaging that is not contacted with the drug (such as the color of flip-off caps, the color of the ring on the ampule, modification on the shield of the needle, used different plastic)	1. Not important past of packaging material that affect to: distribution, usage, safety or drug stability 2. Specification of primary packaging material that contacted with the drug is unmodified	Specification and analytical method of packaging material
6	Eradication of foreign language of drug labelling	1. Claims in product information are unmodified	Picture of primary and/or secondary packaging to be marketed from all angles (including product information).
7	Modification of the dimention of packaging	1. Not for sterile preparation 2. Not any modification or the specification of packaging material except dosage form and/or the dimension 3. Not for head space or surface/volume ratio 4. Claims on product information are unmodified	1. Picture of primary and/or secondary packaging to be marketed from all angles (including product information). 2. Specification of packaging material
8	Modification of design of packaging	1. Claims in product information and claims in labelling are unmodified 2. Valid only for the	Picture of primary and/or secondary packaging to be marketed from all angles (including product

		modification of text located and picture (graphic), color and line 3. Not included the modification of the picture (graphic) 4. Not content the sentences/ information that are characterized of promotion	information).
9	Modification of the address (written) of the applicant/ pharmaceutical industry/license	1. Location of applicant/ pharmaceutical industry/license are unmodified	1. Letter of information of changing address 2. Picture of primary and/or secondary packaging to be marketed from all angles (including product information).
10	Modification of batch number system		1. Explanation of new batch number system
A. Modification related to the quality of active ingredient			
1			
2			
3	Modification of the name and/ or address of the manufacturer of active ingredient	1. Location of the manufacturer of active ingredient is not changed	Supporting document of the modification of name and/or address of active ingredient manufacturer
4	Update Ph. Eur. Certificate of Suitability (CEP)	1. Not included biological product 2. Specification of drug (released and shelf life) are unmodified 3. Manufacturing procedure	New Certificate of Suitability (Ph. Eur.)

		of active ingredients are not used human/animal sources which need viral safety data	
5	Modification of Pharmacopoeia edition stated for active ingredient	1. Analytical method of active ingredients are unmodified 2. Specification of active ingredient and finished drug are unmodified	Refrences of relevant Pharmacopoeia
6	Fixing the limit of specification of active ingredients	1. Modification is still in the limit of valid standard 2. Analytical procedure is unmodified	1. Specification of the active ingredient 2. Certificate analysis of active ingredient
7	Modification of the specification of active ingredient to fulfill the criteria of new Pharmacopoeia	1. Specification of drug (released and shelf life) are unmodified 2. Specification of impurity and active ingredient are unmodified (particle size profile, polymorphism form) 3. Addition of validation from the new method of Pharmacopoeia or modification is not necessary	1. Specification and analytical method of active ingredient 2. Certificate analysis of active ingredient 3. Result of batch analysis of 2 batches of active ingredient of production scales for all analysis in new specification 4. References of relevant Pharmacopoeia
8	Addition of analytical parameters and limit of specification in process control of manufacturing procedure of active ingredient	1. The modification is not due to the affect to drug manufacturing procedure 2. The specification of active ingredients are unmodified 3. The specification of active	1. Manufacturing procedure 2. Details of analytical procedure and validation data of new analytical method/procedure 3. Batch analysis data using 3 batches of active

		ingredients are unmodified	ingredients for all study in new specification
9	Minor modification of analytical procedure of active ingredient	1. Analytical method is unmodified (inexample, modification in the length of coloumn or temperature, but the method and type of coloumn are unchanged) 2. Study of revalidation has been conducted conformed to the study protocol 3. Result of validation method appointed that new analytical procedure is similar/equivalent with the former procedure 4. Specification of drug (released and shelf life) are unmodified 5. Not valid for addition of analytical procedure	1. Specification and analytical method of active ingredient 2. Certificate of analysis of active ingredient 3. Comparison of the result of validation or comparison of the result of drug analysis that the new analytical procedure and the former procedure are similar/equivalent
10	Modification of analytical method to determine the concentration of active ingredient conformed to fulfill the criteria of Pharmacopoeia	1. Specification of active ingredient are unmodified 2. Specification of drug (released and shelf life) are unmodified	1. Analytical method of active ingredient 2. Verification of analytical procedure of active ingredient 3. Certificate analysis of active ingredient 4. Standard reference
11	Modification of storage condition of active ingredient	1. Result of stability study specification still fulfilled approved criteria formerly 2. The modification is not	1. Report of the stability of active ingredient 2. Specification of active ingredient

		due to the affect in manufacturing procedure of active ingredient or the problem of stability 3. No modification of repeated study period of active ingredient	3. Result of batch analysis of finished drug
12	Modification of working cell/ seed bank	1. Manufactured of approved working cell/seed bank and using approved master cell seed bank and approved SOP with the similar passage level of approved working cell/seed bank 2. Statement that specification of drug released and shelf life of finished drugs are unmodified	1. Comparative batch analysis data (tabulated) of minimally 3 batches of active ingredients from the new and submitted cell seed bank 2. Comparative batch of active ingredients shows a comparable result
13			
B.Modification relevant to the quality of finished product			
1	Minor modification of drug manufacturing	1. Not includes biological product and sterile preparation 2. Principally the whole manufacturing is still similar 3. New process gives the similar result from the aspect of quality, validity, specification of drug, safety and efficacy 4. No modification of qualitative and	1. Drug manufacturing procedure 2. Batch analysis data of drug 3. For all solid preparation, dissolution profile data comparable from 1 batch production representative and comparisons of 3 batches of last production of mnaufacturing procedure of former drug 4. Report of drug stability

		quantitative of impurity profile or physicochemical chaacteristics 5. Drug stability study has been conducted on minimally 3 months from 1 batch of pilot scale or production scale 6. Manufacturing location is not modified 7. Dissolution profiles are unmodified	and commitment of drug stabiity if the report of drug stability has not completed 5. Justification of not conducted BE study
2	Modification of addition of drug study location	1. Transfer of drug analytical method from former location to the new location has fulfilled the criteria 2. Specification of drug is unmodified 3. Product owner is still similar 4. Study location has been registered	1. Result of batch analysis of new drug 2. Specification of the drug 3. Reference standard 4. Result of batch analysis of the drug 5. Report of transfered of drug analytical procedure
3	Fixing the limit of specification of drug released	1. The modification is still in the range of approved specification limitation 2. Analytical procedure is unmodified, or only minor modification of analytical procedure	1. Specification of drug 2. Certificate analysis of new drug
4	Addition of parameters of analysis and limit of specification or process control in drug manufacturing	1. The modification is not due to the affect to drug manufacturing procedure 2.Specification of drugs are unmodified	1. Manufacturing procedure 2. Details of analytical procedure and validation data of new analytical

	procedure	3. Vallidation of analytical method has been conducted	method/procedure 3. Batch analysis data using 3 batches of active ingredients for all study in the specification of new drug
5	Fixing the limit of specification of in-process during drug manufacturing	1. The modification is not due to the affect of drug manufacturing procedure or problem of stability 2. Specification of drug (released and shelf life) are unmodified 3. The modification is still in the limit of valid standard 4. Analytical procedure is unmodified for only a minor modification	1. Specification of in-process during manufacturing of new drug
6	Addition of parameters of drug analysis	1. Modification is not due to the affect of drug 2. Specification of drug besides the additional parameters of drug analysis are unmodified	1. Specification of drug 2. Drug analytical procedure 3. Result of batch analysis of finished drug (2 batches) 4. Report of validation of drug analytical procedure (if necessary)
7	Fixing the limit of specification of inactive ingredient	1. Modification not due to the affect of drug manufacturing procedure 2. The modification is still in the limit of valid standard 3. Analytical procedure is unmodified	1. Specification of new active ingredient 2. Certificate analysis of inactive ingredient with new specification
8	Minor modification of analytical procedure of	1. Analytical procedure is unmodified (for example,	1. Specification and analytical method of

	inactive ingredient	modification of coloumn length or temperature, but no different in the method and type of coloumn) 2. Analytical procedure is not biological/immunological / immunochemistry analytical procedure or analytical procedure using biological reagents	inactive ingredient 2. Certificate of analysis of inactive ingredient
9	Modification of analytical procedure of inactive ingredient conforme to compendial monography or relevant one	1. Specification of inactive ingredient is unmodified (such as: particle size, polymorph form)	1. Specification of active ingredient 2. Analytical procedure of inactive ingredient 3. Certificate of analysis of inactive ingredient 4. Compendial references or relevant supporting documents
10	Addition of study parameters of the specification of inactive ingredient	1. Modification not due to the affect of drug manufacturing procedure 2. The modification is still in the limit of valid standard	1. Specification and analytical procedure of inactive ingredient 2. Batch analytical data of inactive ingredient with former specification that is submitting
11	Modification of analytical procedure of inactive ingredient, including the changement of analytical procedure	1.Re-validation study has been conducted conformed to the study protocol 2. Result of validation method appointed that new analytical procedure	1. Specification and analytical procedure of inactive ingredient 2. Review of specification of drug impurities (if any)

		is similar/equivalent to former procedure 3. Specification of drug (released and shelf life) are unmodified	
12	Modification of the specification of inactive ingredient to fulfill the compendial criteria	1. Specification of drug (released and shelf life) are unmodified	1. Specification and analytical procedure of inactive ingredient 2. Certificate of analysis of inactive ingredient 3. Result of batch analysis of finished drug from 2 batches of 2 batches of drugs of production scales 4. Relevant compendial references
13	Modification of the sources of inactive ingredient or reagent with Transmissible Spongiform Encephalophaties (TSE)/ Bovine Spongiform Encephalophatis (BSE) risks	1. Specification of inactive ingredient released and drug released and specification of shelf life are unmodified 2. Not for inactive ingredient or reagent that are used in manufacturing biological product or drugs containing biological active ingredient	A. Quality documents 1. Statement of inactive ingredient or reagents manufacturer that the sources are herbal, animal, or synthesis 2. Certificate of free from BSE/TSE
14	Major modification of heavy tablet coating or heavy capsule shell of the oral preparation immediate release	1. Drug dissolution profile with new heavy tablet coating or heavy capsule shell (minimal 2 batches of pilot scales) equivalent to former drug	1. Description and formula 2. Specification of the drug 3. Result of batch analysis of the drug with old and new heavy tablet coating/capsule shell

		2. Specification ofdrug, only weight and dimention modification 3. Coating is not a critical factor for drug released mechanism	4. Comparable dissolution test data of minimal 1 batch of pilot scale between approved and submitted drug and formula, if required 5. Report of drug stability and commitment of drug stability if the report of drug stability has not completed
15	Modification or adding imprint, bossing or other signs (except middle line of tablet of printing or the capsule, includes the substitution or addition olink used to label the product	1. Specification of drug (released and shelf life) are unmodified 2. The ink which is used should fulfill the criteria and Pharmaceutical regulation 3. The new description not induce ambiguous with registered drug	A. Quality documents 1. Specification of the drug 2. Certificate of analysis of ink/printing material 3. Product information and its photo (if necessary)
16	Modification or inactive ingredient synthesis (non compendial)	1. Not included inactive ingredient of biological product (adjuvant, absorbent, preservative) 2. Not affected to the specification of inactive ingredient 3. No qualitative and quantitative modification of impurity profile or physicochemistry characteristic 4. Route of synthesis and specification of inactive	1. Comparison of batch analysis data of inactive ingredient of minimal 2 batches of drugs of pilot scales which are manufactured using manufacturing procedure of new and old inactive ingredient 2. Comparison of drug's dissolution profile data of minimal 2 batches of drugs of pilot scales

		ingredient are similar and no modfication of impurity profile qualitatively or quantitatively	
17	Subsitution for enlargement of drug secondary location packaging	1. The result of last 2 (two) years inspection and satisfied 2. Manufacturing location is registered	Product information (if necessary) and labelling on the secondary package (if necessary)
18	Fixing the limit of primary packaging specification of drugs	1. The modification is in the range of valid standard 2. Analytical procedures are unmodifie, or only minor modification in the manufacturing procedure	Specification of the packaging
19	Modification of qualitative and quantitative composition of drug primary packaging material	1. Not included biological product and sterile product 2. Modification onlyon the type and material of the same packaging 3. Submitted packaging material similar/equivalent with the approved packaging material	
20	Addition of substitution of measureing device that is not as part of primary packaging (not included spacer device for metered dose inhaler)	1. Submitted measurement device should include accurate dose in lined with approved posology and support by appropriate study data 2. New measurement device compatible with the drug	1. Specification and analytical method of packaging material 2. Data of the result of measurement device calibration 3. Product information and labelling on the primary

		3. Modification not induce the modification of drug information	and secondary package
21	Modification of analytical procedure of primary packaging material of drug including substitution or addition of analytical procedure	Specification of drug are unmodified	Specification and analytical method of packaging material
22	Modification or addition of supplier of the component of packaging or health device associate to drug, not including supplier spacer devices for metered dose inhaler	Specification of packaging material or health device are unmodified	1. Letter of information of substitution or addition of supplier 2. Biological product only complete with comparison result of the study (control) of the component of packaging or health device associate with drug between new supplier and approved supplier
23	Decrease of supplier component of packaging or health device that associated with drug, not included supplier spacer devices for metered dose inhaler	1. Modification not due to the affect of drug manufacturing procedure	
24	Addition of parameters of analytical method of primary packaging of drug	1. Modification is not due to the affect of manufacturing process of drug	A. Quality documents 1. Specification and analytical method of packaging material 2. Report of validation of primary packaging

25	Decreasing the limit of drug expiration date: packaging has not been opened	1. Specification of drug (released and shelf life) are unmodified 2. Stability study has been conducted conformed to the approved study protocol and the result fulfilled the criteria of specification	1. Product information and photo (if necessary) 2. Specification of drug 3. Report of drug stability
26	Reduction of the limit of drug expiration date after the package has been open	1. Specification of drug (released and shelf life) are unmodified 2. Stability study has been conducted conformed to the approved study protocol and the result fulfilled the criteria of specification	1. Product information and photo (if necessary) 2. Specification of drug 3. Report of drug stability

The Head of National Agency of Drug and Food Control
of the Republic of Indonesia

Roy A. Sparringa

THE GOVERNMENT OF VIETNAM	THE SOCIALIST REPUBLIC OF VIETNAM Independence - Freedom - Happiness
No: 54/2017/NĐ-CP	*Hanoi, 08 May 2017*

DECREE
Detailing a number of articles and measures for implementation of Law on Pharmaceutical

Pursuant to the Law on Organization of the Government dated 19 June 2015;
Pursuant to the Law on Pharmacy dated 06 April 2016;
Pursuant to the request of the Minister of Health;
The Government issued the Decree detailing some articles and measures for implementation of the Law on Pharmaceutical.

Chapter I
GENERAL PROVISIONS

Article 1. Scope of regulation and subjects of application

1. This Decree provides for Certificate of pharmacy practice; pharmaceutical business operations; drug exportation, drug importation; marketing registration of medicinal materials, excipients, capsule shells; the assessment of drug manufacturing establishments located in foreign countries; powers, format, formalities pertaining to the recall of drug raw materials; handling measures for recalled drug raw materials; dossiers, procedures, formalities and competence in the issuance of confirmation for drug information, drug advertisement and drug price regulatory measures.
2. This Decree shall apply to national and foreign agencies, organizations, individuals engaging in pharmaceutical related operations in Vietnam.

Article 2. Definition of terms

In this Decree the below terms shall be construed as follows:
1. Drug information is the collection, provision of drug-related information covering indications, contraindications, dosage, administration routes, adverse drug reactions, and other information pertaining to drug quality, safety and efficacy, disseminated by establishments responsible for drug information with the aim of meeting the information requirements of pharmaceutical regulatory authorities, organizations, individuals practicing medicine, pharmacy or users of drugs.
2. Drug introduction workshops are introductory sessions on drugs or drug related scientific symposia intended for healthcare practitioners.
3. Semi-finished drug is a product that has undergone one, several or the all operations in the processing, manufacturing process except the final packaging operation.
4. Drug's import price is the customs value of an imported drug as stated in the customs value declaration form at Vietnam port of entry after customs clearance.
5. Total cost price of a domestically produced drug is the total of the direct cost of raw materials, consumables , tooling, equipment, energy plus (+) direct labour cost plus (+) direct cost of machine depreciation plus (+) production overhead cost plus (+) financing cost (if any) plus (+) selling cost plus (+) management cost minus (-) cost allocated to by-products (if any).
6. Drug's wholesale price is the selling price at which a drug is sold by pharmaceutical businesses to one another or its selling price chargeable by a business establishment to medical service establishments.
7. Drug's intended wholesale price is the price declared by the drug's importer, manufacturer or contract giver (in the case of contract manufacturing drugs) to the competent state authority.
8. Drug's retail price is the price at which a drug is sold directly to buyers at retail establishments.
9. Retail mark-up is the monetary differential between the prices at which a retail establishment sells and buys a drug.
10. Retail mark-up level is the percentage (%) ratio between the retail mark up and purchase price of a drug a incurred by the retail establishment.

Chapter II
CERTIFICATE OF PHARMACY PRACTICE
Section I
DOSSIERS, FORMALITIES FOR THE ISSUANCE, REISSUANCE, CONTENT-MODIFICATION AND WITHDRAWAL OF CERTIFICATE OF PHARMACY PRACTICE

Article 3. Details regarding application dossiers for the issuance of Certificate of pharmacy practice

1. Dossiers applying for Certificate of pharmacy practice issuance shall be prepared in accordance with the provisions of Article 24 of Pharmaceutical law and shall cover the following:

a) Application for Certificate of pharmacy practice, using Form no. 2 in Appendix I of this Decree, 02 4cmx6cm portrait photographs of the applicant taken in front of a white background, not older than 6 months to the date of dossier submission;

b) Authenticated duplicate copy of professional diploma. Diplomas granted by foreign training institutions must be accompanied by an authenticated duplicate copy of the equivalency certificate issued by the competent authority as required in clause 2 Article 18 of this Decree;

c) Original or authenticated copy of Medical certificate issued by a medical service establishment in accordance with the Law on medical examination and treatment;

d) Original or authenticated copy of Certification of length of practice experience conforming to Form no. 3 Appendix I of this Decree. Where the applicant practiced at several establishments, the practice experience length shall be the cumulative total of all practice periods at all such establishments but a separate Certification for each of such establishments must be provided.

đ) When an application for Certificate of pharmacy practice is made for several different operating areas requiring different lengths of practice experience, at different host establishments, the dossier must contain Certifications confirming the length of practice experience and competency areas from one or several establishments meeting the requirements of each of the respective operating areas, job positions applied for. Where the various operating areas applied for require the same length of practice experience and host establishment only one such Certification of practice experience length shall suffice.

e) Original or authenticated copy of Certification of exam results issued by the exam administering establishment referred to in point c clause 1 Article 28 of this Decree must be submitted for exam-based Certificate of pharmacy practice;

g) Foreign nationals, Vietnamese nationals permanently residing abroad applying for Certificate of pharmacy practice through dossier examination route shall submit documentation demonstrating the attainment of language proficiency as stipulated under clause 2 Article 14 of Pharmaceutical law.

2. Documents that are issued by the foreign competent authorities must be consular legalized in accordance with the regulations on consular legalization. These documents must be accompanied by a Vietnamese translated version, notarized in accordance with applicable regulations.

3. The documents required in this Article shall be submitted in 01 set.

Article 4. Details regarding dossiers applying for reissuance of Certificate of pharmacy practice

1. Application dossiers for reissuance of Certificate of pharmacy practice shall be prepared in accordance with the provisions of Article 25 of Pharmaceutical law and shall cover the following:

a) Application for reissuance of Certificate of pharmacy in conformance with Form no. 4 in Appendix I of this Decree, enclosed with 02 4cmx6cm portrait photographs of the applicant taken in front of a white background, not older than 6 months to the date of dossier submission;

b) Duplicate copy of the previously issued Certificate of pharmacy practice, in the case such Certificate was lost.

2. The documents required in this Article shall be submitted in 01 set.

Article 5. Details regarding dossiers applying for content modification of Certificate of pharmacy practice

1. Dossiers requesting content modification of certificate of pharmacy practice shall be prepared in accordance with the provisions of Article 26 of Pharmaceutical law and shall cover the following:
a) Application for content-modification of Certificate of pharmacy practice in conformance with Form no. 5 in Appendix I of this Decree, 02 4cmx6cm portrait photographs of the applicant taken in front of a white background, not older than 6 months to the date of dossier submission;
b) With respect to changes in personal information of the pharmacy practitioner, one of the following documents substantiating the changes under review shall be required: identification card, passport, residence registration booklet, citizenship card or certification papers pertinent to the changes under review issued by the competent authority according to applicable legislation.
c) With respect to changes in scope of professional practice, the following documents substantiating the changes under review shall be required: corresponding professional diploma and certification of length of practice experience at suitable pharmaceutical establishments.
2. The documents stipulated in point b, point c of this clause must be submitted in original or authenticated duplicate copy.
3. Documents that are issued by the foreign competent authorities must be consular legalized in accordance with the regulations on consular legalization. These documents must be accompanied by a Vietnamese translated version, notarized in accordance with applicable regulations.
4. The dossiers as required in this Article shall be submitted in 01 set.

Article 6. Details regarding the issuance, re-issuance, content-modification, of Certificate of pharmacy practice
1. Applicants shall submit application dossiers for the issuance, reissuance, modification of Certificate of pharmacy practice in person or by post to:
a) Ministry of Health in the case of issuance, reissuance, modification of certificate of pharmacy practice through licensure exam route;
b) Health Department of provinces, centrally affiliated cities in the case of issuance, reissuance, modification of Certificate of pharmacy practice through dossier examination.
2. Upon receipt of an application dossier, the dossier receiving authority shall issue the applicant a Dossier receipt using Form no. 6 in Appendix I of this Decree.
3. Where there is no request for follow up supplementation, revision, the dossier receiving authority shall be responsible to:
a) Issue Certificate of pharmacy practice within 20 days from the date recorded in the Dossier; If the application is refused, there shall be written response issued with refusal reasons clearly stated;
b) Issue a certificate of pharmacy practice within 05 days from the date recorded on the Dossier receipt with respect to cases of Certificate being withdrawn under the provisions of clause 3 Article 28 of Pharmaceutical law. If the application is refused there shall be a written response with refusal reasons clearly stated;
c) Reissue, modify the content of, certificate of pharmacy practice within 10 days, from the date recorded on the Dossier receipt. If the application is refused, there shall be a written response with refusal reasons clearly stated.;
4. If there is a follow up request for dossier revision, supplementation, the dossier receiving authority shall issue to the applicant a written notice to the effect within the time limits of:
a) 10 working days, from the date recorded on the Dossier receipt in the case of application for certificate issuance;
b) 05 working days from the date recorded on the Dossier receipt in the case of application for certificate issuance, modification.
5. Upon receipt of the follow up submission the dossier receiving authority shall issue to the applicant a Receipt of follow up submission using Form no. 01 in Appendix I of this Decree
a) If the follow up submission does not correctly address the requirements the certificate issuing authority shall notify the concerned applicant for the latter to complete the dossier according to the provision of clause 4 of this Article.
b) If there is no further follow up request the dossier receiving authority shall proceed according to the provision of clause 3 of this Article.

6. The applicant must respond to the follow up request within 60 days from notification date. Past this timeline or 12 months from the date of initial dossier submission if the applicant fails to respond or the dossier still fails to meet the eligibility requirements the application dossier shall become void.
7. Within 05 working days from the date of Certificate issuance, reissuance, modification, the dossier receiving authority shall update the following information on its web portal
a) Name and address of Certificate holder;
b) Certificate number;
c) Professional practice areas;
8. Certificate of pharmacy practice shall be made in 02 copies, one of which to be issued to the applicant; one for retention at the Certificate issuing authority office.
9. Applicants for certificate reissuance or modification shall surrender the previously issued Certificate upon being issued with a new one.
In the case of Certificate loss, the applicant must submit an Application for reissuance using Form no, 04 Appendix I of this Decree.
10. Form template for Certificate of pharmacy practice:
a) Form no. 6 Appendix I of this Decree shall be applicable for Certificate of pharmacy practice issued through dossier examination route;
b) Form no. 7 Appendix I of this Decree shall be applicable for Certificate of pharmacy practice issued through licensure exam route.
11. The Minister of Health shall provide for the organization and operation of Advisory council for issuance of certificate of pharmacy practice.
12. Applicants for Certificate to be reissued under the provision of clause 8 Article 24 of Pharmaceutical law shall be exempt of fee paying.

Article 7. Formalities for withdrawal of Certificate of pharmacy practice
1. Withdrawal of certificate of pharmacy practice of cases stipulated under clause 1,4, 5, 6, 7, 8, 9, 10 and 11 Article 28 of Pharmaceutical law:
Within 05 working days from receipt of the conclusions of audits, inspections of which a recommendation is made for the withdrawal of a Certificate or the discovery of cases stipulated under clause 1, 4, 5, 6, 7, 8, 9, 10 and 11 Article 28 of Pharmaceutical law, the Certificate issuing authority shall withdraw the concerned Certificate under its jurisdiction; otherwise it shall respond in writing to the recommending authority and state the reasons of non withdrawal
2. Withdrawal of certificate of pharmacy practice of cases stipulated under clause 2, clause 3 Article 28 of Pharmaceutical law:
Within 05 working days from the point an error on a certificate of pharmacy practice is discovered or the point of a withdrawal request or a request regarding an error being found from the certificate holder, the certificate issuing authority shall withdraw the concerned Certificate under its jurisdiction; otherwise it shall respond in writing to the concerned organization or individual and state the reasons of non withdrawal.
3. Responsibilities of the Certificate issuing, withdrawing authority:
a) Issue Certificate withdrawal decision;
b) Publish the withdrawal decision on its web portal, and send the decision to Ministry of Health and Health Departments nationwide;
c) Update its website with information pertinent to the Certificate withdrawal.
d) Within 05 (five) working days from the date of receipt of Certificate withdrawal decision from the Certificate issuing authority, Ministry of Health and Health Departments nationwide shall be responsible to publish such decision on their web portal.

Section 2
TRAINING, REFRESHER TRAINING ON PHARMACY PROFESSIONAL KNOWLEDGE

Article 8. Syllabus, curriculum, format, method, duration of training, refresher training on pharmacy professional knowledge

Establishments offering training, refresher training on pharmacy professional knowledge shall develop a training curriculum covering the following key contents:
1. Training contents:
a) Professional knowledge;
b) Pharmaceutical legislation and management knowledge;
c) Skills and techniques in pharmacy practice;
2. Formats, methods for practical skill teaching-learning, outcome assessment of practical skill participants suitable for each respective module, target participant, training level.
3. Duration of training, refresher training on pharmacy professional knowledge:
a) Professional knowledge: a minimum of 6 hours for university level participants; a minimum of 4 hours for college, technical college, elementary levels and holders of other diplomas, certificates, certifications;
b) Pharmaceutical legislation and management: a minimum of 6 hours;
c) Skills and techniques in pharmacy practice: a minimum of 6 hours;

Article 9. Requirements of establishments offering training, refresher training on pharmacy professional knowledge for practitioners
1. Establishments offering training, refresher training on pharmacy professional knowledge must satisfy the following requirements:
a) Belonging to one of the following categories of organizations: institutional educational/ vocational training establishments offering medicine, pharmacy programs; educational institutions offering field-of-study codes in health science discipline; research institutions having mandate to provide medicine pharmacy training; establishments providing training for healthcare human resources; pharmaceutical trade associations;
b) Having in place curricula for pharmacy training, refresher training in accordance with the provisions of Article 8 of this Decree.
c) Having physical facilities and equipment to support the training programs' requirements.
d) Staffed with facilitators, lecturers for the delivery of training, refresher training courses (hereafter referred to as facilitators) satisfying the following requirements:
- Facilitators of pharmaceutical knowledge modules must possess one of the qualifications set out under Article 17 and 18 of this Decree at a level of attainment not lower that held by class participants' and at least 02 years of experience in the subject they are to facilitate.
- Facilitators of pharmaceutical legislation and management must have at least 02 years of practice experience at a pharmaceutical regulatory, inspection agency or in the teaching of pharmaceutical management at an intermediate or higher level training establishment;
- Facilitators of practical skills, techniques must have at least 03 years of suitable experience in the practical areas they facilitate.
2. Establishments offering training, refresher training of pharmaceutical professional knowledge- that do not directly deliver the training, refresher modules on technical skills must have contractual arrangements with a suitable good practice compliant establishment for the delivery of such training, refresher training.

Article 10. Application dossier for designation, modification of designation of establishments offering training, refresher training of pharmaceutical professional knowledge
1. An application dossier for the designation of establishments offering training, refresher training of pharmaceutical professional knowledge shall comprise:
a) Application for designation conforming to Form no. 08 in Appendix I of this Decree.
b) Training curriculum covering the contents specified under Article 8 of this Decree. The curriculum document must be stamped with a suspending seal on the cover page and one impression of the seal across the margins of all pages if containing more than one page;
c) Tabular list of physical facilities to demonstrate the establishment' capability to provide the training, refresher training it register in the application for designation form stipulated under clause 1 of this Article. The tabular list must be stamped with a suspending seal on the cover page and one impression of the seal across the margins of all pages if containing more than one page;

d) List of facilitators of pharmaceutical training, refresher training of the establishment conforming to Form no. 09 in Appendix I of this Decree, accompanied by the scientist resume and professional qualification of each individual facilitator.
đ) Authenticated duplicate copy of the contract the establishment enters to with the establishment with which it is to jointly deliver practical skills, techniques with regard to the cases referred to under clause 2 Article 9 of this Decree.
2. Application dossier for designation modification in the cases of changes except the cases referred to in point d clause 1 of this Article shall comprise:
a) Application for designation modification conforming to Form no. 10 in Appendix I of this Decree;
b) Duplicate copy of documentation pertaining to the changes, stamped with a certifying seal on the first page of the document or an impression of the seal across the margins of all pages if containing more than one page.
3. For changes in the list of facilitators referred to in point d clause 1 of this Article, the establishment must provide notification using Form no. 11 in Appendix I of this Decree.
4. Application dossier must be submitted in one set enclosed with the electronic version of all constituting documents.

Article 11. Procedures, formalities for designation, modification of designation of establishments offering training, refresher training on pharmacy professional knowledge
1. Establishments applying for designation, modification of designation of establishment offering training, refresher training on pharmacy professional knowledge (hereafter abbreviated as training, refresher training establishment) shall submit in person or by post 01 set of application dossier in accordance with the requirements of Article 10 of this Decree to Health Department of the locality where their office is located.
2. Upon receipt of an application dossier for designation, modification of designation of a training, refresher training establishment (hereafter abbreviated as designation dossier of training, refreshing training establishment), Health Department shall issue a Dossier receipt using Form no. 01 in Appendix I of this Decree.
3. If there is no follow up request for dossier supplementation, revision, Health Department shall be responsible to:
a) In the case of applications for designation, announce on its web portal the establishment eligible for offering training, refresher training on pharmacy professional knowledge within 30 days from the date recorded on Dossier receipt;
b) In the case of applications for modification of one of the information regarding the designation announced made earlier, announce the modified status declaration of the establishment offering training, refresher training within 10 working days from the date recorded on Dossier receipt;
4. If there is a follow up request for dossier revision, supplementation, Health Department shall issue the concerned establishment a written notification to the effect within the time limits of:
a) 15 working days from the date recorded on Dossier receipt in the case of applications for designation;
b) 05 working days from the date recorded on Dossier receipt in the case of applications for modification of designation;
5. Upon receipt of the follow up submission, Health Department shall issue a Dossier receipt using Form no. 01 in Appendix I of this Decree.
a) If the follow up submission does not satisfy the requirements , Health Department shall provide written notification to the effect in accordance with the provision of clause 4 of this Article;
b) If there is no further follow up request, Health Department shall announce the designation, modification of designation in accordance with the provision of clause 4 of this Article.
6. Within 06 months from the notification date of the follow up request of Health Department, the concerned establishment must respond with the required follow up submission. Past this timeline or past 12 months from the date of the initial dossier submission, If the dossier still fails to satisfy the legibility requirements it shall become void.

7. Application for designation from establishments for which the previous designation was cancelled under the provision of clause 3 Article 12 of this Decree shall only be accepted by Department of Health after 12 months from the cancellation date
8. Health Department shall be responsible to announce the designation of training, refresher training establishment on its web portal covering the following information:
a) Name, address of the training, refresher training establishment;
b) Areas of pharmacy professional knowledge the establishment is to provide;

Article 12. Cancellation of designation of establishments offering training, refresher training on pharmacy professional knowledge
a) Termination of pharmaceutical knowledge training, refresher training operations;
b) Failure to meet one of the requirements of establishments offering training, refresher training as set out under Article 9 of this Decree.
c) Falsification of documentation constituting the designation application dossier;
d). Not operating for a consecutive 12 month period without notifying Health Department of the locality where the establishment's office is located.

Article 13. Procedures, formalities for cancellation, modification of designation of establishments offering training, refresher training on pharmacy professional knowledge
1. Within 05 working days from receipt of an audit, inspection conclusion or a conclusion of the competent authority recommending the cancellation, modification of a designation involving the cases stipulated under Article 12 of this Decree, the concerned Health Department shall cancel, modify the designation of the establishment under its jurisdiction; if cancelation is not made it must respond in writing to the recommending authority and state clearly the reasons
2. Within 05 working days from the date a cancellation, modification decision is made, the decision issuing Health Department shall be responsible to:
a) Publish the decision to cancel, modify the designation of the concerned training, refresher training establishment on its web portal and send it to Ministry of Health and Health Departments nationwide;
b) Update information regarding the cancellation, modification of the designation of the concerned training, refresher training establishment on its web portal.
3. Within 05 working date, from the receipt of the cancellation, modification decision, Ministry of Health and Health Departments shall be responsible to publish it on their web portal.

Article 14. Responsibilities of establishments offering training, refresher training on pharmacy professional knowledge
1. Establishments shall only proceed to deliver training, refresher courses after the designation has been announced on Health Department's web portal and shall delivery the training in accordance with the announced curriculum.
2. Assess learning outcomes and award certificates of completion of training, refresher training programs using Form no. 12 in Appendix I of this Decree.
3. Report annually to Health Department of the locality where its office is located the list of participants who have completed the training, refresher training program on professional knowledge using Form no. 13 in Appendix I of this Decree.
4. Inform Health Department in writing of establishments suspending or resuming its operations.

Article 15. Responsibilities of pharmaceutical regulatory authorities
1.Ministry of Health shall be responsible to:
a) Inspect, supervise establishments offering training, refresher training in pharmaceutical knowledge stipulated under Article 9 of this Decree.
2. Request Health Departments for periodic reports, adhoc reports on the regulating of establishments offering
2. Health Departments shall be responsible to:
a) Inspect, supervise and coordinate with establishments in the locality stipulated under Article 9 of this Decree in the delivery of training, refresher training of pharmaceutical knowledge;

b) Update on its web portal the lists of participants completing the training, refresher courses at training establishment in the locality;
c) Publish on its web portal the operating status of establishments delivering training, refresher training in pharmaceutical knowledge in the locality.

Article 16. Cost of providing training, refresher courses on pharmacy professional knowledge

Participants of training, refresher training courses on pharmaceutical knowledge shall pay for the cost of the courses attended in accordance with applicable legislation.

Section 3
DETERMINATION OF PROFESSIONAL QUALIFICATIONS, JOB POSITIONS FOR ISSUANCE OF CERTICATE OF PHARMACY PRACTICE

Article 17. Professional qualifications and job positions eligible for certificate of pharmacy practice

1. Bachelor degree in pharmacy shall mean university level degrees in pharmacy awarded by national education institutions that clearly state the title "Pharmacist", "University level pharmacist" or "Advanced level pharmacist".

2. Bachelor degree in general medicine shall mean university level degrees in general medicine awarded by national education institutions that clearly state the title "Medical doctor" or "General physician".

3. Bachelor degree in traditional medicine or bachelor degree in pharmacognosy shall mean university level degrees in traditional medicine or pharmacognosy awarded by national education institutions.

4. Bachelor degree in biology shall mean university level degrees in biology awarded by national education institutions.

5. Bachelor degree in chemistry shall mean university level degrees in chemistry awarded by national education institutions.

6. Associate degree in pharmacy shall mean college level diplomas in pharmacy awarded by national education institutions.

7. College diploma in pharmacy shall mean technical college level diplomas in pharmacy awarded by national education institutions that clearly state the title "Intermediate level pharmacist" or "technical college level pharmacist" .

8. Associate degree, college diploma in medicine shall mean college level diplomas, technical school level diplomas in medicine awarded by national education institutions.

9. College diploma in traditional medicine or pharmacognosy shall mean technical school level diplomas in traditional medicine or pharmacognosy awarded by national education institutions.

10. Elementary diploma, certificate in pharmacy shall mean certificates, certifications that clearly state the position of "Pharmacist assistant" or "Elementary pharmacist".

Article 18. Determination of practice scope allowed for indeterminate diplomas, job positions

1. With respect to diplomas, certificates awarded by national training institutions the job position stated on does not fall into any of the categories set out under clause 1, 2, 7 and 10 Article 17 of this Decree, the determination of practice scope they confer shall be decided upon by the competent authority for certificate issuance based on consultative opinions of Advisory council for issuance of pharmacy practice certificate.

2. Diplomas, certificates awarded by foreign training institutions must be recognized by Ministry of Training and Education . The determination of practice scope allowed for diplomas, certificates awarded by foreign training institutions shall be undertaken in accordance with the provision of clause 1 of this Article.

Section 4
PHARMACY PRACTICE EXPERIENCE

Article 19. Internship hosting establishments

1. Internship hosting establishments shall be those stipulated under clause 2 Article 12 of Pharmaceutical law, covering: pharmaceutical businesses, pharmacy department of medical service establishments, pharmacy training institutions, pharmaceutical research institution, drug, drug raw

material testing establishments, pharmaceutical regulatory agencies or representative offices of foreign traders operating in pharmaceuticals in Vietnam (hereafter referred to as pharmaceutical establishments); medical service establishments suitable to the intern-practitioner's professional competency.

2. Suitable internship hosting establishment shall be those stipulated under clause 1 of this Article that operate in areas commensurate with the professional competency areas sought by the intern-practitioner as set out under Article 20 of this Decree.

3. The internship hosting establishments shall certify the length of practice experience for the intern-practitioner using Form no.03 in Appendix I of this Decree and be responsible for the content they certify.

4. For drug retailers:

a) Apart from complying with the provision of clause 3 of this Article, prior to providing preceptorship to the intern practitioners, the head of the host establishment must send the list of practitioners registering for internship at their site using Form no 14 in Appendix I of this Decree to Health Department of the locality where it has office, covering: Name, address of the host establishment; full name of practitioners registering for internship; content of the internship program; internship start date; assigned preceptor;

b) Within 05 (five) working days from receipt of the list of practitioners registering for internship, Health Department shall be responsible for publishing on its web portal the contents set out in point a of this clause.

Article 20. Contents of internship program

1. For the position of pharmacist in charge of manufacturers of drugs, pharmaceutical substances, excipients, capsule shells:

a) The pharmacist in charge of drug manufacturing establishments, except the cases referred to in point c of this clause, must have practice experience in one of the following competency areas: drug formulation, drug testing, drug research and development; pharmaceutical regulatory function at a pharmaceutical regulatory agency;

b) The pharmacist in charge of establishments manufacturing drug raw materials that are pharmaceutical substances, excipients, capsule shells must have practice experience in one of the following competency areas: drug manufacture; drug testing; research and development of drugs, drug raw materials; production of drug raw materials, chemicals; pharmaceutical regulatory function at a pharmaceutical regulatory agency;

c) The pharmacist in charge of establishments manufacturing vaccines, biologicals and raw materials for vaccines, biologicals must have practice experience in one of the following competency areas: manufacture of vaccines, biologicals, quality control testing of vaccines, biologicals, product research and development of vaccines, biologicals; pharmaceutical regulatory function at a pharmaceutical regulatory agency;

d) The pharmacist in charge of establishments manufacturing traditional drugs must have practice experience in one of the following competency areas: manufacture, processing of traditional drugs, quality control testing of traditional drugs, product research and development in the production of traditional drugs, regulatory function over pharmacy, pharmacognosy at a pharmaceutical regulatory agency.

2. For the position of quality assurance in charge of establishments manufacturing drugs, pharmaceutical substances, excipients, capsule shells:

a) The quality assurance in charge of establishments manufacturing drugs, except the cases referred to in point c of this clause, must have practice experience in one of the following competency areas: manufacture, testing, quality assurance, product research and development in drug manufacture or drug testing establishment;

b) The quality assurance in charge of establishments manufacturing drug raw materials being pharmaceutical substances, excipients, capsule shells must have practice experience in one of the following competency areas: manufacture, testing, quality assurance, product research and development at manufacturing establishments of drugs drug raw materials.

c) The quality assurance in charge of establishments manufacturing vaccines, biologicals and raw materials for vaccines, biologicals must have practice experience in one of the following

competency areas: manufacture, testing, quality assurance, product research and development at manufacturing or testing establishment of vaccines, biologicals.

3. For the position of pharmacist in charge and quality assurance in charge of establishments manufacturing medicinal materials

a) The pharmacist in charge, the quality assurance in charge of establishments manufacturing medicinal materials must have practice experience in one of the following competency areas: manufacture, formulation, processing of medicinal material drugs, traditional drugs, medicinal materials, testing of drugs, drug raw materials, in process quality assurance, of drugs, drug raw materials, formulation, processing traditional drugs; regulatory functions in pharmaceuticals, traditional medicine and pharmacognosy at a pharmaceutical regulatory agency;

b) The pharmacist in charge, the quality assurance in charge of household businesses, cooperatives manufacturing medicinal materials must have practice experience in on the of following competency areas: manufacture of drug raw materials, drug testing, in process quality assurance, research study of medicinal materials, traditional medicine; formulation, processing traditional drugs; regulatory functions in pharmaceuticals, traditional medicine and pharmacognosy at a pharmaceutical regulatory agency.

4. For the position of pharmacist in charge of establishments wholesaling drugs, drug raw materials

a) The pharmacist in charge of establishments wholesaling drugs except the cases referred to in point c of this clause must have practice experience in one of the following competency areas: wholesaling drugs , drug raw materials, regulatory function at a pharmaceutical regulatory agency;

b) The pharmacist in charge of establishments wholesaling drug raw materials must have practice experience in one of the following competency areas: manufacture of drug raw materials, chemical manufacture, testing of drugs, drug raw materials, research study in chemistry technology, pharmaceutical technology; drug wholesale, drug importation; storage of drugs, drug raw materials; regulatory functions in pharmaceuticals, traditional medicine and pharmacognosy at a pharmaceutical regulatory agency.

c) The pharmacist in charge of establishments wholesaling vaccines, biologicals must have practice experience in one of the following competency areas: manufacture; wholesale; storage; quality control testing of, vaccines, biologicals; research in vaccines, biologicals; regulatory function at a pharmaceutical regulatory agency .

d) The pharmacist in charge of establishments wholesaling medicinal materials, traditional drugs must have practice experience in one of the following competency areas: wholesaling, providing storage service of drugs, medicinal materials; manufacture of drugs, medicinal materials, testing of drugs, drug raw materials, traditional drugs; research in medicinal materials, traditional medicine; regulatory function at a pharmaceutical regulatory agency.

5. For the position of pharmacist in charge of establishments exporting, importing drugs, drug raw materials

a) The pharmacist in charge of establishments exporting, importing drugs, drug raw materials, except the cases referred to in point b and c of this clause, must have practice experience in one of the following competency areas: drug wholesale; drug export import; drug manufacture; testing of drugs, drug raw materials; good practices in drug storage; regulatory functions pertinent to drug marketing, export, import, wholesale of drugs, drug raw materials; regulatory function at a pharmaceutical regulatory agency.

b) The pharmacist in charge of establishments exporting, importing vaccines, biologicals must have practice experience in one of the following competency areas: manufacture; wholesale; commercial storage service; testing of vaccines, biologicals; research in vaccines, biologicals; managerial functions pertinent to vaccines, biologicals; usage of vaccines, biologicals; regulatory function at a pharmaceutical regulatory agency.

c) The pharmacist in charge of establishments exporting, importing medicinal materials, traditional drugs must have practice experience in one of the following competency areas: wholesale of drugs, drug raw materials; storage of drugs, drug raw materials; manufacture of drugs, drug raw materials; testing of drugs, drug raw materials, traditional drugs, research in medicinal materials, traditional medicine; regulatory functions in pharmaceuticals or traditional medicine and pharmacognosy at a pharmaceutical regulatory agency.

6. For the position of pharmacist in charge of drug retailers

a) The pharmacist in charge of drugstores, drug counters, commune health clinics' drug cabinets must have practice experience in one of the following competency areas: drug wholesale, drug retail; drug export import; clinical pharmacy, drug supply in medical service establishments; drug manufacture; testing of drugs, drug raw materials; pharmaceutical research; drug storage; drug distribution; regulatory functions at a pharmaceutical regulatory agency.

b) The pharmacist in charge of establishments specializing in the retail of medicinal materials, medicinal material drugs, traditional drugs, except the cases referred to in point c clause 2 Article 13 of Pharmaceutical law, must have practice experience in one of the competency areas relating to manufacture, research, trading, delivery of medical services using traditional medicine or regulatory function in pharmaceuticals, traditional medicine and pharmacognosy at a pharmaceutical regulatory agency.

7. For the position of pharmacist in charge of drug, drug raw material testing service providers

a) The pharmacist in charge of drug, drug raw material testing service providers, except the cases referred to in point b of this clause, must have practice experience in one of the following competency areas: testing of drugs, drug raw materials, research study pertinent to the manufacture, testing, analysis of drugs, drug raw materials; regulatory function at a pharmaceutical regulatory agency;

b) The pharmacist in charge of vaccine, biological testing service providers must have practice experience in one of the following competency areas: drug testing, drug raw material testing; quality control testing of vaccines biologicals; research study pertinent to the manufacture, testing of vaccines, biologicals; drug storage covering vaccines, biologicals in scope; regulatory function at a pharmaceutical regulatory agency.

8. The pharmacist in charge of providers of clinical trial service, bioequivalence study on drugs must have practice experience in one of the following competency areas: bioequivalence study on drugs, clinical trial on drugs; testing of drugs, drug raw materials; pharmacologic study, clinical pharmacy; regulatory function in pharmaceuticals or traditional medicine and pharmacognosy at a pharmaceutical; regulatory agency.

9. For the position of clinical pharmacist in charge of medical service establishments

a) The clinical pharmacist in charge of medical service establishments must have practice experience in one of the following competency areas: drug bioequivalence study; clinical trial on drugs; research in pharmacology, clinical pharmacy, pharmacovigilance at a drug information centre and surveillance of drug adverse reactions;

b) The clinical pharmacist in charge of traditional medicine medical service establishments must have practice experience in one of the following competency areas: clinical trial on drugs; research in pharmacology, clinical pharmacy; pharmacovigilance at a drug information centre and surveillance of adverse reactions of traditional drugs.

10. Pharmacist in charge of providers of drug, drug raw material storage service

a) The pharmacist in charge of providers of drug, drug raw material storage service must have practice experience in one of the following competency areas: drug storage; regulatory function in pharmaceuticals, traditional medicine and pharmacognosy at a pharmaceutical regulatory agency;

b) The pharmacist in charge of providers of vaccine, biological storage service must have practice experience in one of the following competency areas: drug storage service covering vaccines, biologicals in scope; manufacture of vaccines, biologicals; quality control testing of vaccines, biologicals; regulatory function at a pharmaceutical regulatory agency.

Article 21. Length of practice experience required of holders of post graduate specialty qualifications

1. Holders of post graduate specialty qualification holders shall be those who hold of one of the following degrees:

a) Master degree in pharmacy, traditional medicine and pharmacognosy, chemistry, biology (hereafter referred to as master)

b) Doctorate degrees in pharmacy, traditional medicine and pharmacognosy, chemistry, biology (hereafter referred to as doctorate);

c) Specialization I or specialization II under post graduate specialization track decreed by the Minister of Health.

2. Length of practice experience required of holders of post graduate specialty qualifications shall be commensurate with the respective practice areas as follows:
a) Length of practice experience required of holders of post graduate qualifications in pharmaceutical formulation, pharmaceutical engineering, drug testing shall be reduced with regard to the positions of pharmacist in charge, quality assurance in charge of drug, drug raw material manufacturer, pharmacist in charge of providers of drug, drug raw material testing service, specifically by:
- 06 months for holders of master degrees or specialization I
- 01 year for holders of doctorate degrees or specialization II
b) Length of practice experience required of holders of post graduate qualifications in pharmacology, clinical pharmacy shall be reduced with regard to the positions of pharmacist in charge of providers of services of drug bioequivalence study, clinical trial on drugs, drug retailers, clinical pharmacist in charge of medical service establishments, specifically by:
- 06 months for holders of a Master degree or specialization I
- 01 year for holders of a Doctorate degree or specialization II
c) Length of practice experience required of holders of post graduate qualifications in medicinal materials, traditional medicine and pharmacognosy shall be reduced with regard to the positions of pharmacist in charge of businesses specializing in medicinal materials, traditional drugs, clinical pharmacist in charge establishments providing medical services in traditional medicine, specifically by:
- 06 months for holders of a Master degree or specialization I;
- 01 year for holders of a Doctorate degree or specialization II.
d) Length of practice experience required of holders of post graduate qualifications in infection, microbiology, preventive health, shall be reduced with regard to the positions of pharmacist in charge of wholesalers, providers of storage services for vaccines, biological products, specifically by:
- 06 months for holders of a Master degree or specialization I;
- 01 year for holders of a Doctorate degree or specialization II.
đ) Length of practice experience of holders of post graduate qualifications in pharmaco-economics or pharmaceutical regulatory affairs shall be reduced with regard to the positions of pharmacist in charge of drug wholesalers, chemo pharmaceutical retailers (except commune health clinics' drug cabinets), providers of drug storage services, specifically by:
- 06 months for holders of a Master degree or specialization I;
- 01 year for holders of a Doctorate degree or specialization II.
e) Length of practice experience of persons holding post graduate specialty qualifications in pharmaco-economics or pharmaceutical regulatory affairs shall be reduced for the positions of pharmacist in charge of retailers of medicinal material drugs, traditional drugs, commune health clinics' drug cabinets, specifically by:
- 03 months for holders of a Master degree or specialization I;
- 06 months for holders of a Doctorate degree or specialization II.

Section 5
LICENSURE EXAM FOR PHARMACY PRACTICE

Article 22. Exam format, content, syllabus

1. Exam format: group exams held at the test administration site or online exams.
2. Exam contents, covering:
a) General knowledge for pharmacy practitioners;
b) Professional knowledge commensurate with the respective job positions requiring certificate of pharmacy practice as stipulated under Article 11 of Pharmaceutical law.
3. The Minister of Health shall specify the exam protocol, content, test databank, pass-fail score scale for the issuance of Certificate of pharmacy practice.

Article 23. Requirements of establishments administering licensure exams for Certificate of pharmacy practice

1. Establishments administering licensure exams for Certificate of pharmacy practice shall be universities of pharmacy, traditional medicine and pharmacognosy specialization.

2. They must have a proposal for exam administration conforming to Form no.15 in Appendix I of this Decree

Article 24. Dossier for designation of exam administration establishment for Certificate of pharmacy practice

1. An application dossier for designation of exam administration establishment for Certificate of pharmacy practice shall comprise:

a) Application for designation conforming to Form no.16 in Appendix I of this Decree.

b) Proposal to administer Certificate of pharmacy practice licensure exams in accordance with the provision of clause 2 Article 23 of this Decree;

c) Certified duplicate copy of the Decision for formation or Operating license of the establishment.

2. Dossier for modification of designation the case of establishments undergoing changes in names, addresses:

a) Request for designation modification conforming to Form no. 17 in Appendix I of this Decree.

b) Authenticated duplicate copy of papers demonstrating the changes in the establishment's name, address, issued by the competent authority;

3. Dossier for modification of designation in the case of establishments undergoing changes in the scope of the exams they administer:

a) Request for designation modification conforming to Form no. 17 in Appendix I of this Decree.

b) Proposal to administer Certificate of pharmacy practice licensure exams in accordance with the provision of clause 2 Article 23 of this Decree;

Article 25. Formalities for designation, designation modification of establishments administering certificate of pharmacy practice licensure exams

1. Establishments requesting for designation, modification of designation of establishment administering licensure exams for certificate of pharmacy practice (hereafter abbreviated as designated exam administration establishment) shall submit in person or by post 01 set of application dossier in accordance with the requirements of Article 24 of this Decree to Health Ministry.

2. Upon receipt of an application dossier for designation, designation modification of exam administering establishment (hereafter abbreviated as designation dossier of exam administering establishment), Ministry of Health shall issue a Dossier receipt using Form no. 1 in Appendix I of this Decree.

3. If there is no follow up request for dossier supplementation, revision, Ministry of Health shall be responsible to:

a) Announce on its web portal the designation or modification of designation within 30 days from the date recorded on Dossier receipt in the case of application for designation or modifying scope of exams to be administered. If the application is refused, there must be a written response stating the reasons of the refusal;

b) Modify the designation within 10 working days from the date recorded on Dossier receipt in the case of applications for modification of name and address of the exam administering establishment,. If the application is refused there must be a written response stating the reasons of the refusal;

4. If there is a follow up request for dossier revision, supplementation, Ministry of Health shall issue written notification to the effect to the concerned establishment within the time limits of:

a) 15 working days from the date recorded on Dossier receipt in the case of status declaration applications;

b) 05 working days from the date recorded on Dossier receipt in the case of modification of the exam administering's name, address.

5. Upon receipt of the follow up submission, Ministry of Health shall issue the concerned establishment a Dossier receipt using Form no 01 in Appendix I of this Decree.

a) If the follow up submission does not satisfy the request, Ministry of Health shall issue a written notification to the effect in accordance with the provision of clause 4 of this Article.

b) If there is no request for further follow up revision, supplementation, Ministry of Health shall announce the designation, modification of designation of establishment administering licensure exam for Certificate of pharmacy practice in accordance with the provision of clause 3 of this Article.

6. The concerned establishment must respond within 60 days from the date Ministry of Health issues the written follow up request. Past this time limit if the establishment does not respond with a follow

up submission or past 12 months from the initial dossier submission if the dossier still does not satisfy the requirements, it shall become void.
7. In the case of a designation of an establishment is cancelled according to the provision of clause 3 Article 26 of this Decree, Ministry of Health shall only accept new application for designation of the same establishment after 12 months from the cancellation date.
8. Ministry of Health shall be responsible to make announcement about the designation of establishments administering certificate of pharmacy practice licensure exams on its web portal covering the following information:
a) Name, address of the exam administering establishment;
b) Scope of the exams to be administered;

Article 26. Cancellation, modification of designation of establishments administering licensure exams for Certificate of pharmacy practice

1. The exam administering establishment terminates its operations.
2. The establishment fails to satisfy one of the requirements set out under Article 23 of this Decree.
3. Falsification of documentation constituting the application dossier for designation, designation modification.

Article 27. Procedures, formalities for cancellation, modification of designation of establishments administering licensure exams for Certificate of pharmacy practice

1. Within 05 working days from receipt of an audit, inspection conclusion or a conclusion of the competent authority recommending the cancellation, modifying a designation of an exam administering establishment involving the cases stipulated under Article 26 of this Decree, Ministry of Health shall cancel, modify the designation of the concerned establishment; if cancelation, modification is not made it must respond in writing to the recommending authority and state clearly the reasons
2. Within 05 working days from the date a cancellation, modification decision is issued, Ministry of Health shall be responsible to:
a) Publish the decision to cancel, modify the designation of the concerned exam administering establishment on its web portal and at the same time send it to Health Departments nationwide;
b) Update information regarding the cancellation, modification of the designation of the concerned establishment on its web portal.
3. Within 05 working date, from the receipt of the cancellation, modification decision, from Ministry of Health, Health Departments shall be responsible to publish it on their web portal.

Article 28. Administering licensure exams for Certificate of pharmacy practice

1. Establishments shall only administer licensure exams for Certificate of pharmacy practice after being designated by Ministry of Health on its web portal as eligible to do so and shall ensure the exams they administer satisfy the following requirements:
a) Consistent with the proposal announced by Ministry of Health;
b) In adherence with the exam protocol issued by Ministry of Health.
2. Returning exam results to candidates in the form of result confirmation certificate using Form no. 18 in Appendix I of this Decree and notify Ministry of Health of the list of candidates passing the licensure exams for Certificate of pharmacy practice issuance within 05 working days for the exam completion date.
3. Where there is no establishments designated as qualified, Ministry of Health shall be responsible to nominate establishments that meet the eligibility criteria of Article 23 of this Decree to conduct licensure exams for Certificate of pharmacy practice.

Article 29. Prioritization in pharmacy practice for holders of Certificate of pharmacy practice obtained through licensure exams

Holders of Certificate of pharmacy practice obtained through a licensure exam shall be given priority in recruitment and selection, employment in public healthcare establishments, including
1. Given priority in employment consideration based on a Good grade exam result and the attainment of a Good grade graduate or post graduate qualification.
2. Exemption from probation period after being hired.
3. Given priority in screening process for admission to training, education, capacity strengthening domestic and overseas programs.

Article 30. Exam costs

1. Candidates sitting the licensure exams for Certificate of pharmacy practice shall pay for the cost of the exam in accordance with applicable legislation.

CHAPTER III
CONDUCTING PHARMACEUTICAL BUSINESS
Section 1
CERTIFICATE OF SATISFACTION OF CONDITIONS FOR CONDUCTING PHARMACEUTICAL BUSINESS

Article 31. Eligibility conditions for conducting business in traditional drugs

1. Manufacturers of traditional drugs for countrywide marketing must satisfy the provisions of point a, c and de clause 2 Article 69 of Pharmaceutical law.

2. Importers of traditional drugs must have a location, storage facilities, equipment, transport vehicles, quality management system, technical documents and human resources in conformity with Good storage practice for traditional drugs. The pharmacist in charge of exporters, importers of traditional drugs must conform to the provision of clause 3 Article 17 of Pharmaceutical law.

3. Providers of storage service for traditional drugs must have a location, storage facilities, equipment, transport vehicles, quality management system, technical documents and human resources in conformity with Good storage practice for traditional drugs. The pharmacist in charge of providers of traditional drug storage service must conform to the provision of clause 1 Article 22 of Pharmaceutical law.

4. Wholesalers of traditional drugs must have a location, storage facilities, equipment, transport vehicles, quality management system, technical documents and human resources in conformity with Good distribution practice for traditional drugs. The pharmacist in charge of traditional drug wholesalers must conform to the provision of clause 3 Article 16 of Pharmaceutical law.

5. Conditions required of establishments specializing in the retail of medicinal materials, medicinal material drugs, traditional drugs:

a) Staffed with a pharmacist in charge of retailers of medicinal materials, medicinal material drugs, traditional drugs conforming to the provision of clause 4 Article 18 of Pharmaceutical law;

b) Have a fixed, separate place; solidly constructed; suitably large for the business scale; located in a high, dry, well ventilated, safe, away from polluting sources, equipped with fire prevention and fighting measures;

c) Have a storage area and equipment suitable for the storage conditions stated on drugs' labelling.

Medicinal material drugs, traditional drugs must be stored separately from medicinal materials, traditional medicinals.

Toxic medicinal materials must be displayed for sales (of any) and stored in a dedicated area; if displayed for sales and stored in the same area with other medicinal materials, they must be kept separated and clearly marked "toxic medicinal materials" so as to avoid mix-up.

Prescription medicinal material drugs, prescription traditional drugs must be displayed for sales (if any) and stored in a dedicated area; if displayed and stored in the same area with non-prescription drugs, they must be kept separate and clearly marked "prescription drugs" so as to avoid mix-up.

Establishments specializing in the retail of medicinal material drugs, traditional drugs or the medicinal materials shall only require a storage area suitable for the storage of the respective drugs, either medicinal material drugs, traditional drugs or medicinal materials, traditional medicinals;

d) Tooling, packaging materials in direct contact with medicinal material drugs, traditional drugs, medicinal materials must be in such a way as not impacting the ensure the drug products' quality.

đ) There must be in place a system of documenting or appropriate measures for the retention of information regarding the export import movement, traceability of drugs;

b) Storage equipment, transport vehicles, storage condition monitoring devices must be fitted, located, designed used and maintained to suit the purpose of use, ensuring proper storage conditions and

operations. Where there are cold warehouses, there must be a backup generator and systems for monitoring, alerting of storage conditions;
c) There must be transport vehicles for the transportation of drugs that ensure storage conditions, security, safety requirements of the business establishment;
d) There must be in place systems for quality management, documentation, guidelines, procedures encompassing all operations to be carried out, ensuring effective control of receiving, issuing operations, traceability and tracking of the drug distribution, circulation process.
đ) Storage warehouses, ancillary systems, equipment and processes must be evaluated, validated.
e) The person retailing medicinal materials, medicinal material drugs, traditional drugs must be in possession on of the qualifications set out in point a, c, e, g, i or l clause 1 Article 13 of Pharmaceutical law.
With regard to toxic medicinal materials, prescription medicinal material drugs, prescription traditional drugs, the person retailing the drugs and counselling buyers must be the retailer's pharmacist in charge.
g) Where a retailer also trades in other goods as legally allowed, these goods must be displayed for sales, advertised in a separate area and not to influence the medicinal materials, medical material drugs, traditional drugs.

Article 32. Application dossiers for issuance, re-issuance, modification of Certificate of satisfaction of conditions for pharmaceutical business

Application dossiers the issuance, re-issuance, modification of Certificate of satisfaction of conditions for pharmaceutical business shall be prepared in accordance with the provision of Article 38 of Pharmaceutical law, specifically as follows:
1. Application for the issuance, re-issuance, modification of Certificate of satisfaction of conditions for pharmaceutical business conforming to Form no.19, 20 and 21 respectively in Appendix I of this Decree.
2. The technical documents referred to in point b clause 1 and point b clause 2 Article 38 of Pharmaceutical law shall comprise Certificate of satisfaction of conditions for pharmaceutical business or Certificate of good practice of the place of business (as applicable) and the following technical document:
a) For manufacturers of drugs, drug raw materials: Documents regarding drug manufacturing sites, buildings and premises, laboratories, warehouses for drugs, drug raw materials, auxiliary systems, equipment and machines for manufacturing, testing, storage of drugs, quality management system, documents on the technical specialization and human resources conforming to the principles of Good manufacturing practice for drugs, drug raw materials.
Establishments applying for a Certificate of satisfaction of conditions for pharmaceutical business with as business scope the manufacture of drugs including the selling of drugs, drug raw materials they manufacture to retailers, medical service establishments, must in addition be in possession of documents on the technical specialization and staffed with human resources conforming to the principles of Good distribution practice for drugs, drug raw materials;
b) For exporters, importers of drugs, drug raw materials, providers of storage service of drugs, drug raw materials: Documents regarding sites, warehouses for drugs, drug raw materials, storage equipment, transport vehicles, quality management system, documents on the technical specialization and human resources conforming to the principles of Good storage practice for drugs, drug raw materials.
Establishments applying for a Certificate of satisfaction of conditions for pharmaceutical business with as business scope the manufacture of drugs including the selling of drugs, drug raw materials they import to drug retailers, medical service establishments, must in addition be in possession of documents on the technical specialization and staffed with human resources conforming to the principles of Good distribution practice for drugs, drug raw materials;
c) For wholesalers of drugs, drug raw materials: Documents regarding sites, warehouses for drugs, drug raw materials, storage equipment, transport vehicles, quality management system, documents on the technical specialization and human resources conforming to the principles of Good distribution practice for drugs, drug raw materials.

d) For retailers of drugs, drug raw materials: Documents regarding sites, storage areas, storage equipment, documents on the technical specialization and human resources conforming to the principles of Good pharmacy practice for drugs;
For establishments specializing in the retail of medicinal materials, medicinal material drugs, traditional drugs: Documents demonstrating compliance with the provision of clause 5 Article 31 of this Article according to the Minister of Health's stipulations;
đ) For providers of testing services for drugs, drug raw materials: Documents regarding sites, chemistry, microbiology or biology laboratories, auxiliary systems, test equipment , chemicals, reagents, quality management system, documents on the technical specialization and human resources conforming to the principles of Good laboratory practice for quality control of drugs;
e) For establishments providing services of clinical trial on drugs: Documents regarding sites, clinical trial rooms, laboratories, biochemical test equipment , quality management system, documents on the technical specialization and human resources conforming to the principles of Good clinical practice for trials on drugs.
g) For establishments providing services of drug bioequivalence study: Documents regarding sites, bio fluid analytical laboratories, bio fluid analytical equipment, accommodation and monitoring areas for study subjects to support bioequivalence studies, quality management system, documents on the technical specialization and human resources meeting Good laboratory practice with regard to the bio fluid analysis phase and Good clinical practice for trials on drugs with regard to the clinical study phase.
Where the bioequivalence study service provider establishment contracts out, or has a joint agreement in place with, a Good-clinical-practice-compliant clinical trial service provider, for the conduct of the clinical study phase of the drug bioequivalence study, the technical documentation required shall not have to include documents regarding sites, bio fluid analytical laboratories, bio fluid analytical equipment, accommodation and monitoring areas for study subjects in support of bioequivalence studies, quality management system, documents on the technical specialization and human resources conforming to the principles of Good clinical practice of clinical trials on drugs.
3. The documents set out under clause 2 of this Article must be stamped with the establishment's seal on its cover page and one impression of the seal across the margins of the remainder pages of the technical document. Where the establishment has no seal, the documents must bear the signature of its legal representative.

Article 33. Procedures for the issuance of Certificate of satisfaction of conditions for pharmaceutical business

1. Establishments applying for Certificate of satisfaction of conditions for pharmaceutical business shall submit an application dossier either in person or by post to:
a) Ministry of Health in the case of applications for Certificate of satisfaction of conditions for pharmaceutical business categorized under point a, b, c, e, g and h clause 2 Article 32 of Pharmaceutical law;
2. Upon receipt of an application dossier the dossier receiving authority shall issue to the applicant establishment a Dosser receipt using Form no. 01 in Appendix I of this Decree.
3. If there is no follow up request for dossier revision, supplementation, the certificate issuing authority shall:
a) Issue a Certificate of satisfaction of conditions for pharmaceutical business within 30 days from the date recorded on Dossier receipt in the cases of establishments where the physical technical facilities and human resources have been verified, assessed as conforming to the respective Good practice without the need for an onsite assessment of the establishments' faculties;
b) Conduct an onsite assessment of the establishment's facilities within 20 days from the date recorded on Dossier receipt;
4. Where there is a follow up request for dossier revision, supplementation, within 10 working days from the date recorded on Dossier receipt, the dossier receiving authority shall issue a written notification to the effect to the applicant establishment specifying the documents, contents requiring revision, supplementation;
5. Upon receipt of the follow up submission, the dossier receiving authority shall issue to the applicant establishment a Dossier receipt using Form no. 01 in Appendix I of this Decree.

a) If the follow up submission fails to address the requirements, the dossier receiving authority shall issue a written notification to the effect to the applicant authority in accordance with the provision of clause 4 of this Article.
b) If there is no further request for revision, supplementation in regard to the follow up submission, the dossier receiving authority shall proceed according to the provision of clause 3 of this Article.
6. After completion of the onsite assessment of the establishment's facilities, the certificate issuing authority shall be responsible to:
a) Issue a certificate of satisfaction of conditions for pharmaceutical business within 10 working days from the completion of the onsite assessment to the cases requiring no remedial, corrective actions;
b) Issue a written notification regarding items requiring remediation, correction within 05 working days from the completion of the onsite assessment to the cases requiring remedial, corrective actions.
7. Within 20 days from the receipt of a written response and documents demonstrating the completion of corrective, remedial actions from the applicant establishment, the certificate issuing authority shall issue a Certificate of satisfaction of conditions for pharmaceutical business or a refusal letter stating the reasons of the refusal.
8. Within 06 months from the notification date of the certificate issuing authority requesting follow up revision, supplementation, the applicant establishment must respond to the request. Past this time limit if the establishment fails to respond with follow up submission or past 12 months from the initial dossier submission if the supplemented dossier does not meet the requirements it shall become void.
9. Within 05 working days from the date of certificate issuance, the certificate issuing authority shall be responsible to publicize, update on its web portal the following information:
a) Name, address of the holder establishment of the certificate of satisfaction of conditions for pharmaceutical business that was issued;
b) Full name of the pharmacist in charge of the establishment, number of his/her certificate of pharmacy practice;
c) Number of the certificate of satisfaction of conditions for pharmaceutical business;
10. For the cases of certificate of satisfaction of conditions for pharmaceutical business that are issued under the provisions of point b and point c clause 1 Article 36 of Pharmaceutical law, the applicant establishment must surrender the old certificate upon being issued a new one, except in the case it was lost.
11. Certificate of satisfaction of conditions for pharmaceutical business shall be prepared in 02 copies using Form no. 22 in Appendix I of this Decree: 01 copy to be issued to the applicant establishment, 01 for file retention at the Certificate issuing authority's office.
12. Establishments that have been assessed as in conformity with Good practice shall be issued a Good practice certificate by the authority issuing the Certificate for satisfaction of conditions for pharmaceutical business if they do request for one.

Article 34. Procedures for the reissuance, modification of Certificate of satisfaction of conditions for pharmaceutical business

1. Establishments applying for reissuance, modification of Certificate of satisfaction of conditions for pharmaceutical business shall submit an application dossier either in person or by post to:
a) Ministry of Health in the case of applications for reissuance, modification of Certificate of satisfaction of conditions for pharmaceutical business categorized in point a, b, e, e, g and h clause 2 Article 32 of Pharmaceutical law.
b) Health Department where the applicant establishment has office in the case of applications for reissuance, modification of certificate of satisfaction of conditions for pharmaceutical business categorized in point d and đ clause 2 Article 32 of Pharmaceutical law.
2. Upon receipt of the dossier, the dossier receiving authority shall issue to the applicant establishment a Dossier receipt using Form no. 01 in Appendix I of this Decree.
3. If there is no follow request for dossier revision, supplementation, the Certificate reissuing, modifying authority shall be responsible to:
a) Reissue, modify Certificate of satisfaction of conditions for pharmaceutical business within 20 days from the date recorded on the Dossier receipt to the cases stipulated in point a, clause 2 and clause 3 Article 36 of Pharmaceutical law;

b) Reissue, modify Certificate of satisfaction of conditions for pharmaceutical business within 07 working days from the date recorded on the Dossier receipt to the cases stipulated in point b, clause 2 Article 36 of Pharmaceutical law.
4. If there is a follow up request for dossier revision, supplementation, the dossier receiving authority shall issue a written notification to the effect to the applicant establishment within 05 working days from the date recorded on the Dossier receipt.
5. Upon receipt of the follow up submission, the dossier receiving authority shall issue to the applicant establishment a Dossier receipt using Form no 01 in Appendix I of this Decree.
a) If the follow up submission fails address the requirements, the dossier receiving authority shall issue a written notification to the effect to the applicant establishment in accordance with the provision of clause 4 of this Article;
b) If there is no [further] follow up request, the dossier receiving authority shall reissue, modify Certificate of satisfaction of conditions for pharmaceutical business in accordance with the provision of clause 3 of this Article.
8. Within 06 months from the notification date of the certificate issuing authority requesting follow up revision, supplementation, the applicant establishment must respond to the request. Past this time limit if the establishment fails to respond with follow up submission or past 12 months from the initial dossier submission if the supplemented dossier does not meet the requirements it shall become void.
9. Within 05 working days from the date of certificate reissuance, modification, the dossier receiving authority shall publicize, update on its web portal the following information:
a) Name, address of the holder establishment of the certificate of satisfaction of conditions for pharmaceutical business that was reissued, modified;
b) Full name of the pharmacist in charge of the establishment, number of his/her certificate of pharmacy practice;
c) Number of the certificate of satisfaction of conditions for pharmaceutical business;
8. The applicant establishment must surrender the old certificate upon being issued a new one, except in the case it was lost.
9. Certificate of satisfaction of conditions for pharmaceutical business shall be prepared in 02 copies using Form no. 22 in Appendix I of this Decree: 01 copy to be issued to the applicant establishment, 01 for file retention at the Certificate issuing authority's office.

Article 35. Formalities for the withdrawal of Certificate of satisfaction of conditions for pharmaceutical business
1. Within 05 working days from the date of receipt of a conclusion of an audit, inspection recommending the withdrawal of a Certificate of satisfaction of conditions for pharmaceutical business or discovery of cases categorized under Article 40 of Pharmaceutical law, the Certificate issuing authority shall be responsible to withdraw the concerned Certificate in its jurisdiction; if the withdrawal is not effectuated, it must notify the withdrawal recommending authority in writing and provide the reasons.
2. Within 05 working days from the date the withdrawal decision is issued, the decision issuing authority shall be responsible to:
a) Publish the Certificate withdrawal decision on its web portal and send such decision to Ministry of Health and Health Departments nationwide;
b) Update information regarding the Certificate withdrawal on its web portal.
3. Within 05 working days from the date of receipt of the withdrawal decision, Ministry of Health and Health Departments shall be responsible to publish the decision on their web portal.

Section 2

GEOGRAPHIC AREAS, OPERATING SCOPE OF RETAILERS OPERATING AS DRUG COUNTERS, DRUG CABINETS

Article 36. Geographic areas covered by drug counters, commune clinics' drug cabinets
1. Geographic area covered by drug counters:
a) Commune, township;

b) Geographic areas newly upgraded from commune, township to ward, if not yet covered by a drug counter to serve 2,000 residents shall be allowed to have additional drug counters set up and which are allowed to operate for not longer than 03 years from the date the areas are upgraded to ward level;
c) Drug counters not in the geographic areas referred to in point a of this clause that are in possession of a Certificate of satisfaction of conditions for pharmaceutical business issued before the effective date of this Decree shall be allowed to continue operating until the expiry of the Certificate. Drugs counters holding Certificate of satisfaction of conditions for pharmaceutical business that does not specify a validity term shall be allowed to continue operating for not longer than 03 years counting from the effective date of this Decree.
2. Geographic area covered by drug cabinets:
a) Commune's health clinics;
b) Township's health clinics in ethnic minority areas, mountainous areas, island, areas of extreme economic-social hardship.

Article 37. Operating scope of drug counters, drug cabinets of commune clinics
1. Operating scope of drug counters shall be in compliance with the provision of point b clause 1 Article 48 of Pharmaceutical law;
2. Operating scope of drug cabinets of commune health clinics shall be in compliance with the provision of point b clause 1 Article 49 of Pharmaceutical law.

Section 3

OPERATING AMBULATORY RETAIL OF DRUGS

Article 38. Conditions required for operating ambulatory retail of drugs

1. Establishments eligible to operate ambulatory retail of drugs shall include:

a) Drug manufacturer;

b) Drug wholesaler;

c) Drug retailer.

d) Healthcare establishments affiliated to people's armed force engaging in drug supply operations in ethnic minority areas, mountainous areas, island, areas of extreme economic-social hardship.

2. The person retailing drugs ambulatorily must be an employee of the establishments referred to in clause 1 of this Article and be in possession of one of the qualifications stipulated in point a, b, c, e, g, h, i and k clause 1 Article 13 of Pharmaceutical law.

3. Drugs for sale through an ambulatory retail operation must have at least 06 months of shelf life remaining and stored in facilities, equipment to ensure they are kept sanitary and protected from rain, run exposure.

4. At the drug ambulatory retail outlet there must be a sign clearly indicating the name, address of the establishment operating the ambulatory retail operations, full name of the retailing person, operating geographic areas.

5. An establishment shall only be allowed to operate the ambulatory retail operation after obtaining a Receipt of its letter giving notification of the drug ambulatory operation from Health Department and shall be responsible for management the information pertaining to the operation. The establishment shall operate at the exact geographic area it notified and sell the drugs belonging t the List published by Health Department.

Article 39. List of drugs and geographic areas for ambulatory retail

1. The List of drugs for ambulatory retail covers the drugs meeting the following criteria:

a) Drugs belonging to the List of non-prescription drugs;

b) Drugs that only require to be stored in normal conditions;

c) Drugs meeting the ordinary demand of local residents.

2. Based on the criteria specified under clause 1 of this Article, , the Director of Health Department shall approve and publicize the list of drugs, geographic areas, allowed for ambulatory retail in the jurisdiction.

Article 40. Formalities for announcing drug ambulatory retail operations

1. Prior to conducting the ambulatory retail of drugs, the establishment operating drug ambulatory retail must notify in writing Health Department at the locality where it intends to operate using Form no. 23 in Appendix I of this Decree.

2. Upon receipt of the notification letter from the establishment operating drug ambulatory retail, Health Department shall issue the establishment a Receipt of the notification using Form no. 01 in Appendix I of this Decree.

3. Within 05 (five) working days from the date recorded on the Receipt of the notification letter the drug ambulatory retail, Health Department shall be responsible to publicly announce the information regarding the establishment operating ambulatory retail of drugs on its web portal and inform the district's Health Service for the latter's inspection, supervision.

Section 4

SECURITY MEASURES TO PREVENT DIVERSION OF CONTROLLED DRUGS, DRUG RAW MATERIALS, LICENSING PROCEDURES, FORMALITIES FOR CONDUCTING BUSINESS IN DRUGS ON THE LIST OF CONTROLLED DRUGS RESTRICTED RETAIL DRUGS

Article 41. List of radioactive substances for the use in healthcare sector and the promulgation of the list of drugs, pharmaceutical substances on the list of substances banned from use in certain sectors, fields

1. The list of radioactive substances for the use in healthcare sector is promulgated in Appendix IV of this Decree.

2. Promulgation of the list of drugs, pharmaceutical substances on the list of substances banned from use in certain sectors, fields:

a) Ministries, ministerial level agencies shall be responsible to send to Ministry of Health the list of substances to be banned from use in the sectors, fields under their regulatory purview when the list is promulgated or amended, supplemented;

b) Upon receipt of the notification from ministries, ministerial level agencies, the Health Minister shall be responsible to take appropriate regulatory actions and basing on the risk of abuse, misuse of drugs, drug raw materials, Ministry of Health shall promulgate the list of drugs, drugs, pharmaceutical substances on the list of substances banned from use in certain sectors, fields.

Article 42. Conditions required for conducting business in controlled drugs

1. Establishments conducting business in controlled drugs must fulfil the following conditions:

a) Meeting in full the respective conditions stipulated under Article 33 of Pharmaceutical law commensurate with the specific conditions of the business establishment;

b) Meeting the specific requirements in security measures stipulated under Article 43, 44, 45, 46, 47 and 48 of this Decree.

c) In the case of business operations involving radioactive drugs, apart from fulfilling the requirements in point a and b of this clause, the establishment must also comply to the provisions of the Law on nuclear energy and relevant legal normative documents.

2. Where there is no business establishments operating in controlled drugs in the locality, Health Department shall nominate a wholesaler in the province that fulfils the conditions set out under clause 1 of this Decree to operate in controlled drugs with a view to ensuring an adequate supply of such drugs to meet patients' demand.

3. Ministry of Health, Health Departments shall conduct 03 monthly or unannounced inspections, assessment of conformity with requirements in security measures stipulated under Section 4 Chapter III of this Decree of establishments operating in controlled drugs according to the provisions of the Minister of Health or the International treaty to which Vietnam is a party.

Article 43. Physical facility requirements of business establishments operating in controlled drugs

1. For manufacturers of narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors:

a) There must be a dedicated warehouse or separate storage area meeting good storage practice for drugs, drug raw materials for the storage of narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors. The warehouse or storage area must have strong walls and ceiling constructed of robust materials, with secured doors and locks;

b) There must be a camera system for the monitoring of each operation in the drug manufacturing and storage processes;

c) There must be a record based system of management and monitoring in accordance with the Minister of Health's stipulations;

d) There must be a software monitoring system to support the management of the processes of issuing, receiving, stocking of narcotic drugs, psychotropic drugs, precursor drugs and the processes of issuing, receiving, stocking, using of raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors.

2. For manufacturers of combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic drugs, combination drugs containing drug precursors:

a) There must be a dedicated warehouse or separate storage area meeting good storage practice for drugs, drug raw materials for the storage of drug raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substances, precursors. The warehouse or storage area must have strong walls and ceiling constructed of robust materials, with secured doors and locks;

b) There must be a separate storage area for the storage of combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors;

c) There must be a camera system for the monitoring of each operation in the processes of drug manufacturing and storage;

d) There must be a record based system of management and monitoring in accordance with the Minister of Health's stipulations

đ) There must be a software monitoring system to support the management of the processes of issuing, receiving, stocking, usage of drug raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors; the processes of issuing, receiving, stocking

of combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing drug precursors.

3. For manufacturers of radioactive drugs:

a) There must be a dedicated warehouse or storage area meeting the principles of good storage practice for drugs, drug raw materials the storage of radioactive drugs;

b) The manufacturer must be in possession of a Permit for radioactive work suitable with its operating scope;

c) There must be a software monitoring system supporting the management of the processes of issuing, receiving, stocking of radioactive drugs;

d) There must be a record based system of management and monitoring in accordance with the Minister of Health's stipulations.

đ) The manufacturing areas, storage areas must be fitted with a camera system.

4. For exporters, importers of , providers of storage service for, narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors:

a) There must be a dedicated warehouse meeting the principle of Good storage practice for drugs, drug raw materials for the storage of narcotic drugs, psychotropic drugs, drug raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors. The warehouse for these drugs must be physically segregated from the warehouses for other drugs and have strong walls and ceiling constructed of robust materials; fitted with secure doors and locks.

b) The warehouse for drugs, drug raw materials must be fitted with a camera system;

c) There must be a record based system of management and monitoring in accordance with the Minister of Health's stipulations;

d) There must be a software monitoring system for the management of the processes of issuing, receiving, stocking, of narcotic drugs, psychotropic drugs, and drug raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors.

5. For exporters, importers, wholesalers, providers of storage service, of combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic substances, combination drugs containing precursors:

a) There must be a dedicated warehouse or separate storage area meeting the principle of Good storage practice for drugs, drug raw materials for the storage of combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors. The warehouse must have strong walls and ceiling constructed of solid materials, fitted with secure doors and locks;

b) There must be a record based system of management and monitoring in accordance with the Minister of Health's stipulations.

c) There must be a software monitoring system to support the management of the processes of issuing, receiving, stocking combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors.

6. Exporters, importers, wholesalers of radioactive drugs must have a software monitoring system for the tracking and management of the processes of issuing, receiving, stocking of radioactive drugs and a record based system of management and monitoring in accordance with the Minister of Health's stipulations.

7. For wholesalers of narcotic drugs, psychotropic drugs, precursor drugs:

a) There must be a dedicated warehouse or a separate storage area meeting the principle of good storage practice for drugs, drug raw materials for the storage of narcotic drugs, psychotropic drugs,

precursor drugs. The warehouse must have strong walls and ceiling constructed with solid materials, fitted with secure doors and locks;

b) Storage areas must be fitted with a camera system;

c) There must be a record based system of management, monitoring in accordance with the Minister of Health's stipulations;

d) There must be a software monitoring system for the management of the processes of issuing, receiving, stocking, of narcotic drugs, psychotropic drugs, precursor drugs.

8. For retailers of narcotic drugs, psychotropic drugs, precursor drugs:

a) There must be a dedicated warehouse or a separate storage area for the storage of narcotic drugs, psychotropic drugs, precursor drugs. The warehouse must be fitted with secure doors and locks. If there is no dedicated storage area, narcotic drugs, psychotropic drugs, precursor drugs must be stored in a separate cupboard or drawer, securely locked;

b) There must be a record based system of management, monitoring in accordance with the Minister of Health's stipulations;

9. Retailers of combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors must have in place a software application or record based system for the monitoring in accordance with the Minister of Health's stipulations

10. For retailers of radioactive drugs:

a) There must be a dedicated area for the storage of radioactive drugs;

b) The retailer must be in possession of a Permit for radioactive work commensurate with its operating scope;

c) There must be a record based system of management, monitoring in accordance with the Minister of Health's stipulations;

d) There must be a software monitoring system for the management of the processes of issuing, receiving, stocking, of radioactive drugs.

11. For providers of clinical trial service, providers of bioequivalence study service, providers of testing service, providers of storage service, for radioactive drugs:

a) There must be a dedicated warehouse or separate storage area meeting the principles of Good storage practice for drugs, drug raw materials for the storage of radioactive drugs;

b) The establishment must be in possession of a Permit for radioactive work commensurate with its operating scope;

c) There must be a software monitoring system for the management of the processes of issuing, receiving, stocking, of radioactive drugs;

d) There must be a record based system of management, monitoring in accordance with the Minister of Health's stipulations;

đ) The establishment providing storage service of radioactive drugs must have it facility fitted with a camera system.

12. Providers of clinical trial service, equivalence study service, testing service, of controlled drugs, except for the cases referred to in clause 11 of this Article, must store narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors, combination drugs containing narcotic pharmaceutical substances combination drugs containing psychotropic substances, combination drugs containing precursors, in a separate securely locked area. If there is no separate area for the purpose, they must be stored in a separate cupboard, separate drawer with secure locks.

13. Business establishments operating in toxic drugs, toxic drug raw materials, drugs and pharmaceutical substances belonging to the list of substances banned from use in certain sectors, fields must have a software monitoring system or record based system for the management of the processes of issuing, receiving, stocking of drugs in accordance with the Minister of Health's stipulations.

Article 44. Human resource requirements of business establishments operating in controlled drugs

1. For manufacturers of narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substances drug precursors:

a) The warehouse manager of narcotic drugs, raw materials being narcotic pharmaceutical substances must be in possession of a bachelor or higher level degree in pharmacy, have at least 02 years of professional practice experience at a pharmaceutical business establishment;

b) The warehouse manager of psychotropic drugs, precursor drugs, drug raw materials being psychotropic pharmaceutical substances, drug precursors must be in possession of a secondary or higher level diploma in pharmacy, have at least 02 years of professional practice experience at a pharmaceutical business establishment;

c) The person in charge of record keeping, reporting must be in possession of a secondary or higher level diploma in in pharmacy.

2. For manufacturers of combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors:

a) The warehouse manager of drug raw materials being narcotic pharmaceutical substances must be in possession of a bachelor or higher level degree in pharmacy, have at least 02 years of professional practice experience at a pharmaceutical business establishment;

b) The warehouse manager of drug raw materials being psychotropic pharmaceutical substance, drug precursors must be in possession of a secondary or higher level diploma in pharmacy, have at least 02 years of professional practice experience at a pharmaceutical business establishment;

c) The person in charge of record keeping, reporting must be in possession of a secondary or higher level diploma in in pharmacy;

3. For manufacturers of radioactive drugs

a) The warehouse manager of drugs must be in possession of a secondary or higher level diploma in pharmacy or a bachelor or higher level degree in radioactive chemistry, radiation medicine or nuclear medicine;

b) The person in charge of record keeping, reporting must be in possession of a secondary or higher level diploma in pharmacy or a technical school or higher level diploma in the disciplines of radioactive chemistry, analytical chemistry, radioactive chemo pharmacy, nuclear physics;

c) The person in charge of supervising the processes of research, manufacture, analysis, testing must be in possession of a bachelor degree in radioactive chemistry, bachelor degree in radiation medicine or nuclear medicine or a bachelor or higher level degree in pharmacy;

4. For exporters, importers of narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors:

a) The warehouse manager of narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors must be in possession of a bachelor or higher level degree in pharmacy, have at least 02 years of professional practice experience at a pharmaceutical business establishments;

b) The person in charge of record keeping, reporting on drugs and drug raw materials must be in possession of a secondary or higher level diploma in pharmacy;

5. For exporters, importers of radioactive drugs: The person in charge of record keeping, reporting must be in possession of a secondary or higher level diploma in pharmacy or a technical school or higher level diploma in the disciplines of radioactive chemistry, analytical chemistry, radioactive chemo pharmacy, nuclear physics.

6. For wholesalers of narcotic drugs, psychotropic drugs, precursor drugs:

a) The warehouse manager of narcotic drugs must be in possession of a bachelor or higher level degree in pharmacy, have at least 02 years of professional practice experience at a pharmaceutical business establishment;

b) The warehouse manager of psychotropic drugs, precursor drugs must be in possession of a secondary or higher level diploma in pharmacy, have at least 02 years of professional practical experience at a pharmaceutical business establishment;

c) The person in charge of record keeping, reporting on drugs and drug raw materials must be in possession of a secondary or higher level diploma in pharmacy;

7. For wholesalers of radioactive drugs: The person in charge of record keeping, reporting must be in possession of a secondary or higher level diploma in pharmacy or a technical school or higher level diploma in the disciplines of radioactive chemistry, analytical chemistry, radioactive chemo pharmacy, nuclear physics;

8. Establishments retailing narcotic drugs, psychoactive drugs, precursor drugs

a) The person in charge of retailing narcotic drugs must possess a bachelor degree in pharmacy;

b) The person in charge of retailing psychotropic drugs, precursor drugs must be in possession of a secondary or higher level diploma in pharmacy;

9. For retailers of radioactive drugs: The person in charge of retailing, record keeping, reporting must be in possession of a secondary or higher level diploma in pharmacy.

10. For providers of storage services of narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors:

The warehouse inventory manager of narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors must be in possession of a bachelor or higher level degree in pharmacy, have at least 02 years of professional practice experience at a pharmaceutical business establishment.

For providers of clinical trial service, drug bioequivalence study service, testing service on narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors: The person in charge of monitoring, managing narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors, must be in possession of a secondary or higher level diploma in pharmacy.

12. For providers of clinical trial service, drug bioequivalence study service, drug testing service, storage service for radioactive drugs:

a) The warehouse manager of drugs must be in possession of a secondary or higher level diploma in pharmacy or bachelor degree in radioactive chemistry, bachelor or higher level degree in the specialty of radiation medicine or nuclear medicine;

b) The person in charge of record keeping, reporting must be in possession of a secondary or higher level diploma in pharmacy or a technical school or higher level diploma in the disciplines of radioactive chemistry, analytical chemistry, radioactive chemo pharmacy, nuclear physics;

c) The person in charge of supervising the processes of research, manufacture, analysis, testing must be in possession of a bachelor degree in radioactive chemistry, bachelor or higher level degree in radiation medicine or nuclear medicine or a bachelor or higher level degree in pharmacy.

Article 45. Provisions on the delivery, receipt, transport of business establishments operating in controlled drugs

1. The person delivering, receiving controlled drugs, controlled drug raw materials must be in possession of a technical school or higher level diploma; the person delivering and receiving radioactive drugs must in addition hold a certificate of radiation safety in accordance with Ministry of Science and Technology's regulations.

2. The person transporting narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials that are narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors while being on duty must have with him the task assignment letter from the head of the establishment, valid personal identification papers, sales invoices or warehouse issue slips. Where radioactive drugs are transported, such person must also bring with him the radiation safety certificate.

3. The delivery and receipt of narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substance, drug precursors must be documented by a handover minutes conforming to Form no. 1 Appendix II of this Decree.

4. Drug raw materials that are narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors, narcotic drugs, psychotropic drugs, precursor drugs must be securely protected during transit to prevent diversion; transport of radioactive drugs must be undertaken in adherence to safety guidelines for the transport for radioactive materials issued by the Minister of Science and Technology.

5. Establishments participating in the delivery, receiving process must be in possession of a permit for radiation work with the transport of radioactive sources as permitted scope of work in accordance with Ministry of Science and Technology's regulations.

Article 46. Provisions on the trading controlled drugs

1. With regard to drug raw materials being narcotic substances, psychotropic substances, drug precursors:

a) Manufacturers shall only be allowed to import raw materials for their own drug manufacture operations;

b) Exporters shall only be allowed to sell imported raw materials to manufacturers of narcotic drugs, psychotropic drugs, precursor drugs, combination drugs containing narcotic pharmaceutical substances and combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors; medical service establishments, research, testing establishments, compulsory addiction rehabilitation institutions, institutions for opiate addition treatment by alternative drugs, medicine-pharmacy training institutions nationwide; drugstores for drug per-prescription compounding;

c) Manufacturers that purchase drug raw materials for their production wishing to sell the unused stock of such raw materials to manufacturers, importers qualified for operating in controlled drugs must obtain a written permission to the effect by Ministry of Health.

2. With regard to narcotic drugs, psychotropic drugs, precursor drugs, combination drugs containing precursors:

a) Manufacturers shall only be allowed to sell the drugs they manufactured to manufacturers that are in possession of a certificate of satisfaction of conditions for pharmaceutical business with as operating scope the exportation, importation and wholesale of drugs, medical service establishments, research, testing establishments, compulsory addiction rehabilitation institutions, institutions for opiate addiction treatment by alternative drugs, medicine-pharmacy training institutions nationwide, to select 01 wholesaler for each 01 province geographic area to exclusively sell all the products they manufacture to;

b) Importers shall only be allowed to sell the drugs they import to medical service establishments, research, testing establishments, compulsory addiction rehabilitation institutions, institutions for opiate addiction treatment by alternative drugs, medicine-pharmacy training institutions nationwide, to select 01 wholesaler for each 01 province geographic area to exclusively sell all the products they import to;

c) Establishments that are in possession of a certificate of satisfaction of conditions for pharmaceutical business with as operating scope the exportation, importation of drugs and wholesale of precursor drugs, shall only shell drugs to other establishments that are in possession of a certificate of satisfaction of conditions for pharmaceutical business with as operating scope the exportation, importation and wholesale of drugs, medical service establishments, research, testing establishments, compulsory addiction rehabilitation institutions, institutions for opiate addiction treatment by alternative drugs, medicine-pharmacy training institutions nationwide; drugstores in the province where they have office, to select 01 wholesaler for each 01 province geographic area to exclusively sell all the products they trade to;

d) Wholesalers shall only be allowed to sell the drugs to medical service establishments, research, testing establishments, compulsory addiction rehabilitation institutions, institutions for opiate addition treatment by alternative drugs, medicine-pharmacy training institutions and drugstores at the in the province they have office.

đ) Medical service establishments, research, testing establishments, compulsory addiction rehabilitation institutions, institutions for opiate addiction treatment by alternative drugs shall be allowed to purchase drugs from the establishments referred to in point a, b, c and d of this clause according to the results of the drug tendering they conducted.

3. Combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, radioactive drugs, toxic drugs, toxic drug raw materials, drugs and pharmaceutical substances belonging to the list of drugs, pharmaceutical substances of the list of substances banned from use in certain sectors, fields, shall be allowed for trading in accordance with the provisions of Chapter IV of Pharmaceutical law.

Article 47. Provisions on reporting regime of business establishments operating in controlled drugs

1. Export, import reporting:

a) Within 10 days from the exporting, importing date, the establishment must prepare reports on the export, import of narcotic drugs, psychotropic drugs, precursor drugs, narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors, using Form no. 02 and 03 in Appendix II of this Decree and send them to Ministry of Health and Ministry of Public Security;

b) Within 10 days from the exporting, importing date, the establishment must prepare reports on the export, import of radioactive drugs using Form no. 04 and 05 in Appendix II o this Decree and send them to Ministry of Health;

c) On an annual basis, by the 15th January of the following year, the establishment must prepare reports on the export, import of combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs

containing precursors, radioactive drugs, using Form no. 06, 07 and 08 in Appendix II of this Decree and send them to Ministry of Health;

2. On an annual basis by the 15th July and by the 15th January, manufacturers, exporters, importers shall prepare a 06 monthly report and an annual report for the respective periods on the export, import, inventory, usage of narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors, using Form no. 09 and 10 in Appendix II of this Decree and send them to Ministry of Health.

3. On an annual basis by the 15th July and by the 15 January, manufacturers, exporters, importers shall prepare a 06 month report and an annual report for the respective periods on the export, import, inventory of radioactive drugs, combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic substances, combination drugs containing precursors using Form no. 11 and Form no. 12 in Appendix II of this Decree and send them to Ministry of Health.

4. On an annual basis by the 15th July and by the 15 January, wholesalers, retailers shall prepare a report on the export, import, inventory of radioactive drugs, combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic substances, combination drugs containing precursors, using Form no. 11, 12, 13 in Appendix II of this Decree and send them to Health Department at the locality where they have office.

5. On an annual basis by the 15th January, manufacturers, export-importers shall prepare reports on the issues, receipts, inventory, usage of drugs, pharmaceutical substances on the list of drugs, pharmaceutical substances of the list of substances banned from use in certain sectors, fields and send them to Ministry of Health. Wholesalers shall prepare reports on the issues, receipts, inventory of drugs, pharmaceutical substances on the list of drugs, pharmaceutical substances of the list of substances banned from use in certain fields, sectors, and send them to the relevant Health Department. The report shall be prepared using Form no. 09 in Appendix II of this Decree.

6. Within 48 hours upon discovering errors, diversions of radioactive drugs, narcotic drugs, psychotropic drugs, precursor drugs and drug raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors, manufacturers, exporter, importers, providers of drug storage service, providers of drug clinical trial service, providers of drug bioequivalence study service, provider of drug testing service, shall prepare a report to the effect and send it to Ministry of Health; wholesalers, retailers shall prepare a report to the effect and send it to the relevant Health Department. The report shall be prepared using Form no. 14 in Appendix II of this Decree.

7. On an annual basis by the 15th of January, Health Departments shall report to Ministry of Health the list of wholesalers of narcotic drugs psychotropic drugs, precursor drugs, combination drugs containing precursors in the locality using Form no, 15 in Appendix II of this Decree.

Article 48. Destruction of controlled drugs

1. Establishments requesting for the destruction of narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substances, precursor drugs shall prepare a letter to the effect specifying the name of the drug, drug raw material, strength or concentration quantity, reason of the destruction, destruction method.

2. The formalities for authorizing the destruction of narcotic drugs, psychotropic drugs, drug raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors shall be undertaken as follows:

a) The establishment]concerned, in the case of manufacturers, exporters, importers, shall submit the letter requesting for the destruction either in person or by post to Ministry of Health or to

Health Department where it has office, in the case of pharmaceutical business establishments other than the aforementioned;

b) Upon receipt of the request letter, the receiving authority shall issue the establishment a Dossier receipt using Form no. 01 in Appendix I of this Decree;

c) If there is no follow up request for revision, supplementation, the receiving authority shall issue the establishment a letter authorizing the destruction within 30 days from the date recorded on the Dossier receipt;

d) If there is a follow up request for revision, supplementation, the receiving authority shall issue a written notification to the effect to the establishment within 30 days from the date recorded on the Dossier receipt;

đ) Upon receipt of the follow up submission, the receiving authority shall issue the establishment a Receipt of follow up submission using Form no. 01 in Appendix I of this Decree. If there is no further follow up request, the receiving authority shall issue a letter authorizing the destruction in accordance with the provision of point c of this clause. If the follow up submission does not meet the requirements, the receiving authority shall issue a written notification to the effect to the establishment I accordance with the provision of point d of this clause.

3. The destruction of narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors shall only be carried out after an authorizing letter has been obtained from Ministry of Health or Health Department of the locality where the establishment has office.

4. The destruction of narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic pharmaceutical substances, psychotropic pharmaceutical substances drug precursors shall be carried out as follows:

a) The head of the establishment shall set up a drug destruction committee. The committee shall compose of at least 03 representatives, of whom 01 is the pharmacist in charge of the establishment. The drug destruction committee shall be tasked with executing the destruction, deciding on destruction method, supervising the drug destruction of the establishment;

b) The destruction of drugs and drug raw materials must be witnessed by representative f of Health Department in the locality and recorded in a minutes, using Form no. 16 in Appendix II of this Decree.

c) Within 10 days after completion of the destruction of drugs and drug raw materials, the establishment must send a drug destruction report using Form no. 17 in Appendix II of this Decree, with the destruction minutes enclosed, to Ministry of Health or Health Department.

5. Radioactive drugs, radioactive substances, primary packaging components that are no longer usable must be temporary preserved and stored before being destroyed in accordance with legislation on nuclear energy.

6. Radioactive waste originating from radioactive drugs must be managed in accordance with legislation on nuclear energy.

7. Overrun products, defective products containing narcotic, psychotropic pharmaceutical substances and drug precursors left over from production processes; combination drugs containing psychotropic pharmaceutical substances, combination drugs containing narcotic substances, combination drugs containing drug precursors; packaging materials that have been in contact with narcotic drugs, psychotropic drugs, precursor drugs, narcotic pharmaceutical substances, psychotropic substances and drug precursors no longer in use, toxic drugs, toxic drug raw materials, drugs and pharmaceutical substances in the list of drugs, pharmaceutical substances on the list of substances banned from use in certain sectors, fields, at trading establishments, must be gathered and destroyed of in accordance with the provision of point a clause 4 of this Article and records of the destruction must be retained at the establishment.

Article 49. Application dossier for license to conduct business in controlled drugs

Establishments applying for license to operate in controlled drugs, in addition to the documents required under Article 32 of this Decree, must submit the following:

1. Document to demonstrate that the establishment fulfil the security requirements, to prevent diversion of controlled drugs, conforming to Form no. 18 in Appendix II of this Decree, prepared in A4 paper in Vietnamese language.

2. Original copy or an authenticated duplicate copy of Permit for radiation work issued by the competent authority shall also be required.

3. For retailers that are drugstores engaging in per-prescription compounding, the list of drugs to be compounded and the compounding procedures shall also be required.

4. The documents required in this Article shall be submitted in 01 set.

Article 50. Procedures, formalities for the issuance of certificate of satisfaction of conditions for pharmaceutical business to establishments operating in narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials containing narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors, radioactive drugs; establishments manufacturing combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors:

1. Applicant establishments shall submit an application dossier for Certificate of satisfaction of conditions for pharmaceutical business in person or by post to:

a) Ministry of Health in the case of drug manufacture, exportation, importation, storage service, clinical trial service, bioequivalence study service, drug testing service;

b) Health Department where the establishment is located in the case of wholesale, retail of controlled drugs;

2. Upon receipt of an application dossier, the receiving authority shall issue to the applicant establishment a Dossier receipt using Form no. 01 in Appendix I of this Decree.

3. If there is no follow up request for dossier revision, supplementation, the receiving authority shall present the case to the Advisory council for their consideration within 15 days from the date recorded on Dossier receipt.

4. If there is a follow up request, the receiving authority shall send the applicant establishment a written notification to the effect within 20 days from the date recorded on Dossier receipt, specifying the documents, contents requiring revision, supplementation.

5. Upon receipt of the follow up submission, the receiving authority shall issue the applicant establishment a Dossier receipt using Form no. 01 in Appendix I of this Decree.

a) If the follow up submission does not meet the requirements, the receiving authority shall issue the applicant establishment a written notification to the effect in accordance with the provision of clause 4 of this Article;

b) If there is no further follow up request, the receiving authority shall proceed in accordance with the provision of clause 3 of this Article.

6. The receiving authority shall evaluate the dossier taking into account the Advisory council's opinions.

a) If there is no follow up request for dossier revision, supplementation, the receiving authority shall conduct an on site team assessment at the establishment's facility within 60 days from the date recorded on Dossier receipt;

b) If there is a follow up request for dossier revision, supplementation, the receiving authority shall issue the applicant establishment a written notification to the effect in accordance with clause 4 of this Article.

7. After completion of the on site assessment and taking into account the Advisory council's opinions, the dossier receiving authority shall be responsible to:

a) Issue Certificate of satisfaction of conditions for pharmaceutical business within 20 days from the completion date of the on site assessment where there is no request for remedial, corrective actions;

b) Issue a written notification regarding the areas requiring remedial, corrective actions within 15 working days from the completion date of the on site assessment where there is a request for remedial, corrective actions;

c) Within 06 months from the date the dossier receiving authority issues the written notification, if the applicant establishment still fails to complete the requested remedial, corrective actions, the dossier that was submitted shall become void.

8. Within 20 days from the date of receipt of the letter and supporting documents from the applicant establishment demonstrating that the remedial, corrective actions have been completed, the receiving authority shall issue a certificate of satisfaction of conditions for pharmaceutical business or an explanation as to why it has not been issued.

9. Within 06 months from the date the receiving authority issue the written notification for follow up revision, supplementation, the applicant establishment must respond accordingly. Past this timeline, if the establishment fails to respond or after 12 months from the date of the initial dossier submission, if the dossier still does not meet the requirements it shall become void.

10. Within 05 working days from the date the Certificate of satisfaction of conditions for pharmaceutical business is issued, the dossier receiving authority shall announce, update on its web portal the following information:

a) Name, address of the Certificate holder;

b) Full name of the pharmacist in charge, Number of his/her Certificate of pharmacy practice;

c) Number of Certificate of satisfaction of conditions for pharmaceutical business;

d) Operating scope of the establishment holding the Certificate.

11. The competent authority shall only conduct a on site assessment on the areas not yet verified, assessed for conformity with good practice.

Article 51. Procedures, formalities for the issuance of Certificate of satisfaction of conditions for pharmaceutical business for business establishments operating in combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors (except the manufacturing establishments referred to under Article 50 of this Article); establishments trading in toxic drugs, toxic drug raw materials; drugs, drug raw materials on the list of drugs, pharmaceutical substances of the list of substances banned from use in certain sectors, fields

1. Applicant establishments shall submit an application dossier for Certificate of satisfaction of conditions for pharmaceutical business in person or by post to:

a) Ministry of Health in the case of drug manufacture, exportation, importation, storage service, clinical trial service, bioequivalence study service, drug testing service;

b) Health Department where the establishment is located in the case of wholesale, retail of controlled drugs;

2. Upon receipt of an application dossier, the receiving authority shall issue to the applicant establishment a Dossier receipt using Form no. 01 in Appendix I of this Decree.

3. If there is no follow up request for dossier revision, supplementation, the certificate issuing authority shall:

a) Issue a Certificate of satisfaction of conditions for pharmaceutical business with the trading in controlled drugs added to the operating scope within 30 days from the date recorded on Dossier

receipt in the case of establishments already holding a certificate of satisfaction of conditions for pharmaceutical business and meeting the respective good practice;

b) Conduct an onsite assessment within 30 days from the date recorded on Dossier receipt in the case of establishments applying for the first time for Certificate of satisfaction of conditions for pharmaceutical business or establishments already holding such a certificate but not in compliance the respective good practice.

4. If there is a follow up request, the receiving authority shall send the applicant establishment a written notification to the effect within 30 days from the date recorded on Dossier receipt, specifying the documents, contents requiring revision, supplementation.

5. Upon receipt of the follow up submission, the receiving authority shall issue the applicant establishment a Dossier receipt using Form no. 01 in Appendix I of this Decree.

a) If the follow up submission does not meet the requirements, the receiving authority shall issue the applicant establishment a written notification to the effect in accordance with the provision of clause 4 of this Article;

b) If there is no further follow up request, the receiving authority shall proceed in accordance with the provision of clause 3 of this Article.

6. After completion of the on site assessment the dossier receiving authority shall be responsible to:

a) Issue Certificate of satisfaction of conditions for pharmaceutical business within 20 days from the completion date of the on site assessment where there is no request for remedial, corrective actions;

b) Issue a written notification regarding the areas requiring remedial, corrective actions within 15 working days from the completion date of the on site assessment where there is a request for remedial, corrective actions.

7. Within 20 days from the date of receipt of the letter and supporting documents from the applicant establishment demonstrating that the remedial, corrective actions have been completed, the receiving authority shall issue a certificate of satisfaction of conditions for pharmaceutical business or an explanation as to why it has not been issued.

8. Within 06 months from the date the receiving authority issue the written notification for follow up revision, supplementation, the applicant establishment must respond accordingly. Past this timeline, if the establishment fails to respond or after 12 months from the date of the initial dossier submission, if the dossier still does not meet the requirements it shall become void.

9. Within 05 working days from the date the Certificate of satisfaction of conditions for pharmaceutical business is issued, the dossier receiving authority shall announce, update on its web portal the following information:

a) Name, address of the Certificate holder;

b) Full name of the pharmacist in charge, Number of his/her Certificate of pharmacy practice;

c) Number of Certificate of satisfaction of conditions for pharmaceutical business;

d) Operating scope of the establishment holding the Certificate.

Article 52. Advisory council for the issuance of business license for narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic, psychotropic pharmaceutical substances and drug precursors, radioactive drugs

1. Composition of Advisory council at Ministry of Health

The Minister of Health shall set up an Advisory council composing of at least 05 members to provide advice on business licensing for the aforementioned drugs, made up of:

a) Ministry of Health's representative as Chair of the council;

b) Ministry of Public security with respect to business licensing for drug raw materials containing narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic, psychotropic pharmaceutical substances, drug precursors, narcotic drugs, psychotropic drugs, drug precursors;

c) Ministry of Science and Technology's representative with respect to business licensing for radioactive drugs;

d) Representative of organizations, individuals (as necessary).

2. Composition of Advisory council at Health Departments

The Director of Health Department shall set up an Advisory council composing of at least 03 members to provide advice on business licensing for the aforementioned drugs, made up of:

a) Health Department's representative as Chair of the council;

b) Representative of organizations, individuals (as necessary).

3. The Minister of Health shall provide for the organizational structure and operations of Advisory councils.

Article 53. Application dossier for the purchase of narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic, psychotropic pharmaceutical substances and drug precursors; application dossier for the on selling of drug raw materials being narcotic, psychotropic pharmaceutical substances and drug precursors

1. An application dossier for the purchase of narcotic drugs, psychotropic drugs, precursor drugs shall comprise the following documents:

a) 03 copies of purchase order of narcotic drugs, psychotropic drugs, precursor drugs using Form no, 19 in Appendix II of this Decree;

b) Report on the trading status of narcotic drugs, psychotropic drugs, precursor drugs conforming to Form no. 20 Appendix II of this Decree;

c) Letter explaining the reason for the purchase when the proposed purchase quantity exceeds 150% of the quality previously consumed.

2. An application dossier for the purchase of drug raw materials being narcotic, psychotropic pharmaceutical substances and drug precursors shall comprise the following documents:

a) 03 (three) copies of purchase order of drug raw materials being narcotic, psychotropic pharmaceutical substances, drug precursors conforming to Form no. 19 in Appendix II of this Decree;

b) Report on the trading status of drug raw materials conforming to Form no. 10 in Appendix II of this Decree;

c) Report on the trading status of the drug raw materials being narcotic, psychotropic pharmaceutical substances, drug precursors conforming to Form no. 20 in Appendix II of this Decree;

d) Production plan involving the raw materials subject of the purchase application;

đ) Letter explaining the reason for the purchase when the proposed purchase quantity exceeds 150% of the quality previously consumed.

3. Application dossier for the on selling of drug raw materials being narcotic, psychotropic pharmaceutical substances and drug precursors shall comprise the following documents:

a) Application for the on selling of drug raw materials being narcotic, psychotropic pharmaceutical substances, drug precursors of the on selling establishment, conforming to Form no. 21 in Appendix II of this Decree;

b) 03 copies of on selling orders drug raw materials being narcotic, psychotropic pharmaceutical substances, drug precursors, conforming to Form no. 19 in Appendix II of this Decree;

c) Report of the trading of the drugs, report on the usage of the drug raw materials, conforming to Form no. 10, Form no. 20 in Appendix II of this Decree.

4. The documents required under clause 1, 2, 3 of this Article shall be submitted in 01 set.

Article 54. Procedures, formalities for the licensing of the purchase of narcotic drugs, psychotropic drugs, drug raw materials being narcotic drugs, psychotropic drugs and drug precursors; the on selling of drug raw materials being narcotic, psychotropic pharmaceutical substances and drug precursors

1. Establishments proposing to purchase drugs, drug raw materials or to on sell drug raw materials shall submit an application dossier either in person or by post to:

a) Ministry of Health in the case of manufacturing establishments; establishments holding a Certificate of satisfaction of conditions for both the exporting, importing of drugs ad the wholesale of drugs; medical service establishments, research, testing establishments, compulsory addiction rehabilitation institutions, institutions for opiate addition treatment by alternative drugs, medicine-pharmacy training institutions purchasing drug raw materials for research, testing purposes;

b) Health Department where the establishment is based in the case of research, testing establishments, medicine-pharmacy training institutions, drug wholesalers, drug retailers, compulsory addiction rehabilitation institutions, institutions for opiate addition treatment by alternative drugs (with regard to the drugs not requiring tendering).

2. The dossier receiving authority shall issue to the applicant establishment a Dossier receipt for the application dossier for the purchase, on selling of narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic, psychotropic pharmaceutical substances and drug precursors using Form no. 01 in Appendix I of this Decree.

3. If there is no follow up request for dossier revision, supplementation, the receiving authority shall sign off the purchase order, approving it or issue a letter authorizing the on selling, within 30 days from the date recorded on Dossier receipt.

4. If there is a follow up request for dossier revision, supplementation, the receiving authority shall issue to the applicant establishment a written notification to the effect within 30 days from the date recorded on Dossier receipt, specifying the documents, contents requiring revision, supplementation.

5. Upson receipt of the follow up submission, the receiving authority shall issue the applicant establishment a Dossier receipt for the follow up submission using Form no. 01 in Appendix I of this Decree.

a) If the follow up submission does not meet the requirements, the receiving authority shall issue to the applicant establishment a written notification to the effect in accordance with the provision of clause 4 of this Article.

b) If there is no further follow up request for dossier revision, supplementation, the receiving authority shall sign off the purchase order, approving the purchase of issue a letter authorizing the on selling in accordance with the provision of clause 3 of this Article.

6. Within 06 months from the date the receiving authority issue the written notification the applicant establishment must respond with dossier revision, supplementation as requested. Past this timeline if the establishment fails to respond or if the follow up submission fails to meet the requirements after 12 months from the initial dossier submission, such dossier shall become void.

Article 55. Dossier, procedures for licensing the retail of drugs on the List of restricted retail drugs

1. For establishment not yet in possession of a Certificate of satisfaction of pharmaceutical business covering drug retail in operating scope:

a) An application dossier comprising the following documents: Application for retailing drugs on the List of restricted retail drugs conforming to Form no. 22 in Appendix II of this Decree;

b) Licensing formalities, time limit shall be in conformance with the provisions of Article 33 of tis Decree.

2. For establishments already in possession of a Certificate of satisfaction of conditions for pharmaceutical business covering drug retail in operating scope:

a) An application dossier comprising the following documents: Application for retailing drugs on the List of restricted retail drugs conforming to Form no. 23 in Appendix II of this Decree;

b) Licensing formalities, timelines:

- Retail establishment shall submit an application dossier either in person or by post to Health Department where they have office;

- Upon receipt of the dossier, Health Department shall issue the establishment a Dossier receipt using Form no. 01 in Appendix I of this Decree;

- If there is no follow up request for dossier revision, supplementation, Health Department shall issue a letter authorizing the establishment to retail drugs on the List of restricted retail drugs within 07 working days from the date recorded on Dossier receipt;

- If there is a follow up request for dossier revision, supplementation, within 05 working days from the date recorded on Dossier receipt, Health Department shall issue to the establishment a written notification to the effect;

- Upon receipt of the follow up submission, Health Department shall issue to the establishment a Dossier receipt of the follow up submission using Form no. 01 in Appendix I of this Decree. If the follow up submission fails to meet the requirements, Health Department shall issue to the establishment a written notification to the effect within 05 working days from the date recorded on Dossier receipt. If there is no further follow up request, Health Department shall within 07 working days from the date recorded on Dossier receipt;

- Within 06 months from the date Health Department issue the written notification for follow up revision, supplementation, the establishment must respond with the required follow up submission. Past this timeline, if the establishment fails to respond or after 12 months from the initial dossier submission, if the follow up submission still fails to satisfy the requirements, the submitted dossier shall become void.

3. Within 05 working days from the licensing date, Health Department shall be responsible for publicizing on its website the information on the retail establishment and the list of drugs licensed for retail at its retail outlet.

Article 56. Responsibilities of the competent authority with regard to the compliance with reporting requirements by business establishments operating in controlled drugs

1. With respect to business establishments operating in controlled drugs shall do not comply with the reporting requirements set out under Article 47 of this Decree, the competent authority shall issue an official letter suspending the acceptance, evaluation of all of their application dossiers for the purchase of domestic drugs, drug raw materials, the importation of drugs, drug raw materials.

2. The dossier evaluation shall only be resumed after the business establishment has fully complied with the reporting requirements.

Chapter IV

EXPORTATION, IMPORTATION OF DRUGS, DRUG RAW MATERIALS

Section 1

EXPORTATION OF CONTROLLED DRUGS, MEDICINAL MATERIALS ON THE LIST OF CONTROLLED MEDICINAL MATERIALS OF PRECIOUS, RARE, ENDEMIC SPECIES, BREEDS

Article 57. Criteria, dossier for exportation of narcotic drugs, psychotropic drugs, precursor drugs, combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors, drug raw materials being narcotic drugs, psychotropic drugs, drug precursors

1. A drug shall only be licensed for exportation when meeting one of the following criteria:

a) Produced in Vietnam, licensed for marketing in Vietnam and be the subject of an import license issued by the competent authority of the importing country;

b) Produced in a foreign country, licensed for marketing in Vietnam and be the subject of an import license issued by the competent authority of the importing country.

2. A drug raw material shall only be licensed for exportation when meeting one of the following criteria:

a) Produced in Vietnam, licensed for marketing in Vietnam or not yet licensed for marketing in Vietnam, be the subject of an import license issued by the competent authority of the importing country;

b) Produced in a foreign country, licensed for marketing in Vietnam and be the subject of an import license issued by the competent authority of the importing country.

3. Application dossier for export license:

a) 01 original copy of Export order conforming to Form no. 01 or 02 in Appendix III of this Decree;

b) Report on the quantity, origin of the drug, drug raw material, conforming to Form no. 03 in Appendix III of this Decree;

c) Original copy of the still-valid import license of the drug, drug raw material, issued by the competent authority of the importing country. If the Import license is not in Vietnamese or English language, it must be accompanied by a Vietnamese or English notarized translated version. The

import license must be consular legalized in accordance with legislation of consular legalization, unless exemption for it is provided for in applicable laws.

4. The documents required under this Article shall be submitted in 01 set.

Article 58. Criteria, dossier for exportation of radioactive drugs, drugs, pharmaceutical substances on the list of drugs, pharmaceutical substances belonging to the list of substances banned from use in certain sectors, fields, toxic drugs, toxic drug raw materials

1. A drug, drug raw material shall only be licensed for exportation when meeting one of the following criteria:

a) Produced in Vietnam, licensed for marketing in Vietnam or not yet licensed for marketing in Vietnam;

b) Produced in a foreign country, licensed for marketing in Vietnam.

2. Application dossier for export license:

a) 03 original copies of export order conforming to Form no. 04 or 05 in Appendix III of this Decree;

b) Report on the quantity, origin of the drug, drug raw material conforming to Form no. 03 in Appendix III of this Decree, except for toxic drugs, toxic drug raw materials, radioactive drugs;

c) Authenticated duplicate copy or duplicate copy certified by the exporter's seal of Permit for radiation work of the exporter in the case of exporting radioactive drugs. If a duplicate copy certified by the importer's seal is submitted the original copy must be presented for validation.

3. The documents required in this Article shall be submitted in 01 set.

Article 59. Criteria, dossier for exportation of medicinal materials on the list of controlled, precious, rare, endemic species, breeds

1. A medicinal material on the list of controlled, precious, rare, endemic species, breeds shall only be licensed for exportation when it is not exploited from natural sources and not belonging to the Minister of Health's published List of medicinal materials banned from exportation. Non commercial exportation of medicinal materials shall be carried out in accordance with biodiversity legislation.

2. Application dossier for export license:

a) 03 original copies of export order conforming to Form no. 06 in Appendix III of this Decree;

b) Duplicate copy of certificate of satisfaction of conditions for pharmaceutical business, authenticated or certified by the exporter's seal. If a duplicate copy certified by the exporter is submitted the original copy of it must be presented for validation at the point of dossier submission;

c) Duplicate copy of the certification from the commune level People's committee regarding the cultivation source of the medicinal material, authenticated or certified by the exporter's seal. If a duplicate copy certified by the exporter's seal is submitted the original copy of it must be presented for validation at the point dossier submission;

d) Authenticated duplicate copy or a duplicated copy certified by the exporter's seal of the purchasing contract for the medicinal material. If a duplicate copy certified by the exporter's seal is submitted the original copy of it must be presented for validation at the point of dossier submission;

đ) The documents required in point c and d of this clause shall not be required of non-commercial exportation of medicinal materials.

3. The documents required under this Article shall be submitted in 01 (one) set.

Article 60. Provisions for export licensing of controlled drugs for non commercial purpose

1. A controlled drug must be already licensed for marketing in Vietnam and fall into one of the following categories for it to be licensed for non commercial exportation:

a) Be part of personal belongings of an organization, individual exiting the country, brought out under airway bills or as accompanied luggage for their own therapeutic use and not a controlled drug raw material;

b) Exported for aid, humanitarian assistance;

c) Left over from the stock that was licensed for importation in support of humanitarian medical services.

2. A drug must be licensed for exportation before it can be exported, unless it is of the category referred to in point a clause 1 of this Article and of a quantity not exceeding:
a) a 07 day course in the case of narcotic drug at dosage given in the accompanied prescription;

b) a 10 day course in the case of psychotropic, precursor drugs, at dosage given in the accompanied prescription;

c) a 30 day course in the case of combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic substances, combination drugs containing precursors, toxic drugs, drugs on the list of drugs, substances banned from use in certain fields, sectors, at dosage given in the accompanied prescription.

3. Application dossier for export license for the drugs categorized in point a clause 1 of this Article:

a) Application for exportation conforming to Form no. 07 in Appendix III of this Decree;

b) Authenticated duplicate copy or a duplicate copy bearing the applicant's signature or duplicate copy bearing the applicant organization's seal of the drug prescription, outpatient medical booklet. These documents must show the following information: name, age of patient; drug 'name; strength or concentration and volume; quantity (or number of medication days); dosage; physician's full name, signature; address of the hospital, office where the physician practices'

If the duplicate copy bearing the applicant's signature or duplicate copy bearing the applicant organization's seal is submitted the original copy must be presented for validation at the point of dossier submission;

c) Duplicate copy of one of the following documents: Identity card, citizenship card or passport of the individual concerned, authenticated or bearing the signature of the applicant.

If a duplicate copy bearing the applicant's signature is submitted, the original copy of the document must be presented for validation at the point of dossier submission;

d) The documents required in point b, c of this clause, if not in Vietnamese or English language, must be accompanied by a Vietnamese or English notarized translated version.

4. Application dossier for export license for the drugs categorized in point b clause 1 of this Article:

a) Official letter in Vietnamese or English language applying for export license from the exporter;

b) 03 copies of Export order conforming to Form no. 01 or 04 in Appendix III of this Decree;

c) Original copy or authenticated duplicate copy of the letter authorizing the use of the drug for aid, humanitarian assistance purpose, issued by the competent authority of the importing country;

d) Original copy of the still-valid Import license issued by the competent authority of the importing country in the case of narcotic drugs, psychotropic drugs, precursor drugs, combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors;

đ) The documents required in point c and d of this clause if not in Vietnamese or English language must be accompanied by a notarized Vietnamese or English translated version. The documents must be consular legalized in accordance with legislation on consular legalization, except when there is an exemption provided for under applicable laws.

5. Application document for exportation for the drugs categorized in point c clause 1 of this Article:

a) Official letter in Vietnamese or English language applying for export license from the exporter;

b) 03 copies of Export order conforming to Form no. 01 or 04 in Appendix III of this Decree;

c) Report on the quantity of the drug that has been consumed for humanitarian medical services, conforming to Form no. 08 in Appendix III of this Decree.

6. The documents required under clause 3, 4, 5 of this Article shall be submitted in 01 set.

Article 61. Criteria, dossier for exportation of controlled drugs to be used as display at exhibitions, trade fairs

1. Narcotic drugs, psychotropic drugs, precursor drugs, combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors shall only be licensed for exportation if meeting one of the following criteria:

a) Produced in Vietnam, already or not yet licensed for marketing in Vietnam, be the subject of an import license issued by the competent authority of the importing country;

b) Produced in a foreign country, already licensed for marketing in Vietnam and be the subject of an import license issued by the competent authority of the importing country.

2. Application dossier for export license of narcotic drugs, psychotropic drugs, precursor drugs, combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors:

a) 01 original copy of Export license conforming to Form no. 01 or 02 in Appendix III of this Decree;

b) Original copy of the still-valid import license for the drug, drug raw material, issued by the competent authority of the importing country. The Import license, if not in Vietnamese or English language, must be accompanied by a Vietnamese or English notarized translated version. The import license must be consular legalized in accordance with legislation on consular legalization, unless an exemption for it is provided for under applicable laws;

c) The documents required under this clause shall be submitted in 01 set.

3. The exportation of radioactive drugs, toxic drugs, toxic drug raw materials, drugs, pharmaceutical substances on the list of drugs, drug raw materials of the list of substances banned from use in certain fields, sectors, to be used as display at exhibitions, trade fairs, shall be carried out in accordance with legislation on temporary exportation/re-importation of goods.

Article 62. Criteria, dossier for exportation of controlled drugs for the purposes of clinical trial, bioequivalence study, bioavailability assessment, as samples for testing, scientific research, for drug registration

1. Narcotic drugs, psychotropic drugs, precursor drugs, combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors shall only be licensed for exportation if meeting one of the following criteria:

a) Produced in Vietnam, already or not yet licensed for marketing in Vietnam, be the subject of an import license issued by the competent authority of the importing country;

b) Produced in a foreign country, already licensed for marketing in Vietnam and be the subject of an import license issued by the competent authority of the importing country.

2. Application dossier for export license of narcotic drugs, psychotropic drugs, precursor drugs, combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors:

a) 01 original copy of Export license conforming to Form no. 01 or 02 in Appendix III of this Decree;

b) Original copy of the still-valid import license for the drug, drug raw material, issued by the competent authority of the importing country. The Import license, if not in Vietnamese or English language, must be accompanied by a Vietnamese or English notarized translated version. The import license must be consular legalized in accordance with legislation on consular legalization, unless an exemption for it is provided for under applicable laws;

c) Original copy of the letter certifying that the purpose of the importation, the quantity imported for the drug using establishment, is for clinical trial, bioequivalence study, bioavailability assessment, as samples for testing, scientific research, for drug registration at the importing country. The letter if not in Vietnamese or English language must be accompanied by a Vietnamese or English notarized translated version;

d) The documents required under this clause shall be submitted in 01 set.

3. Radioactive drugs, toxic drugs, toxic drug raw materials, drugs, pharmaceutical substances on he list of drugs, pharmaceutical substances of the list of substances banned from use in certain fields, sectors, shall only be licensed for exportation if meeting one of the following criteria:

a) Produced in Vietnam: already or not yet licensed for marketing in Vietnam;

b) Produced in a foreign country: already licensed for marketing in Vietnam.

4. Application dossier for export licensing of radioactive drugs, toxic drugs, toxic drug raw materials, drugs, pharmaceutical substances on he list of drugs, pharmaceutical substances of the list of substances banned from use in certain fields, sectors:

a) 01 original copy of Export license conforming to Form no. 04 or 05 in Appendix III of this Decree;

b) Original copy of the letter certifying that the purpose of the importation, the quantity imported for the drug using establishment, is for clinical trial, bioequivalence study, bioavailability assessment, as samples for testing, scientific research, for drug registration at the importing country. The letter if not in Vietnamese or English language must be accompanied by a Vietnamese or English notarized translated version.

Article 63. Formalities and time limits for export licensing of controlled drugs, controlled medicinal materials of precious, rare, endemic species, breeds

1. Formalities and time limits for export licensing of controlled drugs, controlled medicinal materials of precious, rare, endemic species, breeds, shall be in conformance with the provisions of Article 57, 58, 59, point b, c clause 1 Article 60, clause 1 Article 61 and Article 62 of this Decree:

a) Establishments applying for export licensing shall submit an application dossier in person or by post to Ministry of Health;

b) Upon receipt of the dossier, Ministry of Health shall issue the applicant establishment a Dossier receipt using Form no. 01 in Appendix I of this Decree;

c) If there is no follow up request for dossier revision, supplementation, Ministry of Health shall issue an export license within 10 working days from the date recorded on Dossier receipt;

d) If there is a follow up request for dossier revision, supplementation, Ministry of Health shall issue the establishment a written notification to the effect within 07 working days from the date recorded on Dossier receipt;

đ) Upon receipt of the follow up submission, Ministry of Health shall issue the establishment a Dossier receipt for it, using Form no. 01 in Appendix I of this Decree. If the follow up submission does not satisfy the requirements Ministry of Health shall issue the establishment a written notification to the effect in accordance with the provision of point d of this clause. If there is no further follow up request for revision, supplementation, Ministry of Health shall issue an export license in accordance with the provision of point c of this clause;

e) Within 06 months from the date Ministry of Health issues the follow up notification, the applicant establishment must respond with dossier revision, supplementation accordingly. Past this time limit if the establishment fails to respond or past 12 months from the initial dossier submission if the supplemented dossier does not meet the requirements the submitted dossier shall become void.

2. Formalities and time limits for export licensing for the drugs categorized under point a clause 1 Article 60 of this Decree:

a) Organizations, individuals applying for export license shall submit an application dossier either in person or by post to the Health Department at the same locality of the port of entry when they enter the country or at the locality where the patient is living, temporarily residing legally or where the organization is based;

b) Upon receipt of the dossier, Health Department shall issue to the applicant organization, individual a Dossier receipt using Form no. 01 in Appendix I of this Decree;

c) If there is no follow up request for dossier revision, supplementation, Health Department shall issue an export license within 07 working days from the date recorded on Dossier receipt;

d) If there is a follow up request for dossier revision, supplementation, Health Department shall issue the applicant organization, individual, a written notification to the effect within 05 working days from the date recorded on Dossier receipt;

đ) Upon receipt of the follow up submission, Ministry of Health shall issue the establishment a Dossier receipt for it, using Form no. 01 in Appendix I of this Decree. If the follow up submission does not satisfy the requirements Ministry of Health shall issue the establishment a written notification to the effect in accordance with the provision of point d of this clause. If there is no further follow up request for revision, supplementation, Ministry of Health shall issue an export license in accordance with the provision of point c of this clause;

e) Within 03 months from the date Ministry of Health issues the follow up notification, the applicant establishment must respond with dossier revision, supplementation accordingly. Past this time limit if

the establishment fails to respond or past 04 months from the initial dossier submission if the supplemented dossier does not meet the requirements the submitted dossier shall become void.

3. Within 20 days from the date the export license is issued, Ministry of Health shall be responsible for publicizing on its web portal the information pertinent to the medicinal material that was licensed for exportation belonging to the List of controlled, precious, rare, endemic species breeds.

4. Export licenses, official letters authorizing the exportation shall be prepared using Form no. 09, 10, 11, 12 or 13 in Appendix III of this Decree.

Article 64. Regulating the exportation of drugs, drug raw materials

1. An export license for narcotic drugs, psychotropic drugs, precursor drugs, combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors, shall be issued for each consignment; the quantity of drugs, drug raw materials licensed for exportation shall not exceed the quantity stated on the Import license issued by the competent authority of the importing country.

2. An export license for medicinal materials on the List of controlled, precious, rare, endemic species, breeds shall be issued for each export consignment.

3. Narcotic drugs, psychotropic drugs, precursor drugs, radioactive drugs, combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors, drug raw materials being narcotic, psychotropic pharmaceutical substances, drug precursors, medicinal materials on the List of controlled, precious, rare, endemic species, breeds shall only be exported through international ports of entry, except for the drugs categorized in point a clause 1 Article 60 of this Decree.

4. Manufacturers of narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic, psychotropic pharmaceutical substances, drug precursors, shall be allowed to export the drugs, drug raw materials they themselves manufacture.

5. Exporters, importers of narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic, psychotropic pharmaceutical substances, drug precursors shall be allowed to export drugs, drug raw materials they themselves trade.

6. Individuals, organizations applying for non commercial exportation of controlled drugs under the provision of point a clause 1 Article 60 of this Decree shall be responsible for the origin, quality, safety, effectiveness of the drugs to be exported and to fulfill the requirements of the importing country.

7. Exporters of narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic, psychotropic pharmaceutical substances, drug precursors, combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors, for displaying at exhibitions, trade fairs, shall be responsible for reimporting them in their entirety at completion of such exhibitions, trade fairs.

8. With regard to the drugs allowed to be exported without a Ministry of Health-issued export license stipulated under clause 5 Article 60 of Pharmaceutical law, but for which the exporter wishes to obtain an Export license:

a) Application dossier for export license shall comprise 03 original copy of Export order conforming to Form no. 14 in Appendix III of this Decree and a duplicate copy of the exporter's Certificate of satisfaction of conditions for pharmaceutical business, authenticated or certified by the exporter's seal;

b) Formalities for export license shall be undertaken in accordance with the provision of clause 1 Article 63 of this Decree.

Section 2
IMPORTATION OF DRUGS NOT YET LICENSED FOR MARKETING IN VIETNAM

Article 65. Criteria, application dossier for import license of drugs containing pharmaceutical substances not yet licensed for marketing in Vietnam, drugs containing medicinal materials used for the first time in Vietnam

1. The drugs shall only be licensed for importation when fulfilling the following criteria:

a) Being licensed for marketing in one of the following countries: Manufacturing country, reference country among the International council for harmonization of technical requirements for pharmaceutical for human use (ICH) member countries or Australia;

b) For the treatment of life threatening diseases, social diseases, dangerous and newly emerging epidemic diseases as declared by the Minister of Health;

c) Drugs for which the clinical data on safety, effectiveness according to the Minister of Health's requirements for registration is adequately available. For vaccines, the results of a clinical trial conducted in Vietnam in conformance with the Minister of Health's stipulations shall also be required;

2. Application dossier for import license:

a) 3 original copies of import order conforming to Form no. 7, 8, 9 or 10 in Appendix III of this Decree;

b) Original or authenticated duplicate copy of Certificate of pharmaceutical product;

c) Duplicate copy of the manufacturer's quality specification and test method for the drug, certified by the importer's seal;

d) 01 set of original copy of specimen labels and package insert of the drug in actual use in the country issuing the certificate of pharmaceutical product, except when they are already attached to Certificate of pharmaceutical product;

đ) 02 sets of mock-up label intended to be used for marketing the product in Vietnam, enclosed with the Vietnamese language package insert, certified by the importing establishment's seal;

e) Clinical data on safety and effectiveness in accordance with the Minister of Health's requirements for drug registration. For vaccines, the results of a clinical trial conducted in Vietnam in conformance with the Minister of Health's stipulations shall also be required;

g) Report on trading results with regard to the import drugs being narcotic drugs, psychotropic drugs, precursor drugs, combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors, drugs on to the List of drugs, pharmaceutical substances belonging to the List of substances banned from use in certain sectors, fields, conforming the Form no. 18 in Appendix III of this Decree;

h) Original or authenticated duplicate copy of Certificate of good manufacturing practice of all establishments participating to the manufacture of the import drugs where the manufacture of such drugs involves several establishments;

i) Authenticated duplicate copy or duplicate copy certified by the exporter's seal of Permit for radiation work of the exporter in the case of exporting radioactive drugs. If a duplicate copy certified by the importer's seal is submitted the original copy must be presented for validation.

3. The documents required in this Article shall be submitted in 01 set.

Article 66. Criteria, application dossier for import license of drugs containing pharmaceutical substances already licensed for marketing in Vietnam but [the supply of such drugs] not yet adequately meeting therapeutic demand and drugs containing pharmaceutical substances already used for drug manufacture in Vietnam but [the supply of] such drugs not yet adequately meeting therapeutic demands

1. The drugs shall only be allowed for importation when fulfilling the following criteria:

a) Belonging to the List issued by the Minister of Health of drugs [the supply of which] not yet adequately meeting therapeutic demand;
b) Being licensed for marketing in one of the following countries: Manufacturing country, a reference country among ICH member countries or Australia.
2. Application dossier for import license:
a) 3 original copies of import order conforming to Form no. 15, 16 or 17 in Appendix III of this Decree;
b) Original or authenticated duplicate copy of Certificate of pharmaceutical product;
c) Quality document in conformance with the Minister of Health's stipulations regarding the adoption of ASEAN common technical dossier (ACTD) in drug registration;
d) 01 set of original copy of specimen label and package insert of the drug in actual use in the country issuing the Certificate of pharmaceutical product, except when they are already attached to Certificate of pharmaceutical product;
đ) 02 sets of mock-up label intended to be used for marketing the product in Vietnam, enclosed with the Vietnamese language package insert, certified by the importer's seal;
e) Clinical document in the case of drugs required clinical document submission according the Minister of Health's stipulations regarding the adoption of ACTD in drug registration;
g) With regard to traditional drugs involving a new combination of medicinal materials already used for drug manufacture in Vietnam, there must be a full clinical dossier demonstrating safety and effectiveness as required under Article 89 of Pharmaceutical law and documentation proving that the drugs are processed, prepared or assembled according to traditional medicine theories.
h) Report on trading results with regard to the import drugs being narcotic drugs, psychotropic drugs, precursor drugs, combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors, drugs on to the List of drugs, pharmaceutical substances belonging to the List of substances banned from use in certain sectors, fields, conforming the Form no. 18 in Appendix III of this Decree;
i) Original or authenticated duplicate copy of Certificate of good manufacturing practice of all establishments participating to the manufacture of the import drugs where the manufacture of such drugs involves several establishments;
k) Authenticated duplicate copy or duplicate copy certified by the exporter's seal of Permit for radiation work of the exporter in the case of exporting radioactive drugs. If a duplicate copy certified by the importer's seal is submitted the original copy must be presented for validation.
3. The documents required in this Article shall be submitted in 01 set.

Article 67. Criteria, application dossier for import license of drugs to support emergency requirements in national defence, security, prevention and combating epidemics, mitigation of consequences of natural disasters, calamities

1. The drugs shall only be licensed for importation if they are already licensed for marketing in at least one country and falling into one of the following categories:
a) Drugs that are requested for importation by Ministry of Defence for emergency response to national defence requirements;
b) Drugs that are requested for importation by Ministry of Public Security for emergency response to security requirements;
c) Drugs that are approved for importation for emergency response to epidemics prevention and combatting, mitigation of consequences of natural disasters, calamities.
2. Application for import license:
a) 03 original of import order conforming to Form no. 15, 16 or 17 in Appendix III of this Decree;
b) Original or authenticated duplicate copy of Certificate of pharmaceutical product or certification by the exporting country's competent authority that the drug has been licensed for marketing in at least one country;
c) Original or duplicate copy, certified by the competent authority's seal, of the letter requesting or approving the importation from the respective competent authority in accordance with the provision of point a, b or c clause 1 of this Article, reflecting the following: Active ingredient in the case of chemo pharmaceutical drugs or name of medicinal materials in the case of medicinal material drugs

and traditional drugs, dosage form, concentration of strength of pharmaceutical substances in the case of chemo pharmaceutical drugs or quantity of medicinal materials in the case of medicinal material drugs and traditional drugs, package form, manufacturer, manufacturing country of the drug.
3. The documents required in this Article shall be submitted in 01 set.

Article 68. Criteria, application dossier for import license of drugs supporting special therapeutic requirements

1. The drugs shall only be licensed for importation when fulfilling one of the following criteria:
a) Having superior therapeutic effectiveness relative to the drugs being marketed in Vietnam or for which there is no substitutable drugs; already licensed for marketing in the manufacturing country or a reference country among ICH member countries or Australia, of which clinical data demonstrating safety, effectiveness according to the Minister of Health's stipulations are adequately available and being recommended for use by the Advisory council for marketing registration certificate of drugs, drug raw materials.
b) Drugs for use in medical emergency service, as antidote, which do not contain the same active ingredients and are not of the same route of administration with those currently available on the market.
c) Vaccine for use in certain special cases at limited quantity decided upon by the Minister of Health on the basis of availability of data demonstrating the vaccine's quality, effectiveness, safety.
2. Application dossier for import license of the drugs stipulated in point a clause 1 of this Article:
a) 03 original copies of import order conforming to Form no. 15, 16 or 17 in Appendix III of this Decree;
b) Clinical data on safety and effectiveness in accordance with the Minister of Health's requirements for drug registration. For vaccines, the results of a clinical trial conducted in Vietnam in conformance with the Minister of Health's stipulations shall also be required;
c) Original or authenticated duplicate copy of Certificate of pharmaceutical product;
d) Duplicate copy of the manufacturer's quality specification and test method for the drug, certified by the importer's seal;
đ) 01 set of original specimen of labels and package insert of the drug in actual use in the country issuing the certificate of pharmaceutical product, except when they are already attached to Certificate of pharmaceutical product;
e) 02 sets of mock-up label intended to be used for marketing the product in Vietnam, enclosed with the Vietnamese language package insert, certified by the importer's seal;
g) Drug trading report with regard to the drugs to be imported being narcotic drugs, psychotropic drugs, precursor drugs, combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors, drugs containing pharmaceutical substances on the list of substances banned from use in certain sectors, fields, conforming the Form no. 18 in Appendix III of this Decree;
h) Report on trading results with regard to the import drugs being narcotic drugs, psychotropic drugs, precursor drugs, combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors, drugs on to the List of drugs, pharmaceutical substances belonging to the List of substances banned from use in certain sectors, fields, conforming the Form no. 18 in Appendix III of this Decree;
i) Original or authenticated duplicate copy of Certificate of good manufacturing practice of all establishments participating to the manufacture of the import drugs where the manufacture of such drugs involves several establishments;
k) Authenticated duplicate copy or duplicate copy certified by the exporter's seal of Permit for radiation work of the exporter in the case of exporting radioactive drugs. If a duplicate copy certified by the importer's seal is submitted the original copy must be presented for validation.
3. Application dossier for import license of the drugs stipulated in point b, c clause 1 of this Article
a) 03 original copies of import order conforming to Form no. 15, 16 or 17 in Appendix III of this Decree;
b) Documents demonstrating the quality, safety, effectiveness of the vaccines to be imported;

c) Original copy of the letter signed off by the medical service establishment's head, stamped with the establishment's seal, providing the rationale for the import licensing request, projected number of patients in need of the drugs; respective quantity in demand and an undertaking to assume responsibility for any possible issues arising from the use of the drugs to be imported; the letter must be accompanied by the original or a duplicate copy certified by the medical service establishment's seal; Minutes of the meeting of the Formulary and therapeutics council regarding the necessity to import the drugs. This Minutes shall be not be required of immunization service establishments having no Formulary and therapeutics council;
d) The list of drugs requested for importation by the medical service establishment conforming to Form no. 19, 20 or 21 in Appendix III of this Decree;
đ) Report of the medical service establishment covering the following information: Quantity of the drugs that have been used, therapeutic effectiveness (except for vaccines), safety of the drugs conforming to Form no. 22 in Appendix III of this Decree;
e) Original copy of the written undertaking by the foreign manufacturer assuring the quality safety, effectiveness the vaccines, biologicals it supplies to Vietnam, conforming to Form no. 23 in Appendix III of this Decree;
g) Duplicate copy certified by the importer's seal of the Power of attorney or Seller permit or Certification of partnership. The content of the document shall be in conformance with the provision of point đ clause 15 Article 91 of this Decree.
If unable to provide the documents, the importer must submit an explanatory letter for the Minister of Health's consideration.
4. The documents required in clause 2, 3 of this Article shall be submitted in 01 set.

Article 69. Criteria, application dossier for import license of orphan drugs
1. The drugs shall only be allowed for importation when fulfilling the following criteria:
a) Belonging to the List of orphan drugs;
b) Already licensed for marketing in at least one country.
2. Application dossier for import license:
a) 3 original copies of import order conforming to Form no. 7, 8, 9 or 10 in Appendix III of this Decree;
b) Original or authenticated duplicate copy of Certificate of pharmaceutical product;
c) Duplicate copy of the manufacturer's quality specification and test method for the drug, certified by the importer's seal;
d) 01 set of original copy of specimen label and package insert of the drug in actual use in the country issuing the certificate of pharmaceutical product, except when they are already attached to Certificate of pharmaceutical product;
đ) 02 sets of mock-up label intended to be used for marketing the product in Vietnam, enclosed with the Vietnamese language package insert, certified by the importing establishment's seal;
e) Report on trading results with regard to the import drugs being narcotic drugs, psychotropic drugs, precursor drugs, combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors, drugs on to the List of drugs, pharmaceutical substances belonging to the List of substances banned from use in certain sectors, fields, conforming the Form no. 18 in Appendix III of this Decree;
g) Original or authenticated duplicate copy of Certificate of good manufacturing practice of all establishments participating to the manufacture of the import drugs if the manufacture of such drugs involves several establishments; unless the Certificate of pharmaceutical product already certifies good manufacturing practice conformity for all establishments involved;
h) Authenticated duplicate copy or duplicate copy certified by the exporter's seal of Permit for radiation work of the exporter in the case of exporting radioactive drugs. If a duplicate copy certified by the establishment's seal is submitted the original copy must be presented for validation.
3. The documents required in this Article shall be submitted in 01 set.

Article 70. Criteria, application dossier for import license of drugs of the same trade name, pharmaceutical ingredient composition, strength or concentration, dosage form with an

originator drug already licensed for marketing in Vietnam, that are manufactured by the same manufacturer with the originator drug or a delegated manufacturer, priced lower than the originator drug being marketed in Vietnam

1. The drugs shall only be allowed for importation when fulfilling the following criteria:
a) Meeting the provisions of point đ Clause 2 Article 60 of Pharmaceutical law;
b) The drugs' intended wholesale price is at least 20% lower than the bid winning price of the originator drug that was licensed for marketing in Vietnam;
c) Being licensed for marketing in and exported to Vietnam from the manufacturing country, or a reference country among ICH member countries or Australia;
d) Not being radioactive drugs, vaccines or biologicals.
2. Application dossier for import license:
a) 03 original copies of import license conforming to Form no. 15, 16 or 17 inn Appendix III of this Decree;
b) Undertaking by the importing establishment pertaining to quality integrity of the drug and notification of the drug's intended selling price;
c) Documentation proving the drug is legally marketed in the manufacturing country or a reference country;
d) 01 set of original copy of specimen label and package insert of the drug as it is being marketed in the exporting country, certified by the importer's seal
đ) 02 sets of supplementary label and package insert in Vietnamese language, certified by the importer's seal. The content of the Vietnamese language package insert must be consistent with that approved by Ministry of Health for the originator drug already licensed for marketing in Vietnam.
3. The documents required in this Article shall be submitted in 01 set.

Article 71. Criteria, application dossier for import license of drugs to support State health programs

1. The drugs shall only be licensed for importation when fulfilling the following criteria:
a) Being approved by the competent authority as drugs for the service of State health programs;
b) Being licensed for marketing in one of the following countries: Manufacturing country, a reference country among ICH member countries or Australia.
2. Application dossier for import license:
a) 3 original copies of import order conforming to Form no. 15, 16 or 17 in Appendix III of this Decree;
b) Original or authenticated duplicate copy of Certificate of pharmaceutical product;
c) Quality document in conformance with the Minister of Health's stipulations regarding the adoption of ASEAN common technical dossier (ACTD) in drug registration;
d) Clinical document in the case of drugs required clinical document submission according the Minister of Health's stipulations regarding the adoption of ACTD in drug registration;
đ) 01 set of original copy of specimen labels and package insert of the drug in actual use in the country issuing the Certificate of pharmaceutical product, except when they are already attached to Certificate of pharmaceutical product;
e) 02 sets of mock-up label intended to be used for marketing the product in Vietnam, enclosed with the Vietnamese language package insert, certified by the importer's seal;
g) Original or authenticated duplicate copy of the competent authority's letter approving the use of the drug in State health programs;
h) Original or authenticated duplicate copy of Certificate of good manufacturing practice of all establishments participating to the manufacture of the import drugs where the manufacture of such drugs involves several establishments;
i). Authenticated duplicate copy or duplicate copy certified by the exporter's seal of Permit for radiation work of the exporter in the case of exporting radioactive drugs If a duplicate copy certified by the importer's seal is submitted the original copy must be presented for validation.
3. The documents required in this Article shall be submitted in 01 set.

Article 72. Criteria, application dossiers for import license of donated, humanitarian assistance drugs

1. The drugs shall only be licensed for importation when simultaneously fulfilling the following criteria:

a) Being licensed for marketing in the manufacturing country or a reference country amongst ICH member countries or Australia;

b) Responding to the actual needs of the assistance recipient entities;

c) Not being radioactive drugs, vaccines or biologicals.

2. Application dossier for import license:

a) Official letter from the importer requesting import license accompanied by the List of donated, humanitarian assistance drugs conforming to Form no. 24, 25 or 26 in Appendix III of this Decree;

b) Original copy of the letter of the entity receiving the donation, humanitarian assistance, specifying the quantity of each type of drugs to be received and undertaking to use the drugs for the right purpose, on the right target beneficiaries;

c) Original copy or authenticated duplicate copy of the competent regulatory authority approving the use of the drugs for State health programs with regard to foreign assistance drugs to be used in programs, projects;

d) Original or authenticated duplicate copy of Certificate of pharmaceutical product;

đ) Quality document in conformance with the Minister of Health's stipulations regarding the adoption of ASEAN common technical dossier (ACTD) in drug registration;

e) Clinical document in the case of drugs required clinical document submission according the Minister of Health's stipulations regarding the adoption of ACTD in drug registration;

g) 01 set of original copy of specimen labels and package insert of the drug in actual use in the country issuing the Certificate of pharmaceutical product, except when they are already attached to Certificate of pharmaceutical product;

h) 02 sets of mock-up label intended to be used for marketing the product in Vietnam, enclosed with the Vietnamese language package insert, certified by the importer's seal;

i) Original or authenticated duplicate copy of Certificate of good manufacturing practice of all establishments participating to the manufacture of the import drugs where the manufacture of such drugs involves several establishments;

k). Authenticated duplicate copy or duplicate copy certified by the exporter's seal of Permit for radiation work of the exporter in the case of exporting radioactive drugs If a duplicate copy certified by the importer's seal is submitted the original copy must be presented for validation.

3. The documents required in this Article shall be submitted in 01 set.

Article 73. Criteria, application dossier for import license of drugs to be used in clinical trials, bioequivalence studies, bioavailability assessments, as samples for testing, research study

1. The drugs shall only be licensed for importation if falling into one of the following categories:

a) For use in clinical trials in Vietnam under protocols already approved by the Minister of Health according to the provision of clause 1 Article 94 of Pharmaceutical law;

b) For use in bioequivalence studies in Vietnam under protocols already approved by the Minister of Health according to the provision of clause 1 Article 100 of Pharmaceutical law;

b) For use as reference standards in bioequivalence studies; if the reference standard is a new drug, it shall be used exclusively for the study according to the already approved protocol under clause 1 Article 100 of Pharmaceutical law;

c) For use in testing, validation at drug manufacturing establishments or drug testing, validating establishments;

d) For use in tests, assays at testing, quality control establishments

đ) For use in scientific research studies other than the purposes outlined in point a, b and c of this clause.

2. Application dossier for import license:

a) 03 original copies of import order conforming to Form no. 15, 16 and 17 in Appendix III of this Decree;

b) Original or authenticated duplicate copy of approval letter from the relevant competent authority or organization in the case of drugs stipulated in point a, b and đ clause 1 of this Article;
c) Original or authenticated duplicate copy of the approved protocol for bioequivalence study according to Article 100 of Pharmaceutical law with regard to new drugs referred to in point c clause 1 of this Article;
d) Explanatory document certified by the exporter's seal regarding the importation purpose, quantity and undertaking to use the drug for the intended purpose;
đ) Document from the importing establishment explaining the importation purpose, quantity and undertaking to use them for the intended purpose;
e) Authenticated duplicate copy or duplicate copy certified by the importer's seal of Permit for radiation work of the exporter in the case of exporting radioactive drugs. If a duplicate copy certified the establishment's seal is submitted the original copy must be presented for validation.
3. The documents required in this Article shall be submitted in 01 set.

Article 74. Criteria, application dossier for import license of drugs to be used as displays at exhibition, trade fairs
1. Application dossiers for import license of combination drugs containing narcotic substances, combination drugs containing psychotropic substances, combination drugs containing precursors for displaying at exhibitions, trade fairs relating to medicine, pharmacy, medical equipment shall comprise:
a) 01 original copy of Import order conforming to Form no. 16 in Appendix III of this Decree;
b) Undertaking by the importer regarding the re-exportation of the drugs in its entirety at completion of the exhibition, trade fair.
2. The documents required in clause 1 of this Article shall be submitted in 01 set.
3. Drugs that do not fall into the categories listed in clause 1 of this Article shall only be imported when simultaneously meeting the following criteria:
a) Used as displays at exhibitions, trade fairs relating to medicine, pharmacy, medical equipment;
b) Not being narcotic drugs, psychotropic drugs, precursor drugs, radioactive drugs.
4. The importation of drugs for display at exhibitions, trade fairs must be carried out in compliance with provisions of the laws regarding temporary importation, re-exportation of goods.

Article 75. Criteria, application dossier for import license of drugs of non-commercial purpose under point I clause 2 Article 60 of Pharmaceutical law
1. The drugs shall be licensed for non-commercial importation if falling into one of the following categories:
a) Being part of travelers' personal luggage brought in under airway bills or as accompanied luggage for their own therapeutic use.
a) Not being narcotic drugs, psychotropic drugs, precursors and being part of inbound belongings of foreign diplomatic missions, international organizations in Vietnam or Vietnam diplomatic missions, organizations in foreign countries and the individuals working at these missions, organizations or organizations introduced by Vietnam diplomatic representative agencies; Vietnam diplomatic missions to foreign countries.
2. An import license must be obtained for the drugs stipulated in Clause 1 of this Article, except the following cases:
a) The quantity of drugs to be imported does not exceed that required for a 07 day course in the case of narcotics and for a 10 day course in the case of psychotropic, precursor drugs, at dosage given the accompanied prescription;
b) The drugs to be imported shall not be narcotic drugs, psychotropic drugs, precursor drugs, of a total import value of not more than 200 (two hundred) USD (USS Dollars) (calculated using the going interbank exchange rate at customs clearance point) at each import time and not to be imported more than 03 times a year for each organization, individual.
With regard to the drugs that are to be used for the treatment of patients suffering from diseases on the List of life threatening diseases stipulated in Decree no. 134/2016/NĐ-CP dated 01 September 2016 of the Government detailing some articles and implementation measures for the Law on export import

tax, the total customs value allowable shall be not more than 10,000,000 (ten million) đồng per import time and not more than 04 import times per year per person.
3. Application dossier for import license:
a) Application for drug importation conforming to Form no. 27 in Appendix III of this Decree;
b) Undertaking by the individual, organization to assume responsibility with regard to the original and quality of the drug to be imported;
c) Authenticated duplicate copy or a duplicate copy bearing the applicant's signature or duplicate copy bearing the applicant organization's seal of the drug prescription, outpatient medical booklet. These documents must show the following information: name, age of patient; drug 'name; strength or concentration and volume; quantity (or number of medication days); dosage; physician's full name, signature; address of the hospital, office where the physician practices'
If the duplicate copy bearing the applicant's signature or duplicate copy bearing the applicant organization's seal is submitted the original copy must be presented for validation at the point of dossier submission.
For the drugs stipulated in point b clause 1 of this Article, the documents listed in this point shall not be required
d) Authenticated duplicate copy or a duplicate copy bearing the applicant's signature of one of the following documents: Identification card, citizenship card or passport of the applicant if the importer is an individual.
If the duplicate copy bearing the applicant's signature or duplicate copy bearing the applicant organization's seal is submitted the original copy must be presented for validation at the point of dossier submission
4. The documents required in this Article shall be submitted in 01 set.

Article 76. Documentation requirements for import license application dossier
1. With regard to the drugs to be imported under the provisions of Article 65, 66, 69, 71, 72 and point a clause 1 Article 68 of this Decree, a separate import order must be prepared for each individual drug, except when they have in common the following elements:
a) Drug name;
b) Dosage form and route of administration;
c) Concentration or strength of pharmaceutical substances in the case of drugs of liquid and semi solid form;
d) Quality specification;
đ) Shelf life;
e) Name and address of manufacturer.
2. The documents constituting the dossier if not in Vietnamese or English language must be accompanied by a notarized Vietnamese or English translated version.
3. The following documents must be consular legalized in accordance with legislation on consular legalization, except when there is an exemption provided for under applicable laws:
a) Certificate of pharmaceutical product;
b) Document proving that the drug is legally marketed in the manufacturing country or a reference country;
c) Certificate of good manufacturing practice for pharmaceutical products;
d) Label and package insert of the drug in actual circulation at the country issuing the Certificate of pharmaceutical product.
4. Requirements specific to Certificate of pharmaceutical product, except in the case of drugs imported to respond to emergencies in national defense, public security, fighting against epidemics, mitigating natural disasters, calamities stipulated under Article 67 of this Decree:
a) Meeting the requirements of clause 2, 3 and 6 of this Article;
b) Bearing the signature, name, position of the signing person; date of issuance and seal of the competent authority for the issuance of Certificate of pharmaceutical product of the exporting country;
c) The signature, name, position of the signing person and the seal of the competent authority for the issuance of Certificate of pharmaceutical product of the issuing country must be certified by a

diplomatic representative mission, consular agency or other agencies delegated to perform consular function for the issuing country;
d) Certificate of pharmaceutical product used in the consular notarization must be the original copy;
đ) There must be a certification that the drug is licensed and marketed in the country issuing the Certificate of pharmaceutical product;
e) For drugs the manufacture of which involves participation from several different manufacturing establishment the Certificate of pharmaceutical product must state the name, address, role of each individual establishment;
g) The Certificate must be in conformance with World Health Organization's model form in use under the Certification scheme on the quality of pharmaceutical products moving in international commerce
5. Requirements regarding the certification of specimens of label and package insert of the drugs as they are in actual circulation in the country issuing the Certificate of pharmaceutical product; except for the drugs having the same trade name, active ingredient composition, strength or concentration, dosage form with those of a brand name licensed for marketing in Vietnam, being manufactured by the same manufacturer of the originator drug or a delegated manufacturer, priced lower than the imported brand name being marketed in Vietnam stipulated under Article 70 of this Decree:
a) Meeting the provision of clause 3 of this Article;
b) Specimen of label and package insert bearing the seal of the state competent authority issuing the Certificate of pharmaceutical product of the issuing country;
c) The specimen of label and package insert used in the consular notarization but be the original copy.
6) Legal documents constituting the dossier must be still valid at the point of dossier submission as recorded on the Dossier receipt.

Article 77. Formalities and time limits for import licensing for drugs not yet licensed for marketing in Vietnam
1. Import licensing for drugs categorized under Article 65, 66, 69, 71, 72 and point a clause 1 Article 63 of this Decree:
a) Establishments applying for import license shall submit an application dossier in person or by post to Ministry of Health;
b) Upon receipt of an application dossier for import license, Ministry of Health shall issue the applicant establishment a Dossier receipt using Form no. 01 in Appendix III of this Decree;
c) If there is no follow up request for dossier revision, supplementation, Ministry of Health shall issue an import license on the basis of dossier evaluation, consultation of the Advisory council for certificate of marketing registration of drugs, drug raw materials, within 60 days from the date recorded on Dossier receipt to the cases not requiring clinical data, documents proving similarity with a reference biological or within 90 days from the date recorded on Dossier receipt to the cases that do require these data or documents;
d) If there is a follow up request for dossier revision, supplementation, Ministry of Health shall issue to the applicant establishment a written notification to the effect within 60 days from the date recorded on Dossier receipt in the cases not requiring clinical data, documents proving similarity to a reference biological or within 90 days from the date recorded on Dossier receipt in the cases requiring these data or documents;
đ) Upon receipt of the follow up submission, Ministry of Health shall issue a Receipt of follow up submission using Form no. 01 in Appendix I of this Decree. If the follow up submission fails to address the requirements, Ministry of Health shall issue a written notification to the effect to the applicant establishment in accordance with the provision of point d of this clause. If there is no [further] follow up request, Ministry of Health shall issue an import license in accordance with the provision of point c of this clause;
e) Within 06 months from the date Ministry of Health issues the follow up notification, the applicant establishment must respond with dossier revision, supplementation accordingly. Past this time limit if the establishment fails to respond or past 12 months from the initial dossier submission if the supplemented dossier does not meet the requirements the submitted dossier shall become void.
g) With respect to the drugs to be imported for use in humanitarian medical services already approved by the competent authority but for which the documents set out in point c, d, đ, e, g or i clause 2

Article 72 of this Decree are not available for submission but such drugs are necessary for therapeutic purpose, the Minister of Health shall consider and make decision on the basis of consultation with the Advisory council on the issuance of certificate of marketing registration of drugs.

2. Import licensing for the drugs to be imported under the provisions of Article 67 of this Decree:

a) Establishments applying for import license shall submit an application dossier in person or by post to Ministry of Heath;

b) Upon receipt of an application dossier for import license, Ministry of Health shall issue the applicant establishment a Dossier receipt using Form no. 01 in Appendix III of this Decree;

c) If there is no follow request for dossier revision, supplementation, Ministry of Health shall issue an import license within 03 working days from the date recorded on Dossier receipt;

d) If there is a follow up request for dossier revision, supplementation, Ministry of Health shall issue a written notification to the effect to the applicant establishment within 03 working days from the date recorded on Dossier receipt;

đ) Upon receipt of the follow up submission, Ministry of Health shall issue a Receipt of follow up submission using Form no. 01 in Appendix I of this Decree. If the follow up submission fails to address the requirements, Ministry of Health shall issue a written notification to the effect to the applicant establishment in accordance with the provision of point d of this clause. If there is not [further] follow up request, Ministry of Health shall issue an import license in accordance with the provision of point c of this clause;

e) If the applicant establishment is unable to provide the documents required in point b clause 2 Article 67 of this Decree but the drug subject of the import application is necessary for disease prevention and treatment demand, the Minister of Health shall consider, make decision on the basis of the undertakings from relevant Ministries

3. Import licensing for the drugs to be imported under the provisions of Article 70, 73 clause 1 Article 74 and point b, c clause 1 Article 68 this Decree:

a) Establishments applying for import license shall submit an application dossier in person or by post to Ministry of Heath;

b) Upon receipt of an application dossier for import license, Ministry of Health shall issue the applicant establishment a Dossier receipt using Form no. 01 in Appendix III of this Decree;

c) If there is no follow request for dossier revision, supplementation, Ministry of Health shall issue an import license within 15 days from the date recorded on Dossier receipt;

d) If there is a follow up request for dossier revision, supplementation, Ministry of Health shall issue a written notification to the effect to the applicant establishment within 15 days from the date recorded on Dossier receipt;

đ) Upon receipt of the follow up submission, Ministry of Health shall issue a Receipt of follow up submission using Form no. 01 in Appendix I of this Decree. If the follow up submission fails to address the requirements, Ministry of Health shall issue a written notification to the effect to the applicant establishment in accordance with the provision of point d of this clause. If there is not [further] follow up request, Ministry of Health shall issue an import license in accordance with the provision of point c of this clause;

e) Within 06 months from the date Ministry of Health issues the follow up notification, the applicant establishment must respond with dossier revision, supplementation accordingly. Past this time limit if the establishment fails to respond or past 12 months from the initial dossier submission if the supplemented dossier does not meet the requirements the submitted dossier shall become void.

4. Import licensing for the drugs to be imported under the provisions of Article 75 of this Decree:

a) Organizations, individuals applying for import license shall submit an application dossier in person or by post to the local Health Department at the locality where the port of entry through which they undertake immigration formalities is located or where the patient is living or legally temporarily residing or where the organization has office;

b) Upon receipt of an application dossier for import license, Health Department shall issue the applicant establishment a Dossier receipt using Form no. 01 in Appendix III of this Decree;

c) If there is no follow request for dossier revision, supplementation, Health Department shall issue an import license within 07 working days from the date recorded on Dossier receipt;

d) If there is a follow up request for dossier revision, supplementation, Health Department shall issue a written notification to the effect to the applicant establishment within 07 working days from the date recorded on Dossier receipt;
đ) Upon receipt of the follow up submission, Health Department shall issue a Receipt of follow up submission using Form no. 01 in Appendix I of this Decree. If the follow up submission fails to address the requirements, Health Department shall issue a written notification to the effect to the applicant establishment in accordance with the provision of point d of this clause. If there is not [further] follow up request, Health Department shall issue an import license in accordance with the provision of point c of this clause;
e) Within 03 months from the date Health Department issues the follow up notification, the applicant establishment must respond with dossier revision, supplementation accordingly. Past this time limit if the establishment fails to respond or past 14 months from the initial dossier submission if the supplemented dossier does not meet the requirements the submitted dossier shall become void.
5) Within 10 working days from the issuance date import licenses under the provisions of Article 65, 66, 67, 68, 69 of this Decree, Ministry of Health shall be responsible to publicize relevant information on its web portal in accordance with the provision of clause 6 Article 60 of Pharmaceutical law.
6. Ministry of Health shall be responsible for publicizing on its web portal information pertinent to the drugs to be used in medical emergency service, as antidote and vaccines to be used in certain special cases at limited quantity that were licensed for importation under the provision of point b, c clause 1 Article 68 of this Decree covering information on the importer, manufacturer, the quantity of drugs licensed for importation, drug name, dosage form, route of administration, concentration or strength of pharmaceutical substances, import license number, issuance date, medical services and immunization service establishment requiring the drugs.
7. Import license, official letter licensing the importation shall be prepared using Form no. 28, 29, 30, 31 or 32 in Appendix III of this Decree.

Article 78. Regulating the importation of drugs not yet licensed for marketing in Vietnam
1. Drugs containing pharmaceutical substances for which a Certificate of marketing registration gas not been granted, drugs containing medicinal materials used for the first time in Vietnam, orphan drugs licensed for importation under the provision of Article 65 and Article 69 of this Decree shall only be supplied to medical service establishments.
2. The Minister of Health shall determine whether a drug meets the criteria in point a clause 1 Article 68 of this Decree or not on the basis of the request of medical service establishments and advice of the Advisory council on the issuance of certificate of marketing registration for drugs, drug raw materials
3. Regarding the drugs for use in for medical emergency service, as antidote and vaccines for use in certain special cases at limited quantity that are licensed for importation under point b, c, clause 1 Article 68 of this Decree:
a) The drugs shall be supplied exclusively to medical service establishments, immunization service establishments requesting for importation of such drugs. Such medical service establishments, immunization service establishments shall be responsible for informing users, patients or patients' family that the drugs are licensed for importation but legal and technical documentation on them are not available. The drugs shall only be administered after a consent from the users, patients or patients' family is obtained.
b) Importers of, establishments using the drugs stipulated in point a of this clause shall be allowed to sell or transfer such drugs to other medical service establishments, immunization service establishments. The establishments receiving the transfer of such drugs must have available the documents stipulated in point c, d clause 3 Article 68 of this Decree and shall be responsible to uphold the provisions of point a of this clause.
4) Before being placed on the market, the lot of drug having the same trade name, active ingredient composition, strength or concentration, dosage form with those of an originator drug already licensed for marketing in Vietnam, that are produced by the same manufacturer or a delegated manufacturer, at a price lower that of the originator drug being marketed in Vietnam, which was imported under the provision of Article 70 of this Decree, must be quality tested by a drug, drug raw material testing

agency of the state against the same quality specification of the originator drug that was licensed for marketing in Vietnam.
5. Drugs that are licensed for importation for the use in State health programs, for the use of clinical trial, research studies, testing assaying must be used for the intended purpose, on the correct target recipients.
6. Controlled drugs that are licensed for marketing to support humanitarian medical services, if not used up must be re-exported by the establishment in accordance with the provision of clause 5 Article 60 of this Decree, not to be used for other purposes.
7. Drugs that are licensed for importation for displaying at exhibitions, trade fairs relating to medicine, pharmacy, medical equipment under the provision of Article 74 of this Decree must be re-exported in its entirety at completion of such exhibition, trade fair and not to be used, marketed in Vietnam.
8. Individuals, organizations applying for noncommercial importation of drugs under the provision of Article 75 of this Decree shall be responsible for the origin and quality of the drugs imported.

Section 3

IMPORTATION OF CONTROLLED DRUGS ALREADY LICENSED FOR MARKETING IN VIETNAM, CONTROLLED DRUG RAW MATERIALS

Article 79. Application dossier for import license of controlled drugs already licensed for marketing in Vietnam

Application dossiers for import license for narcotic drugs, psychotropic drugs, precursor drugs, combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors, radioactive drugs, toxic drugs, drugs on the List of drugs, pharmaceutical substances belonging to the List of substances banned from use in certain sectors, fields, subject of a still valid Certificate of marketing registration, shall comprise the following documents:

1. 01 original copy of Import order conforming to Form no. 33 or 34 in Appendix III of this Decree;

2. Report on the trading results of the imported drugs conforming to Form no. 18 in Appendix III of this Decree; except for toxic drugs

3. Duplicate copy of Permit for radiation work of the exporter, certified by the exporter's seal in the case of importing radioactive drugs. If a duplicate copy certified the exporter's seal is submitted the original copy must be presented at the point of dossier submission for validation.

4. The documents specified in this Article shall be submitted in 01 set.

Article 80. Application dossier, provisions for import licensing of controlled drug raw materials

1. Application dossier for import license of controlled drug raw materials:

a) 01 original copy of Import order conforming to Form no. 35 or 36 in Appendix III of this Decree;

b) Duplicate copy of the manufacturer's quality specification and test method, certified by the importer's seal;

c) Duplicate copy of Manufacturer's license of the drug raw material's manufacturer issued by the competent authority of the foreign country. The Manufacturer's license must be consular legalized in accordance with legislation on consular legalization, except where an exemption is provided for under applicable legislation;

d) Report on the usage of the drug raw material conforming to For no, 37 in Appendix III of this Decree, except for importation of toxic raw materials for drug manufacture, report on the trading results of drug raw materials conforming to Form no. 38 in Appendix III of this Decree, except toxic raw materials for drug manufacture;

đ) Production plan, usage plan of the raw material subject of the import licensing application and trading plan for the finished products produced from the raw material subject of the import licensing application, except for importation of toxic raw materials for drug manufacture;

e) The documents set out in point b and c of this clause shall not be required of raw materials imported for testing, research studies; drug raw materials already licensed for marketing in Vietnam or belonging to the List of pharmaceutical substances, excipients semi-finished products for the manufacture, according to registration dossier, of drugs already licensed for marketing in Vietnam;

g) Original copy of letter from the exporter providing the reasons of the import licensing application, the quantity of the raw material to be imported and undertaking to use them for the intended purpose in the case of importing drug raw materials for testing, research studies;

h) Importation of controlled drug raw materials not yet licensed for marketing in Vietnam or not belonging to the List of pharmaceutical substances, excipients, semi-finished products for the manufacture, according to registration dossier, of drugs already licensed for marketing in Vietnam for compounding per prescription at drugstores, medical service establishments for disease prevention and combatting, shall require in addition a request letter from the compounding establishment conforming to Form no. 39 in Appendix III of this Decree.

2. The documents required in point b, c clause 1 of this Article if not in Vietnamese or English language must be accompanied by a notarized Vietnamese or English translated version.

3. The documents required under clause 1, 2 of this Article shall be submitted in 01 set.

4. Drug raw materials that are narcotic pharmaceutical substances, psychotropic pharmaceutical substances, drug precursors shall not be licensed for importation for the purpose of exhibition, trade fair displaying.

5. Importation of toxic drug raw materials, pharmaceutical substances on the List of drugs, pharmaceutical substances banned from use in certain sectors, fields, for display at exhibitions, trade fairs shall be handled in accordance with the provision of Article 83 of this Decree.

Article 81. Formalities, time limits for import licensing of controlled drugs subject of a still valid certificate of registration for marketing in Vietnam and controlled drug raw materials

1. Establishments applying for import license shall submit an application dossier in person or by post to Ministry of Health.

2. Upon receipt of an application dossier for import license, Ministry of Health shall issue the applicant establishment a Dossier receipt using Form no. 01 in Appendix III of this Decree;

3. If there is no follow request for dossier revision, supplementation, Ministry of Health shall issue an import license within 15 days from the date recorded on Dossier receipt;

4. If there is a follow up request for dossier revision, supplementation, Ministry of Health shall issue a written notification to the effect to the applicant establishment within 15 days from the date recorded on Dossier receipt;

5. Upon receipt of the follow up submission, Ministry of Health shall issue a Receipt of follow up submission using Form no. 01 in Appendix I of this Decree. If the follow up submission fails to address the requirements, Ministry of Health shall issue a written notification to the effect to the applicant establishment in accordance with the provision of clause 4 of this Article. If there is no [further] follow up request, Ministry of Health shall issue an import license in accordance with the provision of clause 3 of this Article;

6. Within 06 months from the date Ministry of Health issues the follow up notification, the applicant establishment must respond with dossier revision, supplementation accordingly. Past this time limit if the establishment fails to respond or past 12 months from the initial dossier submission if the supplemented dossier does not meet the requirements the submitted dossier shall become void.

7) Import licenses, official letters approving the importation of drugs, drug raw materials shall be prepared using Form no, 28, 29, 30, 40 or 44 in Appendix III of this Decree.

Section 4

IMPORTATION OF DRUG RAW MATERIALS NOT YET LICENSED FOR MARKETING IN VIETNAM OTHER THAN CONTROLLED DRUG RAW MATERIALS; IMPORATION OF REFERENCE STANDARDS, EXCIPIENTS, CAPSULE SHELLS, PRIMARY PACKAGING COMPONENTS

Article 82. Criteria, application dossier for import license of pharmaceutical substances, medicinal materials, semi-finished drugs, semi-finished medicinal materials to be used as samples for drug testing, drug research studies

1. Pharmaceutical substances, medicinal materials, semi-finished drugs, semi-finished products for drug manufacture in the form of glue, granule, powder, extract, essential oil, resin, gum, gel (hereafter referred to as semi-finished medicinal materials) not yet licensed for marketing in Vietnam shall be licensed for importation when falling into one of the following categories:

a) For the use in testing, research at drug manufacturing establishments or drug testing, drug research establishments;

b) For the use in scientific research studies approved by the competent authority.

2. Application dossier for import license shall comprise the following documents:

a) 03 original copy of Import order conforming to Form no. 36 or 41 in Appendix III of this Decree;

b) Letter from the importer justifying the purpose of use and quantity required of the drug raw materials and undertaking to use them for the intended purpose.

c) Original or duplicate copy of the approval letter from the competent authority in the cases stipulated in point b clause 1 of this Article.

3. The documents required in this Article shall be submitted in 01 set.

Article 83. Provisions for the importation of pharmaceutical substances, semi-finished drugs, medicinal materials, semi-finished medicinal materials for display at exhibitions, trade fairs

1. Drug raw materials shall only be licensed for importation for display at exhibitions, trade fairs that are related to medicine, pharmacy, medical equipment.

2. The importation of drug raw materials for display at medicine, pharmaceutical related exhibitions, trade fairs shall be carried out in compliance with legislation on temporary importation – re-exportation.

3. The drug raw materials that are licensed for importation under the provision of this Article shall not be marketed in Vietnam and must be re-exported in their entirety at the completion of the exhibition, trade fair.

Article 84. Application dossier for import license of pharmaceutical substances, semi-finished drugs, semi-finished medicinal materials for the manufacture of export-bound drugs

1. Application dossier shall comprise the following documents:

a) 03 original copies of Import order conforming to Form no. 36 or 41 in Appendix III of this Decree;

b) Duplicate copy of the manufacturer's quality specification and test method for the raw material, certified by the importer's seal. If these documents are not in Vietnamese or English language they must be accompanied by a Vietnamese or English translated version;

c) Written undertaking that the drug raw material is to be used for the intended purpose and the finished drugs made of which are exclusively for exportation, not to be marketed in Vietnam.

2. The documents required in this Article shall be submitted in 01 set.

Article 85. Criteria, application dossier for import license of pharmaceutical substances, semi-finished drugs, medicinal materials, semi-finished medicinal materials for the manufacture of drugs in support of requirements in national defense, security, epidemics prevention and combating, mitigating consequences of natural disasters, calamities

1. Drug raw materials shall be licensed for importation for the manufacture of drugs that fall into the following categories:

a) Drugs for the service of national defense requirements;

b) Drugs for the service of public security requirements;
c) Drugs for the service of prevention and combatting epidemic diseases, mitigation of national disasters, calamities including per prescription preparations at drugstores, medical service establishments. The import medicinal materials for per prescription preparations at drugstores, medical service establishments shall be imported in compliance with the provision of Article 87 of this Decree.
2. Application dossier shall comprise the following documents:
a) 03 original copies of Import order conforming to Form no. 36 or 41 in Appendix III of this Decree;
b) With regard to drug raw materials to be imported for the manufacture of drugs in support of national defense, public security requirements, the dossier must include the original copy of the requesting letter from Ministry of National Defense, Ministry of Public Security respectively. The letter must cover at a minimum the following information: Drug name, manufacturer name, active ingredient, concentration or strength, dosage form, package form, route of administration, indications;
c) With regard to the drug raw materials to be imported for the manufacture of drugs in support of prevention and combatting epidemic diseases, mitigation of national disasters, calamities, the dossier must include the original copy of the letter approving the List of drugs from Ministry of Health. The letter must cover at a minimum the following information: Drug name, manufacturer name, active ingredient, concentration or strength, dosage form, package form, route of administration, indications;
d) With regard to the drug raw materials to be imported for per prescription preparations at drug stores, for drug production, preparation at medical service establishments, the dossier must include a request letter from these establishments, conforming to Form no. 42 in Appendix III of this Decree.
đ) Written undertaking from the importer and the establishments using the drug raw material regarding the importation and use of such materials for the correct intended purpose.
e) Duplicate copy of manufacturer's quality specification and test method for the drug raw material, certified by the importer's seal.
g) Authenticated duplicate copy of Manufacturer license of the drug raw materials' manufacturer issued by the foreign competent authority. The Manufacturer license must be consular legalized in accordance with legislation on consular notarization, unless exemption is provided for according to applicable laws.
h) If the documents set out in point e and g of this clause are not in Vietnamese and English language they must be accompanied by a notarized Vietnamese or English translated version.
3. The documents required in this Article shall be submitted in 01 set.

Article 86. Application dossier for import license of excipients, capsule shells, primary packaging components, reference standards

1. Application dossier for import license shall comprise the following documents:
a) 03 original copies of Import order conforming to Form no. 43 in Appendix III of this Decree;
b) Duplicate copy of manufacturer's quality specification and test method for the excipient, capsule shell, primary packaging components, certified by the importer's seal. If the documents are not in Vietnamese or English language, they must be accompanied by a Vietnamese or English translated version.
2. The documents required in this Article shall be submitted in 01 set.

Article 87. Application dossier for import license of medicinal materials other than those stipulated under Article 82, 83, 84 and 85 of this Decree

1. Application dossiers shall comprise the following documents:

a) 03 original copies of import order conforming to Form no. 41 in Appendix III of this Decree;

b) Quality specification of the medicinal material consistent with respective national standards in Vietnam pharmacopoeia or a Ministry of Health's recognized foreign pharmacopeia.

If there is no national standards for the medicinal material in Vietnam pharmacopoeia or a Ministry of Health's recognized foreign pharmacopoeia, the applicant establishment must submit the quality

specialization it developed for the material including test method, which has been validated by a State owned drug, drug raw material testing establishment;

a) Authenticated duplicate copy of License for formation of representative office the foreign supplier of the medicinal material or Certificate of business operation in drugs and drug raw materials of the foreign enterprise in Vietnam with in scope of operation the trading of medicinal materials, semi processed, processed medicinal materials;
b) Authenticated duplicate copy of Business License with medicinal material exportation in scope of operation issued by the competent authority of the exporting country to the foreign supplier supplying the medicinal material to Vietnam.

đ) Authenticated duplicate copy of Certificate of good manufacturing practice covering the manufacture of medicinal materials for the manufacturing facility issued by the competent authority of the exporting country.

e) Duplicate copy certified by the importer power of attorney from the manufacturer to the foreign supplier unless the manufacturer and the supplier are the same entity. Power of attorney shall be prepared in accordance with point đ clause 15 Article 91 of Decree.

2. The documents required in this Article shall be submitted in 01 set.

Article 88. Procedures and time limits for import licensing of drug raw materials not yet licensed for marketing in Vietnam except for controlled drugs; primary packaging components, reference standards

1. Formalities and time limits for import licensing of drug raw materials, primary packaging components, reference standards set out under Article 82, 84, 86 and 87 of this Decree:

a) Establishments applying for import license shall submit an application dossier in person or by post to Ministry of Health;

b) Upon receipt of an application dossier, Ministry of Health shall issue the applicant establishment a Dossier receipt using Form no. 01. in Appendix I of this Decree;
c) If there is no follow request for dossier revision, supplementation, Ministry of Health shall issue an import license within 15 days from the date recorded on Dossier receipt;
d) If there is a follow up request for dossier revision, supplementation, Ministry of Health shall issue a written notification to the effect to the applicant establishment within 15 days from the date recorded on Dossier receipt;
đ) Upon receipt of the follow up submission, Ministry of Health shall issue a Receipt of follow up submission using Form no. 01 in Appendix I of this Decree. If the follow up submission fails to address the requirements, Ministry of Health shall issue a written notification to the effect to the applicant establishment in accordance with the provision of point d of this clause. If there is no [further] follow up request, Ministry of Health shall issue an import license in accordance with the provision of point c of this clause;
e) Within 06 months from the date Ministry of Health issues the follow up notification, the applicant establishment must respond with dossier revision, supplementation accordingly. Past this time limit if the establishment fails to respond or past 12 months from the initial dossier submission if the supplemented dossier does not meet the requirements the submitted dossier shall become void.

2. With regard to the importation of pharmaceutical substances, semi-finished medicinal materials categorized under Article 85 of this Decree:

a) Establishments applying for import license shall submit an application dossier in person or by post to Ministry of Health;

b) Upon receipt of an application dossier, Ministry of Health shall issue the applicant establishment a Dossier receipt using Form no. 01. in Appendix I of this Decree;

c) If there is no follow request for dossier revision, supplementation, Ministry of Health shall issue an import license within 03 working days from the date recorded on Dossier receipt;
d) If there is a follow up request for dossier revision, supplementation, Ministry of Health shall issue a written notification to the effect to the applicant establishment within 03 working days from the date recorded on Dossier receipt;
đ) Upon receipt of the follow up submission, Ministry of Health shall issue a Receipt of follow up submission using Form no. 01 in Appendix I of this Decree. If the follow up submission fails to address the requirements, Ministry of Health shall issue a written notification to the effect to the applicant establishment in accordance with the provision of point d of this clause. If there is no [further] follow up request, Ministry of Health shall issue an import license in accordance with the provision of point c of this clause;
3. Import licenses, official letters approving the importation of drug raw materials shall be prepared using Form no, 44 or 45 n Appendix III of this Decree.

Section 5

PROVISIONS FOR EXPORTATION, IMPORTATION OF DRUGS, DRUG RAW MATERIALS

Article 89. Validity terms of import license, export license of drugs, drug raw materials

1. Export license of drugs, drug raw materials shall have the following validity terms:

a) A maximum of 01 year for drugs, drug raw materials that are licensed for exportation under the provisions of Article 57, 59, 60, 62 and clause 1 Article 61 of this Decree.

b) A maximum of 02 years for the drugs, drug raw materials that are licensed for exportation under the provisions of Article 58 clause 8 Article 64 of this Decree.

2. Import license, official letter approving the importation of drugs, drug raw materials shall have the following validity terms:

a) A maximum of 01 year for Import licenses, official letters approving the importation of drugs;

b) A maximum of 01 year and valid for 01 single importation for Import licenses of narcotic drugs, psychotropic drugs, precursor drugs, drug raw materials being narcotic drugs, psychotropic drugs, drug precursors;

c) A maximum of 02 years for Import licenses, official letters approving the importation of drug raw materials, other than those referred to in point b of this clause.

3. Validity term of Import license, official letter approving importation must be clearly indicated in such licenses, official letters.

Article 90. Provisions on the remaining shelf life of imported drugs, drug raw materials at the point of customs clearance

1. Chemo pharmaceutical drugs, medicinal materials drugs, traditional drugs, drug raw materials imported to Vietnam, other than the drugs, drug raw materials referred to under clause 3 of this Article, must have at the point of customs clearance at least a remaining shelf life as follows

a) 18 months in the case of drugs, drug raw materials of more than 24 month total shelf life;

b) ½ of the total shelf life in the case of drugs, drug raw materials of 24 month or shorter total shelf life;

2. Vaccines, biologicals imported to Vietnam, other than those referred to under clause 3 of this Article, must have at least a ½ shelf life remaining at the point of customs clearance.

3. Drugs, drug raw materials imported under the provisions of Article 67, 73, 74, 75, 82, 83, 84, 85, 86 and point b clause 1 Article 68 of this Decree must have a remaining shelf life at the point of customs clearance.

4. The import licensing of drugs, drugs raw materials that have a remaining shelf life at the point of customs clearance shorter that that regulated under clause 1 or clause 2 of this Article but are necessary to support demands in production, disease prevention and treatment shall be decided upon by the Minister of Health.

5. Application dossier for import license of the drugs, drug raw materials referred to under clause 4 of this Article shall comprise the following documents:

a) Application from the exporter, covering the following information: Name of the drug/drug raw material, remaining shelf life at the point of customs clearance, the reason of such drug, drug raw material having a remaining shelf life shorter than that regulated under clause 1 or 2 of this Article;

b) Documentation demonstrating the lot of drug/drug raw material have a remaining shelf life at the point of customs clearance shorter than that regulated under clause 1 or clause 2 of this Article.

6. Procedures, formalities for import licensing of the drugs, drug raw materials referred to under clause 4 of this Article:

a) Establishments applying for import license shall submit an application dossier in person or by post to Ministry of Health;

b) Upon receipt of an application dossier, Ministry of Health shall issue the applicant establishment a Dossier receipt using Form no. 01. in Appendix I of this Decree;

c) If there is no follow request for dossier revision, supplementation, Ministry of Health shall issue an official letter approving the importation within 15 days from the date recorded on Dossier receipt;

d) If there is a follow up request for dossier revision, supplementation, Ministry of Health shall issue a written notification to the effect to the applicant establishment within 15 days from the date recorded on Dossier receipt;

đ) Upon receipt of the follow up submission, Ministry of Health shall issue a Receipt of follow up submission using Form no. 01 in Appendix I of this Decree. If the follow up submission fails to address the requirements, Ministry of Health shall issue a written notification to the effect to the applicant establishment in accordance with the provision of point d of this clause. If there is no [further] follow up request, Ministry of Health shall issue an official letter approving the importation in accordance with the provision of point c of this clause;

e) Within 03 months from the date Ministry of Health issues the follow up notification, the applicant establishment must respond with dossier revision, supplementation accordingly. Past this time limit if the establishment fails to respond or past 04 months from the initial dossier submission if the supplemented dossier does not meet the requirements the submitted dossier shall become void.

Article 91. Provisions for the importation of drugs, drug raw materials

1. The drug raw materials that are pharmaceutical substances, excipients, semi-finished drugs except semi-finished raw materials for the manufacture in accordance with registration dossier of drugs that have been granted a Certificate of registration for marketing in Vietnam which are published by the Minister of Health in Form 46 Appendix III of this Decree within 15 days, from the date of issuance [or] renewal of Certificate of registration for marketing in Vietnam. The drug raw materials that are pharmaceutical substances, excipients, semi-finished drugs belonging to the List [of those] allowed for importation without import licensing, except for controlled drug raw materials.
2. The List of drugs, drug raw materials that are banned from importation, banned from production according the provision of Appendix V of this Decree.
3. The drug raw materials for which a Certificate of registration for marketing in Vietnam has been granted including medicinal materials, semi-finished medicinal materials, excipients, capsule shell, semi-finished drugs, other than semi-finished controlled drugs, that are allowed for importation without import licensing.

4. Medical, pharmaceutical training institutions, drug research establishments, drug testing establishments shall be allowed to import drugs, drug raw materials and reference standards for their own training, research, testing activities.
5. Representative offices in Vietnam of manufacturers, drug registrants, establishments holding marketing authorization of the drugs subject of clinical trials, bioavailability assessments, bioequivalence studies; establishments contracted for the service of clinical trial, bioavailability assessment, bioequivalence study shall be allowed to import drugs, drug raw materials and reference standards for the service of clinical trials, bioavailability assessments, bioequivalence studies.
6. Traders shall be allowed to import primary packaging components.
7. Drugs, drug raw materials shall only be imported through international ports of entry, except for the drugs that are licensed for noncommercial importation under the provision of Article 75 of this Decree.
8. The Minister of Health shall make decision on the quantity of drugs, drug raw materials licensed for importation according to the following:
a) Quantity licensed for importation of drugs containing pharmaceutical substances not yet licensed for marketing in Vietnam, drugs containing medicinal materials used for the first time in Vietnam according to the provision of Article 65 of this Decree, based on the scale, developments of life threatening diseases, social diseases, dangerous and emerging diseases;
b) Quantity licensed for importation of drugs containing pharmaceutical substances already licensed for marketing in Vietnam but [the supply of which] has not yet adequately met therapeutic demand, drugs containing medicinal materials already used for drug manufacture in Vietnam but the supply of drugs made of which has not yet adequately met therapeutic demand, drugs in support of special therapeutic needs stipulated under Article 66, 68 of this Decree, based on the actual therapeutic demand of medical service establishments;
c) Quantity licensed for importation of drugs for responses to emergency demand in national defense, public security, prevention and combatting epidemics, mitigation of natural disasters, calamities according to the provisions of Article 67 of this Decree, based on the actual demand for these respective purposes;
d) Quantity licensed for importation of orphan drugs according to the provisions of Article 69 of this Decree, based on importers' demand for their business operations;
đ) Quantity licensed for importation of drugs that the same trade name, active ingredient composition, concentration or strength, dosage form with those of an originator drug already licensed for marketing in Vietnam, that are manufactured by the same manufacturer or a delegated manufacturer, at a price lower than that of the originator drug being marketed in Vietnam according to the provisions of Article 70 of this, based on the capacity to achieve price stabilization objectives.;
e) Quantity licensed for importation in support of State health programs according to the provision of Article 71 of this Decree, based on the actual demand of State health programs.;
g) Quantity licensed for importation of donated, humanitarian assistance drugs according to the provisions of Article 72 of this Decree, based on the actual demand of the entities receiving the assistance;
h) Quantity licensed for importation of drugs for the use in clinical trials, bioequivalence studies, bioavailability assessments, as samples for drug testing , scientific studies according to the provisions of Article 73 of this Decree, based on the approved study protocols or the actual demand for testing, studying of the concerned establishments;
i) Quantity licensed for importation of drugs for noncommercial purpose according to the provisions of Article 75 of this Decree, based on the actual medication demand of organizations, individuals;
k) Quantity licensed for importation of controlled drugs according to the provisions of Article 79, 80 of this Decree, based on the establishments' demand for their business operations;
l) Quantity licensed for importation of reference standards, primary packaging components, drug raw materials not yet licensed for marketing in Vietnam according to the provisions of Article 82, 84, 85, 86 and 87 of this Decree, based on the actual demand in raw materials for the establishments' manufacturing, trading operations, except for controlled drug raw materials.
9. Formalities regarding chemical declaration shall not be required for the drug raw materials, reference standards that are imported under the provisions of Pharmaceutical law and this Decree.

10. Establishments that have importation right but not are allowed to exercise the right to distribute drugs, drug raw materials shall not be allowed to perform activities directly related to the distribution of drugs, drug raw materials in Vietnam, except for the drugs, drug raw materials they themselves manufacture in Vietnam, covering:

a) Selling drugs, drug raw materials, delivery of drugs, drug raw materials to medical service establishments, retailers, individuals, organizations that are not wholesalers of drugs, drug raw materials;

b) Receiving purchase orders, accepting to settle payments for drugs, drug raw materials for medical service establishments, retailers, individuals, organizations that are not wholesalers of drugs, drug raw materials.;

c) Transporting, providing storage service of drugs, drug raw materials;

d) Determining, imposing selling price of drugs, drug raw materials that are distributed by other pharmaceutical business establishments;

đ) Making decisions on distribution strategies, trading policies of drugs, drug raw materials that are distributed by other pharmaceutical business establishments;

e) Developing supply plans of drugs, drug raw materials for medical service establishments in Vietnam;

g) Providing financial assistance under any forms to organizations, individuals who purchase drugs directly from them with the aim of manipulating the distribution of imported drugs, drug raw materials;

h) Perform other acts relating to the distribution of drugs according to the provisions of the laws.

11. Wholesalers purchasing drugs, drug raw materials imported by the importers that are not allowed to exercise the right to distribute drugs, drug raw materials in Vietnam must have operational capacity and capability to directly carry out the distribution of drugs, drug raw materials to medical service establishments and pharmaceutical business establishments without being subjected to the imposition, control or regulation over the activities set out under clause 10 of this Article by the establishments that are not allowed to exercise thee right to distribute drugs, drug raw materials in Vietnam.

12. The establishments having importation right but not allowed to exercise the right to distribute drugs, drug raw materials in Vietnam shall be responsible for notifying Ministry of Health in writing the wholesalers that perform the distribution of their drugs, drug raw materials imported to Vietnam prior to selling or discontinuing the sale of drugs to those wholesalers.

Within 03 working days, from the date of receipt of the notification from the establishment (counting from the time recorded on the incoming correspondence stamp), Ministry of Health shall be responsible for publishing on its web portal the information on the wholesalers that purchase drugs for their own distribution from establishments having importation right but not allowed to exercise the right to distribute drugs, drug raw materials in Vietnam.

13. The importation of medicinal materials that are specimen of species on the List of ‘endangered, precious , rare , prioritized for protection’, for the use as testing samples, drug studies must be carried out in accordance with biodiversity legislation.

14. Provisions for Certificate of Test of an imported drug lot, lot of drug raw material:

a) Certificate of Test must be in Vietnamese or English language. A Certificate that is not in Vietnamese or English language must be accompanied by a notarized Vietnamese or English translate version;

b) Where the manufacture of a drug lot, lot of drug raw material involves 02 or more establishments, such imported drug lot, lot of drug raw materials must be accompanied by a certificate of test from the final manufacturing or packaging establishment or from the establishment responsible for batch release.;

c) Certificate of test must cover the following information: Administrative information (name, address of manufacturer, Certificate number, name and signature of the person in charge, date of issuance of Certificate) and information on the sample of the drug, drug raw material (product name, lot number, shelf life, applicable quality specification, quality criteria, quality requirements, test results, conclusion on the quality of the product lot).

15. Suppliers of drugs, drug raw materials shall be a foreign establishment that enters into a sales contract with an importer. Suppliers of drugs, pharmaceutical substances shall be one of the following entities:
a) Manufacturer of the imported drug, pharmaceutical substances;
b) Establishment owning the product or holding the marketing authorization of the imported drug, pharmaceutical substance as recorded on the Certificate of pharmaceutical product with regard to the drugs that are licensed for marketing in Vietnam according to the provision of Pharmaceutical law or those not yet licensed for marketing in Vietnam;
c) Foreign establishment acting as registrant of the drug, drug raw material for which a Certificate of registration for marketing in Vietnam has been granted and is still valid at the point of customs clearance but not the establishment referred to in point a, b of this clause;
d) Establishment that has been granted a Business license of foreign enterprise in drugs and drug raw materials, business license of foreign enterprise in vaccines, biologicals and raw materials for the manufacture of vaccines, biologicals in Vietnam;
đ) A supplier that is the entity referred to in point c or d or this clause must be authorized in writing by the entity referred to in point a or b of this clause the right to supply the drug to Vietnam.
The power of attorney shall include a delegation of authority or seller permit or certification of partnership. The power of attorney must be written in Vietnamese of English language and cover at a minimum the following information: Name, address of the authorizing establishment, scope of authorization covering the supply of drug, drug raw material to Vietnam, validity term of the authorization or seller permit; obligations of the parties in quality assurance, origin of the drug, drug raw material supplied to Vietnam, certifying signature of the parties;
e) Suppliers of the drugs that are imported under the provisions of Article 67, 73 and clause 1 Article 74 of this Decree shall not have to comply with the provision of this clause.
g) Suppliers of the drugs that are imported under the provisions of Article 70 of this Decree shall not have to comply with the provision of point đ of this clause.
16. Suppliers of imported excipients, capsule shell, primary packaging components, reference standards shall not have to comply with the provision of clause 15 of this Article.
17. An import license of a drug shall be withdrawn in the following situations:
a) The imported drug is recalled for a level 1 violation according to the provision of point a clause 2 Article 63 of Pharmaceutical law;
b) The imported drug is subject to marketing authorization revocation by the competent authority of the manufacturing country, a reference country of among ICH member counties or Australia;
c) The imported drug is concluded by the competent authority as subject of an approved registration dossier containing falsified documentation;
d) The imported drug is not manufactured at the address indicated on the approved application dossier for its import license;
đ) The imported drug contains pharmaceutical substances, imported medicinal materials that are subject of a warning by World Health Organization or the competent authority of Vietnam or the country of origin's as not safe, effective for users;
e) The manufacturer, exporter of the drug, drug raw material requests for its import license to be withdrawn;
g) Upon recall notification by the foreign pharmaceutical regulatory authority of the imported drug lot.
18. An import license of a drug raw material shall be withdrawn in the following situations:
a) The drug raw material is recalled under the provisions of point a, b, đ or e clause 2 Article 62 of Pharmaceutical law;
b) The imported pharmaceutical substance, medicinal material is the subject of a warning by World Health Organization or the competent authority of Vietnam or of the country of origin's as not safe, effective for users.
19. Ceasing to accept application dossiers for import license of drugs, drug raw materials for a period of 01 to 02 years; ceasing to issue import license for drugs, drug raw materials for a period of 01 to 02 years shall be applicable in the following cases:
a) Violating cases stipulated under point a, c, d clause 17 of this Decree;

b) Within a 12 month period there are more than 02 lots of imported drugs subject to mandatory recall for level 2 violation according to the provision of point b clause 2 Article 63 of Pharmaceutical law or 03 lots of imported drugs found violating quality standards;
c) Information provided in application dossier for import license is not based on research evidence or empirical evidence of the manufacturer;
d) Failure to update information pertaining to effectiveness, safety of the imported drug on its label, package insert while it is being marketed in Vietnam in accordance with Ministry of Health's requirements.
20. Suspending a manufacturer of drugs, drug raw materials from the importation of all drugs, drug raw materials shall be applicable when such manufacturer commits one of the following acts:
a) Serious degree violation of the principle of good manufacturing practice according to the Minister of Health's stipulations;
b) Within a 12 month period there are more than 02 lots of drugs, drug raw materials found to be at level 1 violation according to the provision of point a clause 2 Article 63 of Pharmaceutical law in relation to quality of drugs, drug raw materials;
c) Within a 12 month period there are more than 03 lots of drugs, drug raw materials found to be at level 2 violation according to the provision of point b clause 2 Article 63 of Pharmaceutical law or more than 04 lots of drugs, drug raw materials found violating quality standards
;d) The importation suspension period shall be from 01 to 02 years with regard to the cases stipulated in point a, b of this clause and from 06 months to 01 years with regard to the cases stipulated in point c of this clause.
21. Provisions for the reporting of exportation, importation of drugs, drug raw materials, except for controlled drugs:
a) Within 10 days, from the importation date of vaccines that already licensed for marketing in Vietnam, drugs that are not yet licensed for marketing in Vietnam, importers shall send a report on each import consignment to Ministry of Health and the National institute for control of vaccines and biologicals in the case of vaccines, using Form no. 47 or 48 in Appendix III of this Decree.
b) By the 15th of July and by the 15th of January every year, importers shall send to Ministry of Health a 6 monthly report and annual report respectively on the export import status of drugs, drug raw materials using Form no. 49 or 50 n Appendix III of this Decree.

Article 92. Pharmaceutical-specific documentation to be presented and submitted by pharmaceutical business establishments, organizations, individuals at customs clearance for exporting, importing of drugs, drug raw materials

Apart from the documentation to be submitted, presented as according to Customs legislation, pharmaceutical business establishments, organizations, individuals shall present and submit the following documents at customs clearance for exporting, importing drugs, drug raw materials:

1. Customs clearance for exporting drugs, drug raw materials:

a) Presentation of the original copy or an authenticated duplicate copy and submission of a duplicate copy, certified by the exporter's seal, of the exporter's Certificate of satisfaction of conditions for pharmaceutical business where the exporter is a pharmaceutical business establishment;

b) Submission of a duplicate copy of the export license certified by the exporter's seal and presentation of the original copy or an authenticated duplicate copy of it for validation purpose when exporting medicinal materials belonging to the List of controlled precious, rare, endemic species, breeds of medicinal material, controlled drugs;

c) Submission of an authenticated duplicate copy of drug prescription, outpatient medical booklet or a duplicate copy certified by the seal of the organization applying for the export licensing and presenting the original for validation purpose in the case of controlled drugs forming part of personal belongings of outbound organizations, individual travelers, brought out under airway bills, accompanied luggage of outbound organizations, individual travelers for their own medication; at

export quantity not exceeding a 07 day course in the case of narcotic drugs; a10 day course in the case of psychotropic drugs, precursor drugs; a 30 day course in the case of combination drugs containing narcotic pharmaceutical substances, combination drugs containing psychotropic pharmaceutical substances, combination drugs containing precursors, toxic drugs, drugs on the list of drugs, pharmaceutical substances banned from use in certain sectors, fields, at dosage given in the accompanied prescription.

2. Customs clearance for importing drugs, drug raw materials already licensed for marketing in Vietnam, drug raw materials belonging to the list of pharmaceutical substances excipients, semi-finished products for the manufacture, according to registration dossier, of drugs already licensed for marketing in Vietnam, except medicinal materials:

a) Presentation of the original or an authenticated duplicate copy, and submission of a duplicate copy certified by the importer's seal, of Certificate of satisfaction of conditions for pharmaceutical business where the importer is a pharmaceutical business establishment;

b) Submission of a duplicate copy certified by the importer's seal of the import license and presentation of the original copy or an authenticated duplicate copy of it for validation in the case of importing drugs.

c) Submission of the original copy or a duplicate copy of Certificate of Test for each of the lot of drugs, drug raw materials imported, certified by the importer's seal, if a duplicate copy is submitted the original must be presented for validation at customs clearance;

d) Submission of a duplicate copy certified the importer's seal the Power of attorney or seller's permit or certification of partnership according the provision of point đ clause 15 Article 91 of this Decree, except for the importation of excipients, capsule shells;

đ) In the case of importation of the drugs, drug raw materials specified in point đ clause 1 Article 59 of Pharmaceutical law, the importer must present the bill of lading of the lots of drug, drug raw material demonstrating that they are exported from the sending port of the exporting country before the expiry date of the certificate of marketing registration.

3. Customs clearance for importing medicinal materials, semi-finished medicinal materials already licensed or not yet licensed for marketing in Vietnam:

a) Submission of an duplicate copy certified by the importer's seal of, and presentation of the original copy or an authenticated duplicate copy for validation purpose of Certificate of satisfaction of conditions for pharmaceutical business where the importer is a pharmaceutical business establishment.;

b) For medicinal materials, semi-finished medicinal materials already licensed for marketing in Vietnam, submission of a duplicate copy of Certificate of marketing registration certified by the importer's seal and presentation of the original or an authenticated duplicate copy for validation;

c) For medicinal materials, semi-finished medicinal materials not yet licensed for marketing in Vietnam, submission of a duplicate copy of the import license of the medicinal material certified by the importer's seal and presentation of the original or an authenticated duplicate copy for validation;

d) Duplicate copy certified by the importer's seal of the Power of attorney from the manufacturer of the medicinal material, semi-finished medicinal material to the foreign supplier, except when the manufacturer and the supplier are the same entity. The power of attorney shall be prepared in accordance with the provision of point đ clause 15 Article 91 of this Decree;

đ) Submission of the original copy or a duplicate copy of the manufacturer's Certificate of Test for each of the lots of medicinal material, semi-finished medicinal materials imported, certified by the importer's seal, if a duplicate copy is submitted the original must be presented for validation at customs clearance;

e) In the case of importation of the medicinal materials, semi-finished medicinal materials specified in point đ clause 1 Article 59 of Pharmaceutical law, the importer must present the bill of lading of the lots of medicinal materials, semi-finished medicinal material demonstrating that they are exported from the sending port of the exporting country before the certificate of marketing registration;

g) The documents required in point b, d đ and e of this clause shall not be required in the case medicinal materials, semi-finished medicinal materials imported under the provisions of Article 82 and Article 83 of this Decree.

4. Customs clearance for importing of drugs, drug raw materials not yet licensed for marketing in Vietnam, except medicinal materials:

a) Presentation of the original copy or an authenticated duplicate copy of, and submission of a duplicate copy certified by the importer's seal, of Certificate of satisfaction of conditions for pharmaceutical business where the importer is a pharmaceutical business establishment;

b) Submission of a duplicate copy certified by the importer's seal of the import license of the drug, drug raw material and presentation of the original copy or an authenticated duplicate copy of it for validation

b) Submission of the original copy or a duplicate copy certified by the importer's seal of the Certificate of Test for each of the lots of drug, drug raw materials imported in the case of importation of drugs, drug raw materials under the provisions of Article 65, 55, 59, 71,72, 79, 80, 84, 85, 86 and point a, c clause 1 Article 68 of this Decree; if a duplicate copy is submitted, the original copy must be presented for validation at customs clearance;

d) Submission of drug prescription, outpatient medical booklet, authenticated or signed off by the incoming traveler or a duplicate copy certified by the importing organization's seal for the importation of the following drug quantity:

Not exceeding the quantity required for a 07 day course of medication in the case of narcotic drugs or a 10 day course in the case of psychotropic drugs, precursor drugs at dosage given in the accompanied prescription;

Drugs that are not narcotic drug, psychotropic drugs, precursor drugs, of total customs value not exceeding US$200 (two hundred) (calculated using interbank exchange rate at the point of customs clearance) for each time of importation and to be imported not more than 03 times in a year for 01 organization, 01 individual. Where the drugs are to be used on patients suffering from diseases on the List of life threatening diseases regulated in Decree no. 134/2016/NĐ-CP dated 01 September 2016 of the Government detailing a number of articles and implementation measures for the Law on export import tax, the drugs to be imported shall be of a total customs value of not more than 10,000,000 (ten million) đồng per time of importation and to be imported not more than 04 times in a year for 01 organization, 01 individual.

If a duplicate copy signed off by the incoming traveler or a duplicate copy certified by the importing organization's seal of the drug prescription, outpatient medical booklet is submitted, such organization, individual must present the original copy of these documents for validation purpose at customs clearance.

đ) Submission of a duplicate copy certified by the importer's seal of the Power of attorney or Seller's permit of certification of partnership required under point đ clause 15 Article 91 of this Decree, except for the drugs imported under the provisions of Article 67, 70, 73 clause 1 Article 71 of this Decree, primary packaging components, reference standards, drug raw materials licensed for importation under the provisions of Article 82, 83, 86 of this Decree, controlled drug raw materials imported for testing, research studies.

CHAPTER V

REGISTRATION FOR MARKETING OF MEDICINAL MATERIALS, EXCIPIENTS, CAPSULE SHELLS AND CONFORMITY ASSESSMENT OF MANUFACTURING FACILITIES IN FOREIGN COUNTRIES

Section 1

MARKETING REGISTRATION FOR MEDICINAL MATERIALS, EXCIPIENTS, CAPSULE SHELLS

Article 93. Subjects of applicability and requirements in marketing registration of medicinal materials, excipients, capsule shells

1. Medicinal materials shall be required to be registered prior to being marketing in Vietnam if falling into one of the following categories:

a) Medicinal materials on the List of toxic medicinal materials;

b) Medicinal materials to be used for the first time in Vietnam;

c) Potentially confusing, counterfeiting vulnerable medicinal materials;

d) Medicinal materials containing pharmaceutical substances the quality of which are easily compromised during manufacturing, processing, and circulation processes;

đ) Medicinal belonging to the List of medicinal materials of domestically cultivated, harvested medicinal materials meeting requirements regarding therapeutics and supply capability, reasonably priced;

e) Semi finished medicinal materials, except when these products are manufactured in house for the production of finished drug products;

The Minister of Health shall issue a specific the list of medicinal materials subject to marketing registration.

2. The medicinal materials that do not belong to the categories stipulated in clause 1 of this Article must have their specification published in accordance with the provisions of clause 2 Article 68 of Pharmaceutical law. Establishments wishing to undertake marketing registration [for them] shall do so in accordance with the provisions of Section 1 Chapter V of this Decree.

3. Excipients for drug manufacture for which a manufacturer's specification was formulated but not applied or the specification for which does not exist in Vietnam pharmacopoeia, national standards and specifications for drugs, or for which a foreign pharmacopoeia was not applied in Vietnam according to the Minister of Health's stipulations, shall require marketing registration, with the exception of excipients used for the manufacture of drugs that are the subject of a still valid certificate of registration for marketing in Vietnam. Establishments wishing to undertake marketing registration [for them] shall do so in accordance with the provisions of Chapter V of this Decree.

4. Capsules for drug manufacture must be registered except the capsule shells that are used for the manufacture of drugs that are the subject of a still valid certificate of registration for marketing in Vietnam. Establishments wishing to undertake marketing registration [for them] shall do so in accordance with the provisions of Chapter V of this Decree.

5. Establishments eligible to act as registrant for medicinal material, excipients, capsule shells shall comprise:

a) The establishments stipulated in clause 3 Article 54 of Pharmaceutical law;

b) The establishments stipulated in point c clause 1 Article 35 of Pharmacy law shall be eligible to act as registrant for medicinal materials.

6. Registration format, rights and responsibilities of establishments registering medicinal materials, excipients, capsule shells shall in conformance with the provisions of Article 55, 57 of Pharmaceutical law.

Article 94. Competence, dossiers, formalities, time limits for the issuance, renewal, modification, supplementation, withdrawal of certificate of marketing registration for medicinal materials, excipients, capsule shells

Competence, dossiers, time limits for the issuance, renewal, modification, supplementation, withdrawal of certificate of marketing registration for medicinal materials, excipients, capsule shells shall be in conformance with the provisions of Article 56, 58 of Pharmaceutical law, except for issuance time limits and the following requirements:

1. With regard to establishments cultivating, harvesting medicinal materials not in possession of a Certificate of satisfaction of conditions for pharmaceutical business, an authenticated duplicate copy of Certificate of business registration must be submitted along with the dossier for marketing registration for medicinal materials.

2. The time limit for issuance of a certificate of marketing registration for medicinal materials, excipients, capsule shells shall be no longer than 06 months from the date of receipt of a complete dossier.

Section 2
CONFORMITY ASSESSMENT FOR GOOD MANUFACTURING PRACTICE OF DRUG, DRUG RAW MATERIAL MANUFACTURING FACILITIES IN FOREIGN COUNTRIES FOR MARKETING REGISTRATION IN VIETNAM

Article 95. Cases requiring filing for conformity assessment of manufacturing facility upon registering for drug marketing in Vietnam

1. With regard to the drugs, drug raw materials not yet licensed for marketing in Vietnam, the registrant establishment, upon dossier submission for marketing registration of foreign drugs, drug raw materials must submit an application dossier for an assessment of conformity with Good manufacturing practice of the manufacturing facility in the following cases:

a) Foreign manufacturers that for the first time have a drug registered for marketing in Vietnam;

b) Drugs that are manufactured on manufacturing lines not yet assessed by Ministry of Health;

c) Drug raw materials that are pharmaceutical substances for the first time registered for marketing in Vietnam;

d) Foreign manufacturers that for the first time have a medicinal material registered for marketing in Vietnam.

2. With regard to the drugs, drug raw materials for which a certificate of marketing registration is issued before the effective date of this Decree but the manufacturing facility where such drugs, drug raw materials are produced has not been assessed for conformity by Ministry of Health, the registrant establishment must submit an application dossier for Good manufacturing practice assessment in the following cases:

a) Upon submission of an application for renewing certificate of marketing registration under the provisions of clause 4 Article 55 of Pharmaceutical law;

b) Upon submission of an application for a new certificate of marketing registration resulting from a change in location of the manufacturing facility under provision of point b clause 2 Article 55 of Pharmaceutical law.

3. Where the manufacture of a drug involves several discrete operations carried out at different manufacturing facilities, the registrant establishment must submit application dossiers for conformity assessment of all such participating facilities.

Article 96. Assessment formats

1. Examination of documentary evidence pertinent to manufacturing conditions shall be applicable to manufactures not falling into the categories stipulated in clause 2 and point b clause 3 of this Article.

2. Mutual recognition, acceptance of inspection, audit outcomes from pharmaceutical regulatory authorities with regard Good manufacturing practice compliance shall be applicable to

a) Manufacturers of countries on the Ministry of Health-issued list of countries with which Vietnam has international mutual recognition treaty regarding Good manufacturing practice inspection outcomes, ICH countries and Australia, except for the cases stipulated in clause 3 of this Article.

b) Manufacturers belonging to ICH member countries, Australia and that are inspected and assessed as in conformity with Good manufacturing practice by US Food and Drug Administration, USFDA, European Union_member countries, European Medicines Agency (EMA), Australia (Therapeutic Goods Administration, TGA), Japan (Pharmaceuticals and Medical Devices Agency, PMDA) or Canada (Health Canada), except for the cases stipulated under clause 3 of this Article.

3. Onsite inspection of manufacturing facility shall be applicable to the following cases:

a) Manufacturers of which registration dossiers of drugs, drug raw materials show signs of being altered or are suspect as regards the integrity of information, data provided therein;

b) Manufacturers of drugs that are concluded by Ministry of Health as to be in level 1 - violation of quality standards;

c) Manufactures filing for conformity assessment of manufacturing conditions that are concluded by Ministry of Health as having insufficient evidence to prove their conformity with Good manufacturing practice.

Article 97. Contents of conformity assessment for good manufacturing practice of foreign manufacturing facilities

1. Documentary basis for conformity assessment:

a) Standards of Good manufacturing practice for drugs, drug raw materials according to the Minister of Health's stipulations;

b) Applicable regulations on registration, quality management for drugs, drug raw materials.

2. Content of assessment under the format of examination of documentary evidence pertinent to manufacturing conditions:

a) The legality of good manufacturing certificate or inspection report of good manufacturing practice;

b) The appropriateness of certification scope recorded on Good manufacturing certificate or inspection report on good manufacturing practice or Manufacturer's license with regard to the dosage form of the registered drug, drug raw material;

c) The appropriateness of premises' conditions covering facility lay out, manufacturing lines, construction materials, manufacturing environment conditions, designed flow of personnel, raw materials, semi-finished products, finished products, manufacturing, testing, storage equipment for drugs, drug raw materials;

d) The instituting and functioning of the manufacturing facility's quality management system;

đ) Assessments of pharmaceutical regulatory authority of the home country and other countries, deficiencies found and remedial and prevention actions by the manufacturer.

3. Content of assessment under the form of mutual recognition of outcomes of Good manufacturing practice inspections, audits carried out by foreign pharmaceutical regulatory authorities:

a) The legality of Good manufacturing practice or inspection report on Good manufacturing practice;

b) The appropriateness in terms of certification scope recorded in Certificate of good manufacturing practice or inspection report on Good manufacturing practice or Manufacturer's license with regard to the dosage form of the registered drug, drug raw material.

4. Content of assessment under the format of on-site inspection of manufacturing facility:

a) The legality of Certificate of good manufacturing practice or inspection report on Good manufacturing practice;

b) Conditions of premises covering plant lay out, manufacturing lines, construction materials, manufacturing environment conditions, designed flow for personnel, raw materials, semi-finished products, finished products, manufacturing, testing, storage equipment for drugs, drug raw materials;

c) Operational process of the manufacturing lines of the drug, drug raw material;

d) The instituting and functioning of the manufacturing facility's quality management system;

đ) Actual status regarding the adoption, attainment of Good manufacturing practice across the entire operations of drug manufacturing, testing, storage at the facility.

Article 98. Application dossier for conformity assessment of Good manufacturing practice

1. With regard to manufacturers of drugs, drug raw materials being pharmaceutical substances of the category stipulated in clause 2 Article 96 of this Decree, the application dossier for conformity assessment shall comprise the following documents:

a) Certificate of good manufacturing practice or Inspection report of Good manufacturing practice conformity or Manufacturer's license covering information pertinent to the dosage form of the drug, drug raw material, issued by the competent authority of the foreign country;

b) Master file of the manufacturing facility conforming to guidelines on site master file of the European Union (EU) or International pharmaceutical convention scheme (PIC/S) or World Health Organization.

2. For manufacturers of drugs, drug raw materials that are pharmaceutical substances categorized under clause 1 and 3 Article 96 of this Decree, the application dossier for conformity assessment shall comprise:

a) Certificate of good manufacturing practice or Good manufacturing practice inspection report or Manufacturer's license covering information on the dosage form of the drug, drug raw material, issued by the competent authority of the foreign country; Certificate of good manufacturing practice or Good manufacturing practice inspection report issued by the pharmaceutical regulatory authority of a member country of European Union or Pharmaceutical inspection cooperation scheme (PIC/S), if applicable;

b) Site master file on the manufacturing facility conforming to the guidelines of European Union (EU) or the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) or the World Health Organization (WHO).

b) List of Good manufacturing practice inspections performed by the pharmaceutical regulatory authority of the establishment's home country or other countries within 3 years up to the date of dossier submission and Report on the latest Good manufacturing practice inspection which has as inspection scope the registered drugs or dosage forms of the registered drugs;

d) List of the drugs along with dosage forms, drug raw materials that have been supplied or are intended to be supplied to Vietnam;

đ) Batch release process for the drugs, drug raw materials intended to be registered for marketing in Vietnam;

e) Reports on periodic quality reviews with regard to the registered drugs, drug raw materials being of sterilized form.

3. With respect to manufacturers of raw materials that are excipients, capsule shells, the application dossier for conformity assessment of manufacturing facility shall comprise:

a) Certificate of good manufacturing practice or inspection report on Good manufacturing practice or Manufacturer's license containing adequate information on the raw materials produced issued by the foreign country's competent authority with regard to the excipients, capsule shells;

b) Quality Manual of the establishment in conformance with the ISO standards (ISO/TR 10013: 2001 or updated edition) or Master file of the manufacturing facility conforming to guidelines on site master file of the European Union (EU) or International pharmaceutical convention scheme (PIC/S) or World Health Organization;

c) Only the document set out in point a of this clause shall be required of manufacturers of drug raw materials that are excipients, capsule shells categorized under clause 2 Article 96 of this Decree shall be required.4. For manufacturers of drug raw materials that are medicinal materials, the application dossier for conformity assessment shall comprise of:

a) Certificate of good manufacturing practice or Good manufacturing practice inspection report;

d) Quality Manual of the establishment in conformance with the ISO standards (ISO/TR 10013: 2001 or updated edition) or Master file of the manufacturing facility conforming to guidelines on site master file of the European Union (EU) or International pharmaceutical convention scheme (PIC/S) or World Health Organization;

c) List of medicinal materials that have been supplied or intended to be supplied to Vietnam;

c) Documentation, information pertaining to the cultivation, exploitation areas of the medicinal materials already supplied or intended to be supplied to Vietnam;

đ) Manufacturers of drug raw materials that are medicinal materials belonging to the cases stipulated under clause 2 Article 96 of this Decree shall only be required to submit the document specified in point a, c and d of this clause.

5. Requirements for dossiers requesting for good manufacturing practice conformity assessment of a manufacturing facility:

a) A dossier requesting for conformity assessment of manufacturing facility shall be prepared in 01 copy in English or Vietnamese language, of which all constituting documents must be printed legibly, assembled following the order prescribed in clause 1, 2, 3 and 4 of this Article; there must be a divider tab between sections, a cover page and an index of documents.

b) Certificate of good manufacturing practice, inspection report on good manufacturing practice shall follow the provisions of clause 1, 2, 3 and 4 of this Article, Manufacturer's license stipulated in clause 1, 2 and 3 of this Article shall be submitted in original copy or authenticated duplicate copy and must be still valid at the point of submission. Documents that do not specify a validity term must be issued or published within the 03 years up to the point of submission.

Article 99. Procedures, formalities, competence in receiving dossiers and conducting conformity assessment of manufacturing facilities

1. Ministry of Health shall receive application dossiers for, and conduct Good manufacturing practice conformity assessment of, foreign manufacturing facilities; prepare assessment reports and provide notification of assessment results according to the following timelines:

a) 30 days from the date of receipt of a complete dossier in the case of mutual recognition; mutual acceptance of inspection, audit outcomes of good manufacturing practice from pharmaceutical regulatory authorities

b) 60 days from the date of receipt of a complete dossier in the case of documentary examination;

c) 90 days from the date of receipt of a complete dossier as regards the cases referred to in point b clause 3 Article 96 of this Decree or from the notification date of results of dossier evaluation for certificate of marketing registration or results of conformity assessment for good manufacturing practice and plan for onsite assessment as regards the cases referred to in point a and c clause 3 Article 96 of this Decree.

2. In the event that the manufacturer requests to change the scheduled plan for on site assessment, the timelines stipulated in point c clause 3 of this Article shall be counted from date of receipt of the manufacturer's request letter.

3. In the event that certificate of good manufacturing practice or manufacturer's license expires at the point of dossier examination, inspection report on good manufacturing practice conformity dated more than 03 years since inspection date or the Site master file on the manufacturing facility does not contain adequate information according to requirements, Ministry of Health shall issue a written notification requesting the manufacturer to submit supplementation;

a) The registrant shall submit the follow supplementation within a maximum of 90 days with regard to the Site master file for manufacturing facility; 06 months with regard to Certificate of good manufacturing practice or manufacturer's license of inspection report on Good manufacturing practice;

b) Within 30 days from the date of receipt of the dossier supplementation, Ministry of Health shall provide notification of the assessment results.

4. Within 10 working days from the date the assessment results become available, Ministry of Health shall publicize on its web portal the List of manufacturing facilities that are recognized, assessed.

Article 100. Responsibilities of foreign registrants, foreign manufacturers of drugs, drug raw materials in the inspection, assessment for good practice conformity of foreign manufacturing facilities and cases warranting suspension from accepting submission of application dossiers for issuance, renewal of certificate of marketing registration for drugs, drug raw materials of registrants, manufacturers

1. Responsibilities of registrants of drugs, drug raw materials in relation to the inspection, assessment of good manufacturing practice conformity:

a) Submission of dossier for conformity assessment of the drug, drug raw material manufacturing facility according to applicable requirements;

b) Responsible for the completeness, accuracy of the dossier requesting good manufacturing practice conformity assessment; providing supplementary supporting documents at Ministry of Health's request.

c) Coordinating with the manufacturer of the drug, drug raw material in complying with Ministry of Health's requirements pertaining to the inspection, conformity assessment of the manufacturing facility.

d) Keeping Ministry of Health updated on the good manufacturing practice conformity status of the manufacturing facility of the drug, drug raw material. In the case the manufacturer has its manufacturer's license revoked or does not conform to good manufacturing practice at the foreign country, the registrant must notify Ministry of Health within 15 days from the notification of the respective competent authority;

đ) Responsible to cover the cost incurred for the onsite assessment of the manufacturing facility in accordance with applicable legislation.

2. Ceasing to accept application dossiers for the issuance, renewal of certificate of marketing registration of drugs, drug raw materials when a registrant, a manufacturer of drugs, drug raw materials commits one of the following violative acts:

a) Having its certificate of marketing registration of the drug, drug raw material withdrawn under the provisions of point a, b, d, đ clause 1 Article 58 of Pharmaceutical law;

b) Manufacturing drugs using raw materials of unknown sources, origins, expired drug raw materials;

c) Having 02 or more lots of drug, drug raw material not meeting quality specification at level 2 or have 03 or more lots of drug, drug raw material not meeting quality specification within 01 year according to the competent authority's conclusion;

d) Providing information pertinent to the technical dossier that are not research based or actual manufacturing reality of the manufacturing facility;

đ) Failure to notify Ministry of Health within 15 days from the date of notification from the foreign country's competent regulatory authority about the revocation of its manufacturer's license or non-conformity with good manufacturing practice for drugs, drug raw materials;

e) Changing, altering a drug's shelf life, except for the cases stipulated under clause 3 Article 61 of Pharmaceutical law;

g) Failure to notify Ministry of Health within 15 days from the date of notification form the foreign country's competent regulatory authority that the drug, drug raw material it registered is recalled or has its marketing authorization revoked in any country in the world;

h) Failure to update information on labels, package insert or summary of product characteristics of a drug according to Ministry of Health's requirements as it is being marketed in Vietnam.

3. The suspension period during which the submission of application dossiers for the issuance, renewal of certificate of marketing registration for drugs, drug raw materials is declined, counting from the notification date of the competent authority regarding the violative act, shall be as follows:

a) From 03 to 05 years as regards the cases stipulated under point d clause 1 Article 58 or Pharmaceutical law;

b) From 01 to 02 years as regards the cases stipulated under point a, đ clause 1 Article 58 of Pharmaceutical law and point b, c, d, đ, e clause 2 of this Article;

c) From 06 months to 01 year as regards the cases stipulated under point b clause 1 Article 58 of Pharmaceutical law and point g, h clause 2 of this Article.

4. Application dossiers for certificate of marketing registration for drugs, drug raw materials from violating establishments referred to under point a, b, c, d, đ, e clause 2 of this Article that are submitted before the date of corrective actions being imposed shall become void. Past the suspension period specified under clause 3 of this Article, an establishment wishing to register drugs, drug raw materials must submit application dossiers in accordance with the provisions of Pharmaceutical law.

Chapter VI

COMPETENCE, FORMAT, FORMALITIES FOR RECALLS OF DRUG RAW MATERIALS, HANDLING MEASURES OF RECALLED DRUG RAW MATERIALS

Article 101. Formalities, scope for the recall of drug raw materials

1. Recall format:

a) Mandatory recalls are recalls effectuated according to the decision of the state competent authority;

b). Voluntary recalls are recall effectuated at the initiative of a registrant, manufacturer, importer, exporter of drugs, drug raw materials.

2. Scope of recall:

a) Drug raw materials shall be recalled in full from establishments trading, using such raw materials, except for the cases referred to in point b of this clause;

b) In the case of raw materials not meeting to quality specification as a result of errors during storage, transport, distribution or raw materials used for incorrect purposes, the recall shall only be effectuated on the impacted raw material portion from the concerned establishments;

c) The scope of the recall must be stated clearly in the competent authority's recall decision or the notice of voluntary recall notice of the registrant, manufacturer, importer of the drug, drug raw material.

Article 102. Competence and formalities for recalls of drug raw materials

1. Competence in issuing recall decisions

a) Ministry of Health shall make judgement on a drug raw material warranting recall and issue a recall decision for the violative drug raw material in the case of mandatory recalls.

b) Domestic manufacturers, importers of drug raw materials shall draw the conclusion if a drug raw material should be recalled and issue a recall decision for it in the case of voluntary recalls.

2. Procedures for drug raw material recalls

a) Within 48 hours from the point a conclusion is made for the recall of a violative raw material, Ministry of Health shall issue the recall decision, or the establishment referred to in point b clause 1 of this Article shall issue the recall decision and report the recall to Ministry of Health. The recall decision shall be sent to domestic manufacturers, importers of raw materials, Health Departments and published on Ministry of Health's web portal in the case of mandatory recall.

b) Within 5 working days from the date of receipt of the recall decision, the domestic manufacturers, importers of drug raw materials must communicate information relating to the drug raw material to be recalled to the manufacturers, trading establishments that purchased the such raw material; they must at the same time conduct the recall, receive the recalled drug raw materials returned from manufacturers, trading establishments.

c) The recall of drug raw materials shall be completed within 30 days from the date the recall decision is issued.

d) Within 10 days from completion of the recall, the establishment responsible for the recall must send Ministry of Health a report on the recall outcomes, accompanied by a duplicate copy of the recall dossier of the drug raw material, certified by the establishment's seal. The recall dossier shall comprise documents reflecting the quantity of the raw materials that was produced, imported, recalled, manufacturing period, import date, list of establishments that purchased the raw material, evidences on the recall being effectuated at establishments trading, using the raw material;

đ) Ministry of Health shall review the recall outcomes, conduct an evaluation of the effectiveness of the recall or enforce a coercive recall in the event that the domestic drug raw material manufacturers, importers are unable to perform the recall according to the provisions of point b or point c of this clause.

Article 103. Responsibilities for recalls of drug raw materials

1. Responsibilities of domestic manufacturers, importers regarding the drug raw material subject of a recall:

a) Making judgement on a drug raw material warranting recall and issuing the decision to recall the drug raw material in the case of voluntary recalls;

b) Discontinuing the business operations involving the drug raw material subject to recall;

c) Taking the lead in, coordinating with relevant organizations, individuals in announcing information regarding the drug raw materials subject to recall and execute the recall, receive the recalled drug raw material;

d) Handling of recalled drug raw materials;

d) Paying the costs associated with the recall (including coercive recall cases), handling the recalled drug raw material, paying damages in accordance with applicable legislation;

đ) Reporting to Ministry of Health on the recall of the drug raw material and its outcome.

2. Responsibilities of distributors regarding the drug raw material subject to recall

a) Discontinuing the trading, distribution of the drug raw material subject to recall;

b) Notifying and carrying out the recall, receive the recalled drug raw material returned by manufacturers of, establishments using, the raw materials;

c) Returning the recalled drug raw material to its suppliers;

d) Paying the costs associated with the recall (including coercive recall cases), handling the recalled drug raw material and pay damages in accordance with applicable legislation if found at fault.

3. Responsibilities of manufacturers using the drug raw material subject to recall

a) Discontinuing the use of drug raw material subject to recall;

b) Returning the recalled drug raw material to its suppliers.

4. Ministry of Health shall be responsible for the following:

a) Drawing the conclusion regarding a drug raw material warranting recall and issuing the decision to recall the drug raw material in the case of mandatory recalls;

b) Reviewing recall reports, recall outcomes and giving feedback opinion on the action proposals from manufactures, trading establishments for the handling, remedial, recycling of the recalled raw material;

c) Inspecting, supervising the deployment and execution of recalls of drugs, drug raw materials; take actions against violating establishments according the applicable legislation;

d) Direct Health Departments in the inspection, supervision of the deployment and execution of recalls of drug raw materials, handling violating establishments in the jurisdiction;

đ) Deciding on the coercive enforcement of recalls where domestic manufacturers, importers of drug raw materials do not execute the recalls as required;

e) Publicizing on its web portal information pertinent to the recalled drug raw material in the case it is subject to being destroyed.

5. Health Department shall have the following responsibilities:

a) Communicating to manufacturers, trading establishments in the jurisdiction information pertinent to recalls of drug raw materials;

b) Inspecting, supervising the deployment and execution of recalls of drug raw materials, handle violating establishments in the jurisdiction;

c) Reporting to Ministry of Health on cases of manufacturers, trading establishments found not carrying out or not fully carrying the recall of drug raw materials.

Article 104. Handling of recalled drugs raw materials

1. Drug raw materials that are recalled medicinal materials, pharmaceutical substances shall be subject to destruction in the following cases:

a) The recalled drug raw materials are raw materials produced not for the purpose of human use but are labelled as such;

b) The recalled drug raw materials are raw materials for which the certificate of marketing registration was issued based on a falsified documentation;

c) The recalled drug raw materials are raw materials of unknown sources, origins;

d) Pharmaceutical materials that are produced, presented or labelled with the intent to fake a manufacturer, manufacturing country, country of origin;

đ) Counterfeit medicinal materials;

e) Medicinal materials that are marketed without a certificate of marketing registration certificate or a published quality specification according to applicable regulations.

g) The recalled drug raw materials are component raw materials of a drug subject of a World Health Organization's warning as not safe, effective for users.

2. Recalled drug raw materials shall be allowed to be corrected and reused in the following cases:

a) Drug raw materials that are recalled for non-conformance with labelling requirements for drugs, drug raw materials according to the provisions of Article 61 of Pharmaceutical law or other applicable legislations;

b) Drugs raw materials that are recalled as a result of them being produced at a site different from that recorded in the registration dossier but by the same manufacturer at another site that has been licensed for manufacturing by the competent authority.

3. Recalled drug raw materials, except raw materials being narcotic, psychotropic substances, drug precursors, that are not of the categories stipulated in clause 1 and 2 of this Article shall be allowed for recycling if they are domestically produced or re-exported if they are imported materials or repurposed in accordance with the provisions of clause 4 of this Article.

Recalled drug raw materials that are stipulated in this clause if not recycled, re-exported or repurposed must be destroyed.

4. Formalities for correction, recycling, re-exportation, repurposing of drug raw materials:

a) Establishments owning the recalled drug raw materials wishing to repurpose, correct, recycle or re-export such materials must prepare and send to Ministry of Health a proposal letter enclosed with a plan for repurposing or of corrective measures or recycling procedures;

b) The correction, recycling, re-exportation of drug raw materials shall only be carried out after a written consent from Ministry of Heath has been obtained;

c) Within 03 months from receipt of the establishment's proposal letter, Ministry of Health shall issue a written response.

With regard to imported raw materials to be re-exported, Ministry of Health shall notify the competent regulatory authority of the receiving country for their information and regulatory coordination.

5. Formalities for drug raw material destruction:

a) The head of the establishment owning the raw materials requiring destruction shall issue a decision to set up a Council for drug raw material destruction. The Council shall compose of at least 03 (three) persons, of whom one must be the head and one the pharmacist in charge of the establishment;

b) The destruction of drug raw materials shall be carried out in such a way as to ensure long term health for humans and animals and prevent environmental pollution in accordance with environmental legislation;

c) The establishments trading in the violative drug raw materials shall be responsible for the cost of destruction of such drug raw materials;

d) The destruction of controlled drug raw materials shall be carried out in accordance with the provisions of Article 48 of this Decree.

CHAPTER VII
DOSSIERS, PROCEDURES, FORMALITIES AND COMPETENCE IN THE CONFIRMATION OF CONTENT OF DRUG INFORMATION, DRUG ADVERTISEMENT

Article 105. Formats of drug information dissemination

Drug information for healthcare practitioners shall be disseminated under the following formats:

1. Drug information disseminated through "Drug introducers".

2. Publication of drug information materials.

3. Drug introducing workshops.

Article 106. Establishments acting as applicant in application dossiers for confirmation of drug information content

1. Establishments eligible to act as applicant in dossiers for content confirmation of drug information shall comprise:

a) The establishment that registers the drug in Vietnam;

b) The delegated representative office in Vietnam of the very foreign establishment that registers the drug in Vietnam, that is delegated by the latter the task of applying for confirmation of drug information content;

c) The pharmaceutical business establishment of Vietnam that is delegated the task by the establishment referred to in point a clause 1 of this Article;

d) Drug importers of Vietnam shall be allowed to disseminate drug information under the format stipulated in clause 3 Article 105 of this Decree only on the drugs not yet licensed for marketing which they themselves imported.

2. The registrant of the drug, even when delegating the task of applying for confirmation of drug information content to the establishment referred to in point b or c clause 1 of this Article, the drug importer of Vietnam acting as applicant in the application dossier, shall be responsible for the content of the drug information .

Article 107. Issuance, reissuance of confirmation certificate of drug information content and modification of drug information for which a confirmation certificate has been issued

1. Confirmation certificate of drug information content shall be issued to the following cases:

a) Drug information contents that are subject of a confirmation application for the first time;

b) Drug information contents for which a confirmation certificate has been issued but have undergone changes in registrant; drug name, composition, strength, concentration, dosage form, indication, contraindication, dosage, route of administration, use of the drug on special target patients, drug alert and safety related information

2. Certificate of confirmation of drug information content shall be reissued on those that were previously confirmed according to the provisions of this Decree and in the following situations:

a) Confirmation certificate of drug information content was lost, damaged;

b) Information recorded in the confirmation certificate of drug information content is erroneous due to the fault of the issuing authority

3. Modification of drug information content for which a Confirmation certificate has been issued shall be applicable in the cases of changes in content other than those specified in point b clause 1 of this Article.

Article 108. Application dossier for confirmation certificate of drug information content

1. An application dossier for confirmation certificate of drug information content under the format stipulated under clause 2 Article 105 of this Decree shall comprise the following documents

a) Letter requesting for confirmation of drug information content conforming to Form no. 01 in Appendix VII of this Decree

b) Mockup of drug information content;

c) Specimen of current label and package inserts of the drug, approved by Ministry of Health;

d) Reference materials related to the drug information content for which confirmation is being sought (if any);

đ) Certificate of marketing registration of the drug;

e) License for formation of representative office in Vietnam of foreign enterprise in the case a foreign establishment applying for confirmation of drug information content; or certificate of satisfaction of conditions for pharmaceutical business in the case a pharmaceutical business establishment of Vietnam applying;

g) Power of attorney, whereby the registrant of the drug delegates to another establishment the task of applying for confirmation of drug information content in the case of delegation of authority.

2. An application dossier for confirmation certificate of drug information content under the formats stipulated under clause 3 Article 105 of this Decree shall comprise the following documents:

a) Letter requesting for confirmation of drug information content conforming to Form 02 in Appendix VI of this Decree;

b) Drug information content;

c) Specimen of current label and package insert of the drug, approved by Ministry of Health;

d) Reference materials related to the drug information content for which confirmation is being sought (if any);

đ) Certificate of marketing registration or import license of the drug;

e) License for formation of representative office in Vietnam of foreign enterprise in the case a foreign establishment applying for confirmation of drug information content; or certificate of satisfaction of conditions for pharmaceutical business in the case a pharmaceutical business establishment of Vietnam applying.

g) Power of attorney, whereby the registrant of the drug delegates the task of applying for confirmation of drug information to another establishment in the case of delegation of authority;

h) Agenda of drug introducing workshop.

Article 109. Application dossier for reissuance of confirmation certificate of drug information content

1. Application for reissuance of Confirmation certificate of drug information content conforming to Form no. 03 in Appendix VI of this Decree.

2. Mockup of the drug information or content of the drug information subject of the application for Certificate reissuance.

3. Certification that the drug content was incorrectly written due to an error of the certificate issuing authority with regard to the case stipulated in point b clause 2 Article 017 of this Decree.

Article 110. Application dossier for modification of drug information content of which a Confirmation certificate has been issued

1. Application dossier for modification of drug information content of which a Confirmation certificate has been issued conforming to Form no. 04 in Appendix VI of this Decree, calling out the contents requiring modification, reasons of the modification request.

2. Documentation substantiating the changes leading to the modification request.

Article 111. Requirements of documents constituting the dossier for the issuance, reissuance of confirmation certificate of drug information content , modification of drug information content for which a confirmation certificate has been issued

1. The documents stipulated in point c and đ clause 1; point c and đ clause 2 Article 108 of this Decree shall be submitted in duplicate copy.

2. The documents stipulated in point d and e clause 1 and point d and e clause 2 Article 108 and clause 2 Article 110 of 7 of this Decree shall be submitted in duplicate copy certified by the applicant establishment if issued by Ministry of Health, in authenticated duplicate copy if not issued by Ministry of Health.

3. The documents stipulated in point g clause 1 and point g clause 2 Article 108 of this Decree shall be submitted in original or authenticated duplicate copy.

4. The documents stipulated in clause 3 Article 109 of this Decree shall be submitted in original copy.

5. The documents stipulated in point b clause 1, point b clause 2 Article 108 and clause 2 Article 109 of this Decree shall be submitted in original and in 02 copies each.

6. An application dossier for issuance, reissuance of Confirmation certificate of drug information content shall be prepared as follows:

a) 01 mockup in the case of the dossier stipulated in clause 1 Article 108 of this Decree or 01 content of drug information in the case of the dossier stipulated in clause 2 Article 108 of this Decree for a drug;

b). 01 mockup in the case of the dossier stipulated in clause 1 Article 108 of this Decree or 01 content of drug information in the case of the dossier stipulated in clause 2 Article 108 of this Decree for 02 or more drugs of the same active ingredient and route of administration by the same manufacturer but of different strength or dosage form.

7. The documents shall be printed on A4 sized paper. All constituting documents of the dossier must be stamped across the margins with one impression of the seal of the establishment requesting for content confirmation.

Article 112. Requirements of presentation format of drug information

1. Drug information content must satisfy the following requirements:

a) Containing the drug information stipulated in point a clause 5 Article 76 of Pharmaceutical law and shall not contain information, images not directly related to the drug or the use of the drug and similar information, images stipulated in Article 126 of this Decree;

b) Drug information content must have its supporting references clearly footnoted, citations from supporting literatures must be annotated as such. Citations must convey the information correctly, without inferences or redactions, additions intending to create misunderstanding as to the drugs' safety, effectiveness.

c) Drug information must be presented in Vietnamese language, except when the information cannot be translated or would be devoid of meaning if translated into Vietnamese language.

d) The font used in drug advertisement content should be clear, legible but should not be smaller than 12 font type of Vntime or Times New Roman on A4 sized paper.

2. Drug information content must have the wording "Drug information materials" printed on top of every page. Materials composing of multiple pages must be consecutively numbered, the top page must indicate clearly where to find detailed information on the product (specific page number) and printed: Number of Confirmation certificate of drug information content Ministry of Health XNTT/XX/QLD-TT, date ... month ... year...

3. In the case of drug information being disseminated by means of drug introducing workshops, the content of drug information shall also indicate the name, academic title of presenters who are holder of professional qualifications in medicine or pharmacy suitable with the type of drugs to be introduced.

Article 113. Formalities for the issuance of confirmation certificate of drug information content

1. Establishments applying for content confirmation of drug information shall submit a request dossier to the competent authority in accordance with Article 116 of this Decree.

2. Within 15 days from the date of receipt of a complete dossier, the dossier receiving authority shall issue a Confirmation certificate using Form no. 05 or 06 in Appendix VII of this Decree. In case of refusal, the dossier receiving authority shall respond in writing and provide the reasons of the refusal.

3. Where there is a follow up request for dossier revision, supplementation, within 15 days from the date of receipt of a complete dossier, the dossier receiving authority shall issue a written notification requesting the establishment to revise, supplement the contents in accordance with the following:

a) The written notification shall specify the documents, contents requiring revision, supplementation;

b) Within 15 days from the date of receipt of the follow up submission addressing the requirements, the dossier receiving authority shall issue a Confirmation certificate using Form no. 05 or 06 enclosed in Appendix VI of this Decree, otherwise it shall issue a non-issuance notification stating the reasons;

c) Within 90 days from the date the dossier receiving authority issue the written notification for dossier revision, supplementation, the establishment shall submit the revised, supplemented dossier as required. Past this timeline [if the establishment fails to respond] the dossier that was submitted shall become void.

4. During the pendency of dossier processing, the dossier receiving authority may suspend the confirmation and issue a written notification of the suspension reasons if it discovers that the information about the drug safety and effectiveness in the package insert is not yet appropriate, not yet updated to reflect the competent regulatory authority's requirements or the drug specific professional materials, guidelines that are issued, recognized by Ministry of Health. The confirmation suspension period shall last until the establishment resubmit the updated, revised drug information so as to ensure safety for drug users.

5. At least 03 days prior to proceeding with drug information dissemination under the formats stipulated in clause 03 Article 105 of this Decree, the establishment holder of confirmation certificate for drug information content shall send a letter to the Health Department where the workshop is to take place informing them of the event format, location and time, accompanied by a duplicate copy of the Confirmation certificate.

If there are changes in the venue, time of the workshop relative to that recorded on the confirmation certificate, the establishment shall inform the local Health Department of such changes at least 01 (one) working day in advance.

6. Temporary cessation of accepting new dossiers and from processing dossiers already submitted by establishments applying for confirmation of drug information including establishments that are delegated to apply for it referred to in point b, c clause 1 Article 106 of this Decree when they commit one of the following violative acts:

a) Altering, falsifying legal documents of competent regulatory authorities constituting the application dossier for confirmation of content of drug information, drug advertisement;

b) Dissemination of drug information, drug advertisement before obtaining a confirmation by the competent authority or disseminating drug information, drug advertisement that deviates from the contents that were confirmed;

c) Using certifications not yet confirmed by Ministry of Health, using material interests, misusing the reputation of organizations, individuals, symbols, images, positions, prestige, correspondences, testimonials for drug information, drug advertising purpose;

d) Using the results of clinical trials, pre-clinical trials, test results, results of bioequivalence studies not yet recognized by Ministry of Health for drug information, drug advertising purpose;

đ) Drug information, drug advertisements undergoing changes in content requiring the issuance of a confirmation certificate referred to in point b clause 1 Article 107 or point b clause 1 Article 120 of this Decree.

7. The suspension period during which the submission of application dossiers for confirmation of drug information, drug advertisement is declined, counting from the date the notification of the competent authority regarding the violative act is issued, shall be as follows:

a) From 01 to 02 years for the cases stipulated in point a clause 6 of this Article;

b) From 06 to 12 months for the cases stipulated in point b, c or d clause 6 of this Article;

c) From 03 to 06 months for the cases stipulated in point đ clause 6 of this Article.

Article 114. Formalities for the reissuance of confirmation certificate of drug information content

1. Establishments applying for reissuance of confirmation certificate of drug information content shall submit an application dossier to the competent authority in accordance with Article 115 of this Decree.

2. Within 10 working days from the date of receipt of a complete dossier, the dossier receiving authority shall reissue a Confirmation certificate using Form no. 05 or 06 enclosed in Appendix VI of this Decree.

Article 115. Formalities for the modification of drug information content for which a confirmation certificate has been issued

1. Establishments applying for modification of drug information content for which a confirmation certificate has been issued shall submit an application dossier to the competent authority in accordance with Article 116 of this.

2. Within 07 working days from the date of receipt of the written request, if the dossier receiving authority does not respond in writing, the establishment shall proceed with the modification. If the modification request is refused, the dossier receiving authority shall respond in writing and provide the reasons of the refusal.

Article 116. Competence for the issuance, reissuance of confirmation certificate of drug information content and modification of drug information content for which a confirmation certificate has been issued

1. Ministry of Health shall issue, reissue Confirmation certificates of drug information content and modify the drug information content for which a Confirmation certificate has been issued with regard to the format stipulated in clause 2 Article 105 of this Decree.

2. Health Departments shall issue, reissue Confirmation certificates of drug information content and modify the drug information content for which a confirmation certificate has been issued with regard to the formats stipulated in clause 1 and 3 Article 105 of this Decree.

Article 117. Validity term of Confirmation certificate of drug information content

1. Confirmation certificate of drug information content shall be valid nationwide.
2. Confirmation certificate of drug advertisement content shall not specify a validity term and shall cease to be valid in the following cases:

a) The Certificate of marketing registration, import license of a drug is withdrawn;

b) Changes in information resulting in the need for the issuance of a Confirmation certificate of drug information under the provision of point b clause 1 Article 107 of this Decree.

Section 2

CONFIRMATION OF DRUG ADVERTISEMENTCONTENT

Article 118. Media for drug advertising media

Drugs shall be advertised to the public on media according the provision of Article 17 of the Law on advertising.

Article 119. Establishments acting as applicant in application dossiers for confirmation of drug advertisement content

1. Establishments eligible to act as applicant in dossiers for confirmation of drug advertisement content shall comprise:

a) The registrant of the drug in Vietnam;

b) The representative office in Vietnam of the foreign establishment registering the drug in Vietnam and which is delegated by the latter;

c) The pharmaceutical business establishment of Vietnam that is delegated by the establishment referred to in point a clause 1 of this Article;

2. The drug registrants, including cases where the application for confirmation is delegated to establishments referred to in point b, c clause 1 of this Article shall be responsible for the content of drug advertisement disseminated.

Article 120. Issuance, reissuance of confirmation certificate of drug advertisement content and modification of drug advertisement content for which a confirmation certificate has been issued

1. Confirmation certificate of drug advertisement shall be issued in the following cases:

a) Drug advertisement contents that are requested for confirmation for the first time;

b) Drug information contents for which a confirmation certificate has been issued but have undergone changes in the certificate of marketing registration, import license or the registrant of the the drug; drug name, composition, strength, concentration, dosage form, indication, contraindication, dosage, route of administration, use of the drug on special target patients, drug alert and safety related information;

2. Confirmation certificate for drug advertisement content shall be reissued in the following cases:

a) Confirmation certificate of drug advertisement content was lost, damaged;

b) Information on the Confirmation certificate of drug advertisement content is erroneously recorded due to the fault of the issuing authority.

3. Modification of drug advertisement content for which a Confirmation certificate has been already issued shall be effected for the cases undergoing changes other than those stipulated in point b clause 1 of this Article.

Article 121. Application dossier for confirmation certificate of drug advertisement content

1. An Application dossier for Confirmation certificate of drug advertisement content, except for advertisement under the format of workshops, conferences, drug introducing events, shall comprise the following documents:

a) Application for content confirmation of drug advertisement conforming to Form no. 01 in Appendix VI of this Decree;

b) Mockup of the drug advertisement subject of the confirmation application; audio recording, visual recording of the advertisement to be placed on audio, visual press or electronic devices, display screens and other advertisement media according to the laws on audio, dynamic advertising.

c) Specimen of drug's current label and package insert approved by Ministry of Health;

d) Reference materials relevant to the drug advertisement content (if any);

đ) Certificate of marketing registration of the drug;

e) License for formation of representative office of foreign enterprise in Vietnam in the case of foreign establishments applying for confirmation of drug advertisement or Certificate of satisfaction of conditions for pharmaceutical business in the case of pharmaceutical business establishment applying for it;

g) Power of attorney from the drug registrant to the establishment applying for content confirmation of drug advertisement in the case of delegation.

2. An application dossier for confirmation certificate of drug advertisement under the format of workshop, conference, event shall comprise the following documents:

a) Application for confirmation of drug advertisement content conforming to Form no. 02 In Appendix VI of this Decree;

b) Content of drug advertisement;

c) Specimen of drug's label and package insert approved by Ministry of Health;

d) Drug related materials to be presented at the drug introducing workshop, conference, event (if applicable);

đ) Certificate of marketing registration of the drug;

e) License for formation of representative office of foreign enterprise in Vietnam in the case of foreign establishments applying for confirmation of drug advertisement or Certificate of satisfaction of conditions for pharmaceutical business in the case of pharmaceutical business establishment applying for it;

g) Power of attorney from the drug registrant to the establishment applying for content confirmation of drug advertisement in the case of delegation.

h) Proposed agenda for the drug introducing workshop, conference, event.

Article 122 Application dossier for reissuance of confirmation certificate of drug advertisement content

1. Application for reissuance of confirmation certificate of drug advertisement conforming to Form no. 03 in Appendix VII of this Decree.

2. Mockup of the drug advertisement, audio, visual recording of the advertisement or the content of the advertisement subject of the application for confirmation certificate reissuance.

3. The Confirmation certificate that is erroneously recorded due to the fault of the issuing authority in the case referred to in point b clause 2 Article 120 of this Decree.

Article 123. Application dossier for modification of drug advertisement content for which a confirmation certificate has been issued

1. Application for modification of the drug advertisement for which a Confirmation certificate has been issued conforming to Form no. 04 in Appendix VI of this Decree calling out the contents to be modified, reasons of the modification;

2. Documentation supporting the modification of the drug advertisement content.

Article 124. Requirements of application dossier for issuance, reissuance, of confirmation certificate, for modification of drug advertisement content

1. The documents stipulated in point c and đ clause 1, point c and đ clause 2 Article 121 of this Decree shall be submitted in duplicate copy.

2. The documents stipulated in point e clause 1, point e clause 2 Article 121 and clause 2 Article 123 of this Decree shall be submitted in duplicate copy if issued by Ministry of Health and in authenticated duplicate copy if not issued by Ministry of Health.

3. The documents stipulated in point g clause 1, point g clause 2 Article 121 of this Decree shall be submitted in original copy or authenticated duplicate copy.

4. The documents stipulated under clause 3 Article 122 of this Decree shall be submitted in original copy.

5. The documents stipulated in point b clause 1, point b clause 2 Article 121 and clause 2 Article 122 of this Decree shall be submitted in original copy and in 02 copies.

6. An application dossier for the issuance, reissuance of Confirmation certificate of a drug advertising content shall be prepared in accordance with the following:

a) 01 mockup of or the audio recording, visual recording of the drug advertisement in the case of application dossiers referred to under clause 1 Article 121 of this Decree of 01 drug advertisement content in the case of application dossiers referred to under clause 2 Article 121 of this Decree of for a drug;

b) 01 mock up or audio recording, visual recording of the drug advertisement in the case of application dossiers referred to under clause 1 Article 11 of this Decree or 01 drug advertisement content in the case of applications dossiers referred to under clause 2 Article 121 of this Decree for two or more drugs of the same active ingredients, administration route by the same manufacturer but of different strength or dosage form.

7. The documents shall be printed on A4 sized paper. For large sized, outdoors advertisement, A3 sized paper may be used with the reduction scale factor indicated. All component documents of the dossier must be stamped across the margins with one impression of the seal of the applicant establishment. If the mockup of the advertisement object is made out in special dimension, a description on A3 sized paper shall be included in the dossier, covering the following mandatory contents:

a) Spatial structure;

b) Numbering and measurement of each dimension;

c) Reduction scale factor.

Article 125. Requirements of drug advertisement content

1. The content of drug advertisement must be consistent with the following documents:

a) Specimen of the drug label and package insert approved by Ministry of Health;

b) The drug monograph written in Vietnam National Formulary;

c) Professional materials, guidelines related to the drug issued or recognized by Ministry of Health.

2. Drug advertisement content must cover the following mandatory information:

a) Drug name;

b) Composition of pharmaceutical substances or medicinal materials recorded in the approved package insert. Vietnamese name must be used for medicinal materials, if Vietnamese name does not exist, Latin name must be used.

c) Indications;

d) Route of administration;

đ) Dosage;

e) Contraindications and/or warnings for specific populations (pregnant women, nursing mothers, children, elderly patients, patients with chronic conditions).

g) Precautions and things to avoid, to pay attention to in the course of medication;

h) Side effects and adverse reactions;

i) Manufacturer's name and address

k) Warning "Read the instructions for use carefully before use";

l) The bottom of the first page of the advertisement content must be printed with: Number of Confirmation certificate of the advertisement content of Ministry of Health: …./XNQC, date ... month ... year.

m) With regard to advertisement content composed of multiple pages, the document must be page numbered, with indication of the number of pages it contains and at which page to find detailed information of the product;

n) Information about the drugs must have its supporting references clearly footnoted, citations from supporting literatures must be annotated as such. Citations must convey the information correctly, without inferences or redaction aiming to create misunderstandings as to the drugs' safety, effectiveness.

3. Advertisement contents for audio, visual press: must cover all the information set out in point a, b, c, e, i and k Clause 2 of this Article of which the content in point a, b, c, e and k must be distinctly and amply pronounced. If a drug contains more than 03 active ingredients, the name of each active ingredient or the common name of groups of vitamin, mineral, medicinal material should be read out.

4. Advertisement contents on electronic newspapers, webpages, electronic devices and advertising display screens and other advertising media shall be in compliance with legislation on advertising:

a) Content of audio enhanced advertisement: advertisement content must be presented in the same way as with audio news, visual news specified in clause 3 of this Article;

b) Content of non-audio advertisement: must cover all the information specified in in Clause 2 of this Article;

If the advertisement content cover several pages or storyboard frames, the pages or frames must be projected consecutively, with in-between pauses sufficiently long for viewers to read all the information presented; the page, frame displaying the product information must be still-standing, non-dynamic, for viewers to digest the product information. The script must be descriptive of how each of the content page is displayed in the case of multiple page advertisement.

Advertising in this form requires the advertisement content to be exclusively about one product, not to be cross advertising several products concurrently so as to prevent misunderstanding.

5. Content of outdoors advertisement shall only be displayed on onside of the media and shall cover the information set out in point a, b, i, k and l clause 2 of this Article. If the advertisement presents information related to the uses, activity, indications of the drug it must as well include all the information listed under clause 2 of this Article.

6. The utterances, wordings in drug advertisement content shall be in compliance with the provisions of Article 18 of Advertisement law.

7. The font size used in drug advertisement content should be clear, easy to read, easy to see under normal conditions and should not be smaller than 12 font size of Vntime or Times New Roman font type on A4 sized paper.

8. The advertisement script must be descriptive of the graphic, narrative, wording, music portions.

9. Drug advertisement content must contain exclusively drug related information, non-related information should not be included.

Article 126. Information, images prohibited from use in drug advertisement content

1. The information, images specified in Article 8 of Advertisement law.

2. Contents that are misleading in terms of composition, action, indication, origin of the drug.

3. Contents suggesting the interpretation that: this drug is number one; this drug is better than all other drugs; using this drugs is the best solution; using this drug does not require a physician's opinion; this drug is completely innocuous; the drug does not have any contraindications; the drug does not cause any undesirable effects; the drug does not cause any harmful effects.

4. Phrasings, words, images implying excessive inferences as to create misunderstanding as to the drug's action, indication, efficacy or over claiming the drug's action, indication, efficacy relative to those that were actually approved.

5. Stating the discrete action of the drug's components severally so as to over claim the drug's use or to confound the separate action of the drug's individual ingredients with that of the drug in its entirety.

6. Words, group of words such as "radical cure", "eliminate", "specialized in the cure of", "leading", "premier league", "first ever", "choice", "high quality", "100% guaranteed", "safe", "rid of", "cut away", "stop in its track", "immediately alleviate", "promptly alleviate", "alleviate on the spot", "immediately relieved", "completely relieved", "peace of mind", "not to worry", "no worries", recommended for use, hotline, telephone for consultation and words,, group of words denoting similar meaning.

7. Indications not allowed to be included in drug advertisement content:

a) Indications for tuberculosis, leprosy;

b) Indications for sexually transmitted diseases;

c) Indications for insomnia;

d) Indications of aphrodisiac nature;

đ) Indications for cancer, tumor conditions;

e) Treatment for opioid withdrawal

g) Indications for diabetes or similar metabolic disorders;

h) Indications for virus causing hepatitis, newly emerging dangerous diseases.

8. Test results of drugs, drug raw materials.

9. Results of pre-clinical studies;

10. Results of clinical trials or bioequivalence studies not yet recognized by Ministry of Health;

11. Using title, position, reputation, correspondences, and testimonials from organizations, individuals for drug promotion, advertising purposes;

12. Misusing the drugs' origin, raw materials for drug information dissemination, advertising purposes;

13. Images, name, logos of healthcare professionals;

14. Images of animals, plants belonging to the list of protected endangered, precious, rare animals;

15. Phrasings, words of anecdotal, word-of-mouth nature recommending the use of the drug.

16. Use of patients' images to describe pathologic conditions or the drug's action that is not appropriate with the materials relevant to the drug and the professional guidelines issued or recognized by Ministry of Health.

Article 127. Procedures, formalities for issuance, reissuance of confirmation certificate of drug advertisement content, modification of drug advertisement content for which a confirmation certificate has been issued

1. Establishments applying for the issuance, reissuance of Confirmation certificate of drug advertisement content, modification of drug advertisement content for which a Confirmation certificate has been issued shall submit an application dossier to Ministry of Health.

2. Procedures, formalities for the issuance of confirmation certificate of drug advertisement content, modification of advertisement content for which a confirmation certificate has been issued shall be undertaken along the same line with the provisions of Article 113, 114 and 115 of this Decree.

Article 128. Competence in the issuance, reissuance of confirmation certificate of drug advertisement content, modification of drug advertisement content for which a confirmation certificate has been issued

Ministry of Health shall issue, reissue certificates of confirmation for advertisement content, modify drug advertisement contents for which a confirmation certificate has been issued.

Article 129. Validity of confirmation certificate of drug advertisement content

1. Confirmation certificate of drug advertisement content shall not specify its validity term and shall lapse in the following cases:

a) Certificate of registration for marketing in Vietnam of the drug expires;

b) Certificate of registration for marketing of the drug is withdrawn;

c) Changes in information resulting in the need for the issuance of a Confirmation certificate of drug advertisement under the provision of point b clause 1 Article 120 of this Decree;

d) The drug is subject to a warning by the pharmaceutical state authority regarding its restricted use or use under supervision of a medical practitioner;

đ) The drug contains active ingredients or medicinal materials that are removed from the Ministry of Health-issued list of non-prescription drugs.

2. When the Certificate of registration for marketing in Vietnam of a drug is renewed, the confirmation certificate of the drug advertisement content shall be automatically extended to match the extended validity term of Certificate of registration for marketing in Vietnam.

Chapter VIII
DRUG PRICE REGULATORY MEASURES

Section 1
DRUG PRICE DECLARATION, REDECLARATION

Article 130. Dossiers declaring, redeclaring drug prices

1. Drug price declaration dossier:

a) Price declaration table of foreign drugs imported to Vietnam conforming to Form. 01 in Appendix VII of this Decree.

b) Price declaration table of domestically produced drugs conforming to Form no. 02 in Appendix VII of this Decree.

2. Drug price redeclaration dossiers:

a) Drug price redeclaration table of foreign drugs imported to Vietnam conforming to Form no. 03 in Appendix VII of this Decree.

b) Drug price redeclaration table of domestically produced drugs conforming to Form no. 04 in Appendix VII of this Decree

3. Dossiers for drug price declaration in the case of change of Certificate of marketing registration shall be prepared in accordance with the provisions in Clause 1 of this Article.

4. Dossiers requesting for supplementation, changes in information on a drug, the price of which have been declared, redeclared but have since undergone changes in information that are published but the price of which remains unchanged (except the cases referred to under clause 3 of this Article) shall be prepared as follows:

a) Letter requesting for modification, supplementation of information of drugs the prices of which have been declared and/or redeclared conforming to Form no. 05 in Appendix VII of this Decree;

b) Duplicate copy of the letter approved by the regulatory authority regarding the drug information content to be modified;

5. The dossier shall be made in 02 sets: 01 set to be sent to Ministry of Health or the People's Committee of provinces/centrally-affiliated cities in the case of price redeclaration for domestically produced drugs, the other set to be retained at the establishment premises.

6. Drug price shall be declared/ redeclared in Vietnamese currency inclusive of value added tax and shall be calculated on the smallest package unit. For import price, the declaration, redeclaration must be supported by information on the exchange rate at which the foreign currency is converted into Vietnam Đong at the point of declaration. The foreign currency exchange rate applicable shall be the one the drug trading businesses actually use in bank transactions either in loan repayment or currency purchase, where the drug trading business has yet to settle with the bank, the selling rate at the point of price calculation of the commercial bank where the loan was secured or the currency purchased shall be used.

Article 131. Procedures, formalities, competence for receiving dossiers for drug price declaration/redeclaration, modification, supplementation of information on the drugs of which the price has been declared/redeclared and for reviewing, publicizing declared, redeclared drug prices

1. For foreign drugs imported to Vietnam:

a) Drug importers shall undertake to declare: the intended wholesale price, intended retail price of a drug (where there is a need to declare the retail price) prior to placing the first lot of the drug it imported on Vietnam market. Unless there are adjustments to be made in the intended wholesale price, retail price the importer previously declared, price declaration shall not be required on the subsequent import consignments of the drug;

b) Drug importing establishments shall undertake to redeclare a drug's intended wholesale price, retail price where there is a need to adjust the intended whole sale price, the intended retail price upwards relative to those last declared/redeclared by the establishment itself, that are publicized on Ministry of Health's web portal;

c) Where there is a change in Certificate of marketing registration, and prior to placing the first lot of a drug on Vietnam market, the establishment shall submit a price declaration dossier for such drug.

d) In the course of business operation, if an exporter wishes to adjust downwards the intended wholesale price, intended retail price of a drug which it previously declared, redeclared, it shall proceed to redeclaring the reduced intended wholesale price, intended retail price accordingly.

2. For domestically produced drugs:

a) Manufacturers or contract givers (in the case of contract manufactured drugs) of a drug shall undertake to declare: the intended wholesale price, intended retail price of a drug (where there is a need to declare the retail price) of a drug before place the first lot of the drug on Vietnam market.

Unless there are adjustments to be made in the intended wholesale price, retail price they previously declared, price declaration shall not be required on the subsequent lots of drug produced;

b) Manufacturers or contract givers (in the case of contract manufactured drugs) of a drug shall undertake to redeclare the intended wholesale price, intended retail price when there is a need to adjust upwards the intended wholesale price, intended retail price publicized on Ministry of Health's web portal that they previously declared;

c) Where there is a change in Certificate of marketing registration, and prior to placing the first lot of a drug on Vietnam market, the establishment shall submit a price declaration dossier for such;

d) In the course of business operation, if a manufacturer or a contract giver (in the case of contract manufactured drugs) of a drug wishes to adjust downwards the intended wholesale price, intended retail price it previously declared, redeclared, it shall proceed to redeclaring the reduced intended wholesale price, intended retail price accordingly.

3. Competence for receiving dossiers declaring, redeclaring drug prices:

a) Ministry of Health shall arrange to receive and review dossiers declaring, redeclaring prices of foreign drugs imported to Vietnam, dossiers declaring prices of domestically produced drugs, dossiers requesting supplementation, modification of information of drugs of which the prices have been declared, redeclared;

b) People's Committee of provinces, centrally affiliated cities shall arrange to receive and review dossiers redeclaring prices of domestically produced drugs from establishments having manufacturing facilities located in the respective provinces, cities.

Article 132. Responsibilities of drug price regulatory authorities in the implementation of drug price declaration, re-declaration regulations

1. In the course of drug price inspection, control, if a published declared, redeclared price point is found not reasonable at the time of the inspection, a written notification shall be issued by the competent authority referred to under Clause 3 Article 131 of this Decree to the declarant establishment requesting it to review the price point that was declared, redeclared and providing the reasons for such request.

2. If, in the course of inspection, the drug price regulatory authority over drug price and competent persons find a drug business establishment to be in violation of drug price regulations, they shall handle the case themselves, refer the case to the competent authority for corrective actions according relevant legislation in the following situations:

a) Not declaring, not redeclaring drug prices; incomplete declaration of drug prices according to applicable regulations;

b) Not reviewing and adjusting the declared price after receiving written notification to the effect from the drug price regulatory authority;

c) Selling drugs at a price higher than the still effective declared, redeclared price.

3. With regard to pharmaceutical business establishments that commit more than 02 violations or have more than 02 violative products within a period of 01 year, the drug price regulatory authority shall consider and impose the following sanctions:

a) Ceasing to accept their submission of application dossiers for confirmation of drug information, drug advertisement content;

b) Ceasing to accept their submission of application dossier for importation of drugs that are not yet licensed for marketing in Vietnam;

c) Ceasing to accept their submission of application dossiers for the issuance, renewal of certificate of marketing registration of drugs, drug raw materials

4. The suspension period during which submission of application dossiers is not accepted as stipulated in Clause 3 of this Article shall be from 03 to 12 months starting from the day the notification letter of violative conducts is issued by the competent authority.

Article 133. Responsibilities of business establishments in the implementation of price declaration, redeclaration requirements

1. Pharmaceutical business establishments shall be responsible for complying with the provisions on drug price declaration, redeclaration and other provisions regarding the management of drug price of this Decree and pertinent legal normative documents; they shall be responsible before the laws regarding the drug price they declare, redeclare and the accuracy of the data, reports, information they provide.

2. Pharmaceutical business establishments shall not sell a drug before its declared, redeclared prices are publicized on Ministry of Health's web portal, which were declared either by the manufacturer, or the manufacturing contract giver, exporter of such drug.

3. Pharmaceutical business establishments shall not wholesale, retail a drug at a price higher than the price it declared, redeclared for such drugs that is publicized on Ministry of Health's web portal.

4. In the case the competent regulatory authority issues a written notification to the declarant establishment requesting for the review of the price point it has declared, redeclared, which was publicized on Ministry of Health's web portal, within 60 days from the date of such notification, the declarant establishment must respond in writing, enclosing pertinent documents to justify the rationality of the price point it has declared, redeclared or adjust the price downward to a reasonable level. Past this time limit, if the establishment fails to respond, the declared, redeclared price point that was publicized shall cease to be valid and removed from Ministry of Health's web portal.

Article 134. Principles for reviewing, publicizing declared, redeclared drug prices

1. The review, determination of the rationality of declared, redeclared drug prices shall be based on the following factors:

a) Prevailing price of similar drugs of the same technical grouping in the domestic market or the price of the drug in other countries' market where there are no similar drugs in the domestic market.

If a declarant establishment proposed a declared price for a drug that is higher than the prevailing price level of similar drugs of the same technical criteria group in the domestic market or average price of the drug in other countries, the competent authority shall consider and review the declared price against the supporting documentation provided by the declarant establishment to substantiate the drug's therapeutic effectiveness, compare cost and benefit of the drug, demonstrate the manufacturing technology and techniques involved, illustrate the cost structure of the drug, using Form no. 09 and 10 in Appendix VII of this Decree, and other documents justifying the rationality of the declared price of the drug.

b) Price movement of input factors such as raw materials, consumables, exchange rates, wage and some other related costs in the case of price upward adjustment. The competent authority shall consider and review the declared price against the supporting documentation provided by the declarant establishment regarding the price movement of input factors such as raw materials, consumables, exchange rates, labor costs, other associated costs to justify the rationale and the rate of the adjustment, ensuring that the price increase rate is not be higher than the impact rate resulted from such price movement of input factors.

c) Import price, total cost price of the drug.

d) Market demand and supply relationship, competitive capabilities, quality factors of the drug, bioequivalence-proven drugs other factors influencing the price of the drug and the assurance of drug supply sources.

2. A declared drug price that is fair and publicized on Ministry of Health's web portal when fulfilling the following principles:

a) Not higher than the price that was declared for the same drug product or a drug product of different trade name but of the same active ingredient, concentration, strength, dosage form from the same manufacturing establishment that was publicized on Ministry of Health's web portal.

b) Not higher than the highest price that was declared within the most recent 03 years for a drug of the same active ingredient, concentration, strength, dosage form and of the same technical criteria group, that was publicized on Ministry of Health's web portal, taking into account the price appreciation announced by General Office of Statistics which is calculated from the point the price of the drug having the highest price was declared, redeclared.

c) In the case of a drug having no comparator the same active ingredient, concentration strength, dosage form available in Vietnam market, the declared import price, wholesale price for the drug shall not be higher than the average import price, average wholesale price of such drug as it is imported to and marketed in ASEAN countries.

d) The declared import price of foreign drugs imported to Vietnam must match the import price of the drugs recorded on the customs declaration form at the point of declaration.

3. Redeclared drug prices that are adjusted upwards shall be publicized if satisfying the requirements of point b and point d clause 1 of this Article. In case a redeclared drug price is adjusted downwards, due consideration shall be taken and announcement made on Ministry of Health's web portal.

4. If a declared, redeclared drug price that is found not yet reasonable and not yet publicized on Ministry of Health's web portal and the declarant, redeclarant establishment provides a written justification for it, the price review and publication shall be carried out based on the following principles:

a) If the declarant, redeclarant establishment responds with price adjustment to a level in line with the provisions of clause 2 of this Article, such adjusted price shall be publicized on Ministry of Health's web portal.

b) If the declarant, redeclarant establishment responds with justifications and declares, redeclares a price point that is still not in line with the provisions of clause 2 of this Article, the redeclared price shall be considered and reviewed against the supporting documentation provided by the declarant establishment referred to in clause 1 of this Article and if found reasonable shall be publicized on Ministry of Health' web portal.

5. Drug price regulatory authority shall form an expert panel on drug prices to review the justification of dossiers declaring/ redeclaring drug prices.

6. The Minister of Health shall set up a Cross functional council on drug price composing of representatives of Ministry of Health, Ministry of Finance, Vietnam Social Insurance and relevant entities for the latter to provide Minister of Health with consultative inputs on reviewing drug prices and making decision on the rationality of declared, redeclared drug prices in the cases of:

a) The declared drugs having a concentration, strength that is different from those of the drugs already publicized on Ministry of Health's web portal;

b) Drugs that have a dosage form different from that of the drugs which were publicized on Ministry of Health's web portal and have a price point higher than the highest price of a drug of the same active ingredients, concentration, strength and of the same technical criteria that was publicized on Ministry of Health's in the most recent 03 years;

c) New drugs;

d) Drugs belonging to the List of drugs subject to price negotiation, originator drugs, drugs produced on EU-GMP or PIC/S-GMP-compliant manufacturing lines of manufacturers belonging to ICH member countries or Australia, drugs produced on WHO-GMP-compliant manufacturing lines

certified by Ministry of Health, and licensed for marketing by the competent authority of ICH member countries or Australia, that are subject of a redeclared price increase of the following rates:

- More than 10% for a drug of which the price of the smallest package unit ranges from 5,000 (five thousand) đồng to 100,000 (one hundred thousand) đồng.

- More than 7% for a drug of which the price of the smallest package unit ranges from 100,000 (one hundred thousand) đồng to 1,000,000 (one million) đồng.

- More than 5% for a drug of which the price of the smallest package unit is more than 1,000,000 (one million) đồng.

7. The Minister of Health shall provide for the specifics of the organizational structure and operation of the Cross-functional council on drug price.

Article 135. Drug price posting

1. Responsibilities for drug price posting:

a) Drug wholesalers shall undertake to post the wholesale price of each type of drugs at the place of transaction or the drug selling place of the drug wholesalers.

b) Drug retailers shall undertake to post the retail price of each of the drug type of drugs sold at their retail outlets.

c) Drug wholesalers, drug retailers shall not sell drugs at a price higher than the one they have posted.

2. Requirements of drug price posting:

a) The posting of wholesale price shall be performed by way of public announcement on a board, in paper or other suitable means and shall ensure visibility, identification by customers, competent state authorities.

b) The posting of drug retail price shall be performed by way printing, writing down, or sticking the retail price on the packaging containing the drugs or the drugs' outer packaging; or announcing the prices on a board, in paper or other suitable means and shall facilitate visibility, identification by customers, competent authorities, and that the mandatory content of drug's drug labels are not obscured from view.

c) The currency used for price posting shall be Vietnam Đồng.

d) The posted price shall cover taxes, fees and charges (if any) associated with the drugs.

Article 136. Provisions for retail mark-ups of retailers operating on the premises of medical service establishments

1. The retail price of a drug at a drug retail outlet shall comprise the drug purchase price recorded on its invoice and the retail mark-up calculated as retail mark-up level multiplied by purchase price, specifically:

Retail price = Purchase price + Retail mark-up level (%) × Purchase price

2. Retailers operating on the premises of medical service establishments shall only purchase drugs that are the bid winning ones of the same medical service establishment and the drugs that are announced as bid winning ones on Ministry of Health's web portal within 12 months up to the point of purchase at the following purchase prices:

a) For the drugs that are on the List of bid winning drugs of the medical service establishment itself, the purchase price of a drug incurred by a drug retailer shall not be higher than the bid winning price of such drug at the time.

b) For the drugs that are not on the List of bid winning drugs of the medical service establishment itself, the purchase price of a drug shall not be higher the bid winning price of such drug that was publicized on Ministry of Health's web portal within 12 months up to the point of purchase.

3. The retail mark-up levels of drug retailers operating on the premises of medical service establishments shall not be higher than the following retail mark-up levels:

a) For the drugs of which the purchase price of the smallest package unit is less than or equal to 1.000 (one thousand) đồng, the maximum retail mark-up level is 15%.

b) For the drugs of which the purchase price of the smallest package unit ranges from more than 1.000 (one thousand) đồng to 5.000 (five thousand) Đồng, the maximum retail mark-up is 10%.

c) For the drugs of which the purchase price of the smallest package unit ranges from more than 5.000 (five thousand) đồng to 100.000 (one hundred thousand) Đồng, the maximum retail mark-up is 7%.

d) For the drugs of which the purchase price of the smallest package unit ranges from more than 100.000 (one hundred thousand) đồng to 1.000.000 (one million) Đồng, the maximum retail mark-up is 5%.

đ) For the drugs of which the purchase price of the smallest package unit is more than 1.000.000 (one million) đồng, the maximum retail mark-up is 2%.

4. The smallest package unit as the basis for retail mark-up calculation shall be defined as follows:

a) For tablet dosage form, the smallest package unit is tablet;

b) For liquid dosage form, the smallest package units are ampoule, bottle, vial, bag, syringe, drug-prefilled injection pump;

c) For dosage form of powder for injection, the smallest package units are ampoule, bottle, vial, bag, syringe, drug-prefilled injection pump;

d) For dosage forms of powder, granule for oral solution, the smallest package units are sachet, bottle, vial, bag;

đ) For dosage forms of cream, ointment, gel for topical application, the smallest package units are tube, vial;

e) For dosage form of plaster, the smallest package unit is patch;

g) For dosage forms of pharmaceutical spray or pharmaceutical aerosol, the smallest package units are spray can, spray bottle or drug container for aerosol machine;

h) For pharmaceutical kit dosage form, the smallest package unit is kit.

Section 3

DRUG TENDERING, DRUG PRICE NEGOTIATION AND DRUG PRICE STABILIZATION MEASURES

Article 137. Drug tendering

1. The tendering for drugs that are funded by the state budget, health insurance fund, revenue from the service delivery of medical services and other lawful revenue streams of public healthcare establishments shall be undertaken in compliance with the provisions of tendering legislation and the principles set out under clause 4 Article 7, clause 6 Article 107 of Pharmaceutical law.

2. The criteria for the determination of a fair price as a basis to promulgate the List of medicinal materials cultivated and harvested domestically meeting therapeutic and supply requirements at reasonable prices include:

a) Bid winning price, actual selling price in the domestic and imported medicinal materials markets;

b) Priority shall be given to medicinal materials with relevant technical criteria: those cultivated and harvested domestically in ways compliant with good cultivation and harvesting practices; domestically produced medicinal materials produced at establishments meeting good manufacturing practices for traditional and medicinal material drugs; and domestic medicinal materials of which the active ingredients and strength or concentration have been clearly identified.

3. The Minister of Health shall provide specific guidelines for the tendering of the drugs stipulated in clause 1 and 2 of this Article, announce a list of originators, and set out the specifics for the purchase of originators that are not on the List of drugs, medicinal materials subject to price negotiation

stipulated under Article 138 of this Decree, through appropriate supplier selection methods in line with the tendering legislation.

Article 138.List of drugs, drug raw materials subject to procurement through price negotiation method

The Minister of Health shall issue the List of drugs, drug raw materials subject to procurement through price negotiation method according to the provisions of clause 6 Article 107 of Pharmaceutical law based on recommendations of the Drug Tendering National Advisory Board.

Article 139. Drug price stabilization

Situations warranting drug price stabilization, drug price stabilization measures and the competence, responsibilities in the implementation and execution of such measures shall be in compliance with the provisions of the Law on Price and relevant documents guiding its implementation.

Chapter IX
IMPLEMENTATION PROVISIONS

Article 140. Implementation roadmap for Certificate of pharmacy practice

1. By no later than 01 January 2019, the pharmacist in charge, the person in charge of quality assurance of manufacturers of pharmaceutical substances, except for sterile pharmaceutical substances must be in possession of a Certificate of pharmacy practice. By no later than 01 January 2021, the pharmacist in charge, the person in charge of quality assurance of manufacturers of excipients, capsule shells, establishments manufacturing, processing medicinal materials, traditional medicinals must be in possession of a Certificate of pharmacy practice.

2. By no later than 01 July 2018, the person in charge of quality assurance of manufactures of chemo pharmaceutical drugs, medicinal material drugs, traditional drugs, except manufacturers of traditional medicinals, vaccines and biologicals, must be in possession of a Certificate of pharmacy practice.

3. By no later than 01 January 2021, the clinical pharmacist in charge of hospital referred to in clause 3 Article 116 of Pharmaceutical law must be in possession of a Certificate of pharmacy practice.

4. As from the effective date of this Decree, the pharmacist in charge of pharmaceutical business establishments, the person in charge of quality assurance of manufacturers of drugs, drug raw materials must be in possession of a Certificate of pharmacy practice, except for the cases referred to under clause 1 and 2 of this Article.

5. The pharmacist in charge of pharmaceutical business establishments, owners of drug retailers, of which a Certificate of satisfaction of conditions for pharmaceutical business was issued under Pharmaceutical law no. 34/2005/QH11 shall continue to assume the position of pharmacist in charge of such establishments.

Article 141. Implementation roadmap for Good practice adoption by pharmaceutical business establishments

1. As from the effective date of this Decree, manufacturers of chemo pharmaceutical drugs, medicinal material drugs, vaccines biologicals, importers, exporters, wholesalers, retailers that are drug store, drug counter, providers of testing service, providers of storage service, providers of bioequivalence study service, providers of drug clinical trial service, manufacturers of drug raw materials that are sterile pharmaceutical substances, shall comply with the Good practice respective to their specific type of operation, except for the cases stipulated under clause 2 and 5 of this Article.

2. By no later than 01 January 2019, manufacturers of drug raw materials that are pharmaceutical substances, except the raw materials that are sterile pharmaceutical substances referred to under clause 1 of this Article, must comply to good manufacturing practice.

3. As from the effective date of this Decree, retailers that are drug cabinets applying for Certificate of satisfaction of conditions for pharmaceutical business must be in compliance with good pharmacy practice respective to their specific type of operation.

By no later than 01 July 2019, drug retailers that are drug cabinet that are granted a Certificate of satisfaction of conditions for pharmaceutical business before the effective date of this Decree must be in compliance with good pharmacy practice respective to their specific type of operation. Prior to this cutoff date, these drug retailers must maintain the conditions strictly in accordance with those based on which the Certificate was issued.

4. As from the effective date of this Decree, manufacturers of traditional drugs applying for Certificate of satisfaction of conditions for pharmaceutical business must be in compliance with good manufacturing practice for traditional drugs, except for manufacturers of traditional medicinals.

By no later than 01 July 2019, manufacturers of oriental drugs that are granted a Certificate of satisfaction of conditions for pharmaceutical business before the effective date of this Decree must be in compliance with good manufacturing practice for traditional drugs. Prior to this cutoff date, such establishments must maintain the conditions strictly in accordance with those based on which the Certificate was issued.

5. By no later than 01 January 2021, manufacturers of excipients, capsule shells, establishments manufacturing, processing medicinal materials, traditional medicinals must be in compliance with the respective good manufacturing practice for drugs, drug raw materials.

Article 142. Implementation road map for good practice adoption by establishments operating in pharmaceuticals for noncommercial purposes

1. As from the effective date of this Decree, establishments that have been operating in pharmaceuticals for noncommercial purposes, referred to in point a clause 1 Article 35 of Pharmaceutical law, that are not yet fully compliant with good practice shall only be allowed to operate within the scope commensurate with their level of compliance with the respective good practice and must be in full compliance with the respective good practice according to the implementation roadmap set out as follows:

a) By no later than 01 July 2019, establishments storing, stockpiling, supplying vaccines must be in full compliance with the respective good practice commensurate with their operating scope;

b) By no later than 01 January 2021, establishments operating in pharmaceuticals for noncommercial purposes, except for the cases stipulated in point a of this clause must be in full compliance with the respective good practice commensurate with their operating scope.

2. As from the effective date of this Decree, establishments operating in pharmaceuticals for noncommercial purposes referred to in point a clause 1 Article 35 of Pharmaceutical law that initiates their pharmaceutical operations or has pharmaceutical operations added to their operating scope of the for the very first time must be in compliance with the respective good practice commensurate with the specific type of operation.

Article 143. Transitional provisions

1. Administrative dossiers required under the provisions of Pharmaceutical law No. 34/2005/QH11, related guiding documents and not relevant to the provisions of clause 2 Article 115 of Pharmaceutical law no. 105/2016/QH13 that are submitted before the effective date of this Decree shall be governed the provisions of Pharmaceutical law no. 34/2005/QH11 and related guiding documents, unless the concerned establishments wish to follow the provisions of Pharmaceutical law no. 105/2016/QH13

2. By no later than the 1st of July 2018, on submission of applications for renewal of Certificate of marketing registration for imported drugs, establishments acting as registrant must submit application dossier for assessment of GMP conformity of the manufacturing facility concerned.

3. Import and export licenses for drugs and raw drug materials, drug and raw drug material import and/or export orders issued according to provisions of the Pharmaceutical Law No. 34/2005/QH11

and relevant documents guiding its implementation shall continue to be effective until such licenses expire.

For the drugs and raw drug materials which are governed by this clause and imported/exported into/out of Vietnam where customs clearance is completed before 1 January 2018, such customs clearance dossiers shall be handled in accordance with the provisions of Pharmaceutical law 34/2005/QH11 and related guiding documents, or in accordance with the provisions of this Decree from the day it becomes effective.

4. For the drugs and raw drug materials for which a Certificate of marketing registration was granted or which were announced before the effective date of this Decree and which are imported to Vietnam with customs clearance completed before 1 January 2018, such customs clearance dossiers shall be handled in accordance with the provisions of Pharmaceutical law 34/2005/QH11 and related guiding documents, or in accordance with the provisions of this Decree from the day it becomes effective.

5. Drugs business establishments operating in controlled drugs shall comply with the following provisions:

a) Business establishments operating in controlled drugs that are those stipulated in point a and b clause 26 Article 2 of the Pharmaceutical Law shall be allowed to continue operations until 30 June 2018 inclusive. Past this timeline, business establishments wishing to continue operations shall secure a Certificate of satisfaction of conditions for pharmaceutical business covering the trading of controlled drugs in its operating scope in line with its actual operational activities according to the provisions of Section 4 Chapter III of this Decree.

b) Business establishment operating in controlled drugs that are those stipulated in point c, d, clause 26 Article 2 of Pharmaceutical law shall be allowed to continue operations until the expiry date as recorded on the Certificate of satisfaction of conditions for pharmaceutical business or the expiry date of Certificate of good practice in the case where the former Certificate does not specify an expiry date. Past this timeline, business establishments wishing to continue operations shall secure a Certificate of satisfaction of conditions for pharmaceutical business covering the trading of controlled drugs in its operating scope in line with its actual operational activities according to the provisions of Section 4 Chapter III of this Decree.

6. By no later than 1st July 2018, establishments retailing the drugs belonging to the List of restricted retail drugs must comply with the provisions of clause 2, Article 55 of this Decree.

7. By no later than 1st March 2018, a Certificate of marketing registration must be obtained for a medicinal material or its specification must be publicized in accordance with the provision of clause 1 and 2, Article 93 of this Decree before it can be marketed in Vietnam.

8. By no later than 1st January 2019, before being marketed in Vietnam a Certificate of marketing registration must be obtained for a capsule shell in accordance with the provision of clause 4, Article 93 of this Decree. By no later than 1st January 2021, before being marketed in Vietnam a Certificate of marketing registration must be obtained for an excipient in accordance with the provision of clause 3, Article 93 of this Decree..

9. By no later than 1st January 2018, drug retailers operating on the premises of medical service establishments must comply with the provisions of Article 136 of this Decree.

10. Receipt of drug information content, Confirmation certificate of drug advertisement content that are issued before the effective date of this Decree shall continue to be effective until their expiry date.

11. Establishments that have been granted a Business license for foreign enterprise in drugs and drug raw materials in Vietnam, Business license for foreign enterprise in vaccines biologicals and raw materials for the manufacture of vaccines, biologicals in Vietnam which expires after 31 December 2016 shall be allowed to continue supplying drugs to Vietnam until the effective date of this Decree and supplying drug raw materials until 01 January 2018.

12. As from 01 January 2021, drug raw materials that are excipients used for the manufacture, according to registration dossier, of drugs for which a Certificate of registration in Vietnam has been granted, shall be allowed for importation according to the List published by the Minister of Health without having to undergo import licensing.

Article 144. Entry into force

1. This Decree takes effect from 1st July 2017.

2. The following documents shall be repealed:

a) The provisions on drug advertisement under Article 3, Decree 181/2013/NĐ-CP dated 14 November 2013 by the Government providing for implementation details of some articles of the Law on Advertisement;

b) Decree 79/2006/NĐ-CP dated 9 August 2006 by the Government providing for implementation details of some articles of the Pharmaceutical law;

c) Decree 89/2012/NĐ-CP dated 24 October 2012 by the Government amending and supplementing some articles of Decree 79/2006/NĐ-CP dated 9 August 2006 by the Government providing for implementation details of some articles of the Pharmaceutical law;

d) Decree 102/2016/NĐ-CP dated 1 July 2016 by the Government providing for drug business conditions.

3. In case any legal normative document or regulation referenced to in this Decree undergoes any change, supplementation or replacement, the new legal normative documents shall apply.

Article 145. Execution responsibilities

1. The Minister of Health shall be responsible for providing guidance for, and organize for the execution of this Decree.

2. Chairs of People's committees of provinces, central affiliated cities shall delegate to the local Health Departments the task of receiving, reviewing price redeclaration dossiers of domestically produced drugs from establishments having their manufacturing facilities located in the locality.

3. The online licensing publication, registration, application shall be implemented in accordance with the Minister of Health's specified roadmap.

4. Ministers, Heads of ministerial level agencies, Heads of Government-affiliated agencies, Chairs of People's Committees of provinces, centrally-affiliated cities shall be responsible for the implementation of this Decree./.

PRIME MINISTER

(Signed)

Nguyen Xuan Phuc

Table 2. Supporting documents for CTA, CTN and CTC applications to HSA

Supporting Document	Clinical Trial Authorisation (CTA)	Clinical Trial Notification (CTN)	Clinical Trial Certificate (CTC)
Clinical Trial Protocol	✓	✓	✓
Informed Consent Form (English)	✓	✓	✓
Investigator's Brochure	✓	✗	✓
List of Overseas Trial Site, where applicable	✓	✓	✓
Principal Investigator's CV	✓	✗	✓
Good Manufacturing Practice (GMP) Certificate[1]	✓	✗	✓
Certificate of Analysis (COA) for study batches of Investigational Products	✓	✗	✓
Chemistry. Manufacturing and Control (CMC) information, if requested by HSA	✓	✗	✓
Approved Product Label	✗	✓	✗
IRB Approval Letter	✗	✓	✗

Source : GUIDANCE ON MEDICINAL PRODUCT REGISTRATION IN SINGAPORE, HSA

Central Drugs Standards Control Organization
Directorate General of Health Services
Ministry of Health & Family Welfare
(Office of DCGI)

FDA Bhavan, Kotla Road,
New Delhi-110002.

Dated: 26th March, 2016

NOTICE

The Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India, 2012 are in the process of revision. The proposed revised Guidelines on Similar Biologics 2016 are uploaded for suggestions/ comments of the stakeholders.

All the stakeholders are requested to submit their suggestions or comments to the Office of Drugs Controller General (India) by 30th April, 2016 through e-mail (dci@nic.in) or fax (no.011-23236973) or by post to the address as under:

Central Drugs Standards Control Organization HQ,
Office of DCG (I),
FDA Bhavan,
Kotla Road, New Delhi – 110002

Office of Drugs Controller General (India)

Table 3. Labelling elements for registered investigational product which fulfils the three conditions, and registered auxiliary product

	Labelling Element	Wholesale Supply	Supply to Subject	
			Investigational Product	Auxiliary product
(a)	the words “For clinical trial use only” or similar wordings;	X	✓	X
(b)	a clinical trial reference code allowing identification of the trial, site, investigator and sponsor;	X	✓	X
(c)	the name of the person to whom the product is to be administered or the trial subject identification number;	X	✓	✓
(d)	the name, address and any identification number or logo of the licensed healthcare institution, licensed retail pharmacy, or trial site where the product is supplied or dispensed;	X	✓	✓
(e)	the name of the product, being the appropriate non- proprietary name and the proprietary designation;	✓	✓	✓
(f)	where the appropriate non-proprietary name is included on the label of the product, the appropriate quantitative particulars of any active ingredient of the product;	✓	✓	✓
(g)	the directions for use of the product;	X	✓	✓
(h)	an appropriate control number, such as a serial number, batch number or lot number;	✓	✓	✓
(i)	the expiry date of the product;	✓	✓	✓
(j)	the date that the product is dispensed;	X	✓	✓
(k)	where the product is registered/ approved, the registration number/ product licence number assigned to the product by the Authority.	✓	✓	✓

Source : GUIDANCE ON MEDICINAL PRODUCT REGISTRATION IN SINGAPORE, HSA

MINISTRY OF HEALTH

No. 01/2018/TT-BYT

SOCIALIST REPUBLIC OF VIETNAM

Independence – Freedom - Happiness

Hanoi, 18 January 2018

CIRCULAR

Regulating the labeling of drugs, drug raw materials and package inserts

Pursuant to Pharmaceutical Law No. 105/2016 / QH13 of 6 Apr 2016;
Pursuant to the Government's Decree No. 54/2017 / ND-CP of 8 May 2017, detailing a number of articles and implementation measures of the Pharmaceutical Law;
Pursuant to the Government's Decree No. 43/2017 / ND-CP of 14 Apr 2017 on goods labeling;
Pursuant to the Government's Decree No.75/2017 / ND-CP of 20 Jun 2017 defining the functions, tasks, powers and organizational structure of the Ministry of Health;
At the proposal of the Director of the Drug Administration of Vietnam,The Minister of Health hereby issues the Circular on the labeling of drugs, drug raw materials and package inserts.

Chapter I
GENERAL PROVISIONS

Article 1. Scope of regulation

1. This Circular provides for the contents, the labeling of drugs, raw materials and the package inserts of drugs in market circulation; the revising of drug shelf life for reasons of national defense, security, preventing and combatting epidemics, mitigation of natural disasters'consequences.
2. The following drugs, drug raw materials are not in scope of regulation of this Circular:
a) Drugs, drug raw materials for export having no registration certificate for marketing in Vietnam;
b) Drugs imported for non-commercial purposes as stipulated under clause 1 Article 75 of the Government's Decree No. 54/2017/ND-CP of 8 May 2017, detailing a number of articles and implementation measures of the Pharmaceutical Law (hereinafter referred to as Decree No. 54/2017/ND-CP);
c) Drugs imported to meet urgent requirements in national defense, security, preventing and combating epidemics, mitagation of natural disasters' consequences as stipulated under clause 1 Article 67 of Decree No. 54/2017/ND-CP.

Article 2. Interpretation of terms

In this Circular, the terms below are construed as follows:
1. *Commercial packaging* of drugs meansthe enclosure containing the drug and package insert that are marketed together with the drug; commercial packaging of drugs covers primary packaging, outer packaging or intermediate packaging (if any).
2. *Secondary packaging* means an enclosure wrapping one or several drug units covering the primary packaging and placed inside an outer packaging.
3. *Lot number* means a sign in alphabetical and/or numerical characters or a combination of both to identify a lot of drugs, drug raw materials and to allow for the traceability of the entire origin of a lot of drugs, drug raw materials including all steps in the manufacturing process, quality control and marketing operations of such lot of drugs, drugs raw materials.
3. *Original label* of drugs, drug raw materials means the label that is initially presented by the manufacturer, affixed on the commercial packaging of the drug, drug raw material.

Article 3. Location of the label of drugs, drug raw materials and package insert

1. The location of a drug, drug raw material labeling shall follow the provisions of Article 4 of the Government's Decree No. 43/2017/ND-CP of 14 Apr 2017 on the goods labeling (hereinafter referred to as Decree No.43/2017/ND-CP).
2. The package insert shall be an integral part of the drug labeling and contained inside the outer packaging of a drug. In cases of drugs that do not have an outer packaging, the package insert must be printed on or affixed to the drug primary packaging.

Article 4. Size of labels, size of letters and numbers on labels, colors of letters, symbols and images on labels, presentation language of labels and package insert

1. The label size, the size of letters and numbers, color of letters, symbols and images on the label of drugs, drug raw materials and package insert shall comply with the provisions of Article 5 (except for the contents specified in point b, clause 2 of Article 5 and Article 6 of Decree No. 43/2017/ND-CP.
2. The mandatory contents of drug, drug raw material labels and package inserts must be in Vietnamese language, except for a number of contents permitted to be presented in other languages of Latin origin as stipulated under clause 4 Article 7 of Decree No. 43/2017/ND-CP.

Article 5. Adding supplementary labels, supplementing, replacing package inserts in in Vietnam

1. With regard to drugs, drug raw materials imported to Vietnam the label of which has not covered all the contents of the label that was appoved by Health Ministry, the importer shall have to add supplementary label to ensure consistency with the Ministry of Health's approved label before placing the drugs on the market and the original label must be retained intact.

2. The following cases are allowed for customs clearance in order to add or replace package inserts with a Vietnamese language version in Vietnam:
a) Imported drugs already licensed for marketing in Vietnam the commercial packaging of which already includes a Vietnamese package insert but the content of which has not been updated in accordance with Ministry of Health's requirements, except for the cases of drugs not requiring package inserts stipuated in points a, b, c and d clause 1, Article 13 of this Circular;
b) Imported drugs not yet licensed for marketing in Vietnam the commercial packaging of which does not include a Vietnamese package insert, except for the cases of drugs not requiring package inserts stipuated in points a, b, c and d clause 1, Article 13 of this Circular;

3. Principles, places to carry out the adding of supplementary labels, supplementation or replacement of package inserts in Vietnam:
After customs clearance, the imported drugs, drug raw materials stipulated under clause 1 and clause 2 of this Article must be have a supplementary label added, the package insert must be supplemented or replaced with a Vietnamese version according to the following principles:
a) The adding of supplementary labels must be carried out at a Good storage practice for drugs, drug raw materials (GSP)-compliant storage facility of the very same importer importing the drugs, drug raw materials;
b) The supplementation or replacement of package inserts with a Vietnamese version shall be carried out at a secondary packaging facility of a Good manufacturing practice for drugs (GMP)-compliant establishment according to the scope of the Certificate of satisfaction of conditions for pharmaceutical business;

c) The process of supplementary label adding, replacing or supplementing package inserts with Vietnamese versions should not impact the quality of the drugs, drug raw materials.

4. With regard to the supplementation or replacement of package inserts stipulated in point b clause 3 of this Article, the secondary packaging facility carrying out the supplementation, replacement must fully comply with Good manufacturing practices' principles and starndards and report [the work] to Ministry of Health for pharmaceutical regulatory, inspection, auditing purposes, specifically:

a) The report must be submitted within one (1) month from the date of completion of the package insert supplemation or replacement in Vietnam;

b) The report shall cover the following information: name of the importer; drug name; the number of import license; lot number; date of manufacture; expiry date; quantity of drugs to which package inserts are supplemented or replaced.

5. The organizations responsible for drug labeling shall be responsible for providing supervision, coordinating with the entity carrying out the supplementary label adding, the package insert supplementing or replacing and be responsible for the quality of the drugs, drug raw materials throughout the process.

Article 6. Responsibility for the labeling of drugs, drug raw materials and package inserts

1. The organization responsible for labeling drugs, drug raw materials, including supplementary labels, package inserts must ensure the integrity, clarity, accurary of the labeling to reflect the true nature of the drugs, drug raw materials.

2. For domestically manufactured drugs and raw materials:

a) The manufacturer, the registrant of drugs, drug raw materials shall be responsible for the labeling, package inserts of the drugs, drug raw materials it manufactures, registers for marketing;

b) Medical service establishments allowed to process, prepare and weigh (assemble) traditional drugs according to the provisions of clause and clause 2, Article 70 of Pharmaceutical Law; to produce, compound drugs according to the provisions of clauses 2 and clause 3, Article 85 of Pharmaceutical Law, shall be responsible for labeling drugs they manufacture, prepare, assemble, produce, coumpound;

c) Drugstores providing extemporaneous prepraration according to the provisions in point b clause 1 Article 47 of Pharmaceutical Law shall be responsible for labeling the drugs they coumpound.

3. For imported drugs, imported drug raw materials:

a) Drug importers, drug registrants shall be responsible for the labeling, package inserts of the drugs for which a marketing registration certificate has been issued that they import;

b) Importers, registrants of drug raw materials shall be responsible for the labeling of the drug raw materials they import;

c) Importers shall be responsible for drug labeling, package inserts of the drugs not yet having a certificate of marketing registration that they import.

4. With respect to the drugs that are divided, repacked into smaller package units during wholesaling, retailing: the business establishment performing the repacking shall be responsible for the supplementary labeling in accordance with the provisions of clause 2 and clause 3 Article 7 of this Circular.

Chapter II
CONTENT OF DRUG LABELS, PACKAGE INSERTS

Section I
MANDATORY CONTENT OF DRUG LABELS

Article 7. Labels on outer packaging of drugs, drug raw materials

1. The outer packaging label of a drug must show the following contents:

a) Drug name;

b) Dosage form;

c) Composition, strength, weight or concentration of pharmaceutical substances, medicinal materials in the drug formulation;

d) Packaging specification;

đ) Indications, method of administration, contraindications;

e) Number of certificate of marketing registration or number of import license (if applicable);

g) Lot number, manufacturing date, expiry date, quality specification, storage conditions;

h) Warnings and precautions;

i) Name, address of manufacturer;

k) Name, address of importer (in the case o imported drugs);

l) Origin of the drug.

2. The outer packaging label of a drug raw material (including medicinal materials, traditional medicinals, semi finished medicinal materials, semi finished drugs) must show the following contents:

a) Name of the drug raw material;

b) Weight or volume of the drug raw material in the smallest package unit;

c) Quality specification of the drug raw material;

d) Number of certificate of marketing registration or number of import license (if applicable);

đ) Lot number, manufacturing date, expiry date, storage conditions of the drug raw material;

e) Name, address of manufacturer;

g) Name, address of importer (in the case of imported drug raw materials);

l) Origin of the drug raw material.

3. Labels of controlled drug raw materials (including semi finished drugs):

Apart from the contents stipulated under clause 2 of this Article, raw materials being pharmaceuticals, medicinal material or semi finished drugs containing pharmaceutical substances, medicinal materials belonging to the List of narcotic, psychotropic substances, drug precursors, hazardous drug raw materials, hazardous medicinal materials, radioactive drug raw materials, must have outer packaging printed with the wording "Narcotic raw materials", "Psychotropic raw materials", "Drug precursor raw materials", " Hazardous raw materials", "Hazardous medicinal materials "," Radioactive materials" respectively.

The wording "Narcotic raw materials", "Psychotropic raw materials", "Drug precursor raw materials", " Hazardous raw materials", "Hazardous medicinal materials ","Radioactive materials" must be printed in Bold in a textbox and on the label’s facesheet bearing the name of the drug raw materials.

4. Where the contents stipulated in clause 1 of this Article cannot be fitted into the outer packaging label, the contents stipulated in point đ clause 1 of this Article may be summarily presented as follows: indications, contraindications and other information: see enclosed package insert".

Article 8. Secondary packaging labels

1. The secondary packaging label must show at a minimum the following contents:
 a) Name of the drug;
 b) Lot number;
 c) Expiry date.

2. In cases where the secondary packaging is made of a transparent material that allows for information on the primary packaging label to be seen through, such secondary packaging does not have to be printed with the contents stipulated in clause 1 of this Article.

Article 9. Primary packaging labels of drugs, drug raw materials

1. Labels of drug primary packaging must show all the following mandatory contents:
 a) Drug name;
 b) The quantitative composition, strength, concentration or volume of pharmaceutical substances, medicinal materials in the drug formulation;
 c) Lot number;
 d) Expiry date;
 đ) Name of manufacturer.

2. Labels of primary packaging of drug raw materials

With regard to drug raw materials that have an outer packaging showing all the contents stipulated in clause 2 and clause 3 Article, unless they are removed from the outer packaging for retailing, labelling on the drug primary packaging shall not be required.

3. With regard to drugs, drug raw materials having no outer packaging, the contents stipulated for outer packaging labels under Article 7 of this Circular must be printed in full on the primary packaging.

Article 10. Format of supplementary labeling

1. Supplementary labels must show all the mandatory contents in Vietnamese language that are not yet available or still missing from the original label in accordance with the provisions of Article 7 of this Circular.
2. Where the size of supplementary labels is to small to fit all the mandatory contents stipulated under clause 1 of this Article, some of such contents shall be presented as follows:
a) Indications, method of administration, contraindications and other information: see enclosed package insert;
b) Cross reference of manufacturing date, expiry date, lot number that are presented on the original label;
c) Number of certificate of marketing registration or number of import license: may be left blank but number of certificate of marketing registration or import license (if applicable) must be filled in before placing the drug on the market.

Article 11. Drug labeling in some other cases

1. Traditional drugs that are processed, prepared and weighed (assembled) according to the provisions of clause 1 and clause 2 Article 70 of Pharmaceutical law and drugs manufactured, prepared according to the provisions of clause 2 and 3, Article 85 of Pharmaceutical law must be

labeled with the following mandatory contents, except for the cases stipulated in clause 3 of this Article:

a) The outer packaging label of traditional drugs, drug preparations must show the following contents:

- The contents stipulated in points a, b, c, d, đ, g and h clause 1 Article 7 of this Circular;
- Name, address of the medical service establishment manufacturing, preparing processing, formulating weighing (assembling) drugs.

b) The primary packaging label of traditional drugs must dispaly the following mandatory contents:

- The contents stipulated in points a, b, c and d clause 1 Article 9 of this Circular;
- Name of the medical service establishment manufacturing, preparing processing, formulating weighing (assembling) drugs.

c) With regard to traditional drugs, drug preparations that do not have an outer packaging, the contents required for outer packaging stipulated in point a clause 1 of this Article must be printed on the primary packaging.

2. Extemporaneously compounded drugs sold at drugstores according to the provision of point b clause 1 Article 47 of Pharmaceutical law must have an outer packaging label or primary packaging label showing the following mandatory contents:

a) Drug name, dosage form;
b) Active ingredient, strength or concentration;
c) Compounding date, expiry date, storage conditions;
d) Name, address of the compounding drugstore;
đ) Name of the patient subject of the prescription;
e) Cautions with regard to drugs belonging to the list of controlled drugs.

3. Traditional drugs that are are weighed, assembled per prescription according to the provisions clause 1 Article 70 of Pharmaceutical law are not required to be labeled under this Circular but must have an outer packaging bearing the patient's full name and age to avoid mix up when dispensing.

4. Drugs without a certificate of registration for marketing in Vietnam for which an import license is issued for the purposes of bioequivalence studies, bioavailability testing, registration sample, test samples, scientific research, displays at exhibitions, trade fairs, are not required to be labeled with the mandatory contents stipulated under Article 7 and Article 8 of this Circular, but the original label must be retained intact and must have a supplementary label added as per the followings:

a) Drugs used for bioequivalence studies, bioavailability testing, test samples, scientific research studies must be printed with "Drugs for research purposes";

b) Drugs used as sample in drug registration must be printed with "Sample for drug registration";

c) Drugs used for displays at exhibitions and trade fairs must be printed with "Drug sample for display".

5. Drug raw materials without a certificate of registration in Vietnam for which an import license is issued for purposes of drug registration, test sample, sample for research studies, displays at exhibitions, trade fairs under the provisions of clause 3, Article 60 of Pharmaceutical law are not required to be labeled with the mandatory contents stipulated under Article 7 and Article 8 of this Circular but the original label must be kept intact.

6. Drug raw materials being pharmaceutical substances, excipients and semi-finished drugs not yet licensed for marketing in Vietnam that are imported for the manufacture of drugs already

licensed for marketing in Vietnam according the registration dossier must have a supplementary label showing the contents stipulated under clause 2 and clause 3 Article 7 of this Circular (except importer's name and address). If these mandatory contents are already presented on the original label in other Latin based languages, no supplementary labeling is required.

7. Drugs imported under the provisions of point b clause 1 Article 68 of Decree No. 54/2017/ND-CP are not required to have Vietnamese language labels according to the provisions of this Circular but the original label must be retained intact.

Section II
CONTENT OF PACKAGE INSERTS

Article 12. Content of package inserts

The drug package insert shall cover the following contents:

1. Drug name
2. Cautions and instructions
3. Composition of formulation
4. Dosage form
5. Indications
6. Administration, dosage
7. Contraindications
8. Warnings and precautions
9. Use in pregnant and breastfeeding women
10. Effects of drugs on ability to drive, operate machinery
11. Drug interaction, drug incompability
12. Unwanted side effects
13. Overdosage and management
14. Pharmacodynamic properties (not required for non prescription drugs, medicinal material drugs, traditional drugs)
15. Pharmacokinetic properties (not required for non prescription drugs, medicinal material drugs, traditional drugs)
16. Packaging specification
17. Storage conditions, shelf life, quality specification
18. Manufacturer's name and address

Article 13. General requirements of package inserts

1. Drugs circulated on the market, drugs manufactured, prepared, processed at medical service establishments as stipulated under clause 1 Article 11 of this Circular must have a Viettnamese language package insert, except the following cases:

a) Drugs manufactured, processed, formulated per recipes, prescriptions according to the provisions of clause 1 Article 70 and clause 2 Article 85 of Pharmaceutical law for the use and direct retail per prescriptions at the same medical service establishment;

b) Drugs compounded to prescriptions and retailed at drugstores according to the provision of point b clause 1 Article 47 of the Pharmaceutical law;

c) Drugs without a certificate of registration for marketing in Vietnam that are licensed for importation for purposes of bioequivalence studies, bioavailability testing, as sample for drug registration, test samples, for scientific research, displays at exhibitions, trade fairs;

d) Drugs imported according to the provisions of point b clause 1 Article 68 of Decree No.54/2017/ND-CP;

đ) Non prescription drugs with labels showing all package insert contents stipulated under Article 12 of this Circular.

2. The original foreign language package insert of the drugs stipulated in point d clause 1 of this Article must be retained intact.

3. Drugs having the same name, active ingredients, medicinal materials, dosage form, route of administration, indications and manufacturer but come in multiple different volumes, strengths, concentrations or quantities, with different packing forms and which are all licensed for marketing shall be allowed to share one same package insert. Where the contents differ among different strengths, concentration, such differences must be specified for each of the respective strengths, concentrations, volumes, packaging forms.

4. Within each outer packaging of a drug there must be at least one Vietnamese language-package insert enclosed. If the drug does not have an outer packaging, there must be at least one package insert for every primary packaging unit.

Chapter III
LABELING FORMAT AND PACKAGE INSERTS

Article 14. Format for presenting names of drugs, drug raw materials

1. The name of a drug, drug material must be prominently placed, clearly legible and of the largest type size relative to other mandatory contents of the label and package insert.

2. The name of a drug, drug raw material shall be printed in Roman alphabet and may be additionally presented in numerals, roman numerals or certain other Greek alphabet (such as alpha, beta).

3. The name of a drug shall be presented under trade name or international non proprietary name. Traditional drugs belonging to the list of Ministry of Health-recognized drugs may be presented under trade name or the name of the traditional remedy recognized by Ministry of Health, except for traditional medicinals. Trade names of drugs must follow the following principles:

a) Not of advertising character;

b) Not causing confusions regarding the composition, origin of the drug. If a drug contains several pharmaceutical substances, medicinal materials, the name of individual components shall not be used to name the drug;

c) Not misleading or excessively characterizing as regards the drug's action, effectiveness, indications;

d) Not in contravention with Vietnam's fine customs and traditions;

đ)Not causing conflicts with protected intellectual property rights of other individuals, organizations;

e) Not duplicative of or similar to the names of drugs already granted a certificate of marketing registration of other registrants;

g) Not to name drugs of different active ingredients by the same name;

h) Not to name drugs by different names if they share all of the following elements: active ingredient, medicinal material, dosage form, route of administration, concentration, strength and manufacturer. This provision shall not apply to contract manufactured drugs that are manufactured in compliance with the Minister of Health's stipulations regarding drug contract manufacturing;

i) With regard to drugs of the same name, same manufacturer, same dosage form, same active ingredients but come in multiple strengths, concentratons, the drugs' name may be printed in conjunction with the respective strength, concentration for ease of identification and distinguishing the differences.

4. The name of drug raw materials (other than medicinal materials, semi finished drugs) shall be presented in accordance with the provisions of clause 2 Article 16 of this Circular.
5. Traditional drugs shall be named after the medicinal material's name as stipulated in clause 3 Article 16 of this Circular, with the group words "traditional drugs" preceding the medicinal material's Vietnamese name.
6. The name of medicinal materials shall be presented in accordance with the provisions of clause 3 Article 16 of this Circular.
7. The name of semi finished medicinal materials shall be presented in accordance with the provisions of clause 4 and clause 5 Article 16 of this Circular.
8. The name of semi finished drugs (other than semi finished medicinal materials) shall be presented in accordance with the provisions of clause 6 Article 16 of this Circular.

Article 15. Cautions and instructions

1. Cautions and instructions must be printed on the drug label, package insert, covering

a) The statements "Keep out of reach of children", "Read instructions carefully before use";

b) For prescription drugs:

- On the outer packaging label: the "Rx" symbol must be marked on the upper left corner of the drug name and the wording "prescription drug";

-On the package insert: the "Rx" symbol must be marked on the upper left corner of the drug name; with the wording "Prescription only drug"

c) For controlled drugs or other drugs:

- Radioactive drugs must be marked with the wording "**RADIOACTIVE DRUGS**" in bolded capital letters;

- Drugs belonging to the list of hazardous drugs according to Ministry of Health's classiication: must be marked with "**HAZARDOUS DRUGS**" in bolded capital letters;

- Drugs to support state health programs: marked with "Program drugs, not for sale";

- Donation drugs, drugs for humanitarian assitance: marked with "Donation drugs, not for sale";

- Drugs for clinical trials: The label must display the statement "Drugs for clinical trials. Use for other purposes prohibited";

- For biosimilars: the statement "name of the biosimilar" is a biologic similar to the reference biologic "name of the reference biologic" must be printed.

d) Other cautions and instructions for specific types of drugs are as follows:

- Injectable drugs: The label of the injectable or infusion drugs must show in full or in abbreviated form the specific route of administration e.g. intramuscular injection (imi), subcutaneous injection (sq), intravenous injection (ivj), intravenous infusion (ivi) or other specific injection routes;

- Eye drop, eye ointment: The wording "eye drops" or "eye ointment" must be printed. Nose drops must be printed with "nose drops"; ear drops printed with "ear drops";

- Drugs for external application must be printed with "For external application"; Drugs packed in ampoules for oral administration must be printed with "Not for injection";

- Drugs requiring shaking well before use (e.g. suspension drugs, powder drugs, multidose granules for suspension reconstitution or dosage forms prone to precipitation, sedimentation or layering after reconstitution) must be marked with "Shake well before use".

2. Format for presenting of cautions and instructions:

a) The instruction statements, caution signs must be clearly printed on the outer packaging labels or supplementary labels and the package insert. The content printed must be easily recognizable under normal viewing conditions;

b) For package inserts: The cautions and instructions specified in point a, b and c clause 1 of this Article, except for the Rx, must be printed immediately under the drug name;

c) If a drug warrants multiple cautions, all such cautions must be fully presented.

Article 16. Formulation of drugs and semi finished drugs

1. General provisions:

a) The outer package labels of drugs, semi finished drugs:

- The name and strength, weight or concentration of each component of pharmaceutical substances, medicinal materias in the formulation of a smallest unit dose or package unit of the drug, semi finished drug must be presented in full;

- For vaccines: The active ingredient composition of each unit dose must be indicated;

- For biologics: The strength of biologics should be expressed in terms of units of weight, units of biological activity or international units per biologic;

- For traditional drugs, medicinal material drugs, semi finished traditional drugs, semi finished medicinal material drugs: Each medicinal material component should be presented in its Vietnamese name, scientific name presentation is not mandatory;

- Presentation of composition, strength, weigth, volume or concentration of excipient components is not mandatory;

- In particular for traditional drugs belonging to Ministry of Health's List of state secrets and intergenerational family drugs, omission on the product's commercial packaging label of certain medicinal material components, and their respective strength, weight, volume in the formulation is allowed. In this case, the statement "Formulation of the drug is state secret" or "Formulation of the drug is intergenerational family secret" must be printed on the product's outer packaging label.

b) Primary packaging labels of drugs, semi finished drugs:

- Drugs, semi finished drugs in the form of single pharmaceutical substance, single medicinal material component or combination of 03 (three) or fewer pharmaceutical substances, medicinal materials: the composition of the drug, semi finished drug must be presented in full in accordance with the provision of point a of this Clause;

- Drugs, semi finished drugs being a combination of more than 03 (three) pharmaceutical substances, medicinal materials: presentation of the full composition is not required. If the composition is presented the presentation must follow the provision of point a of this clause.

- If the drug is in liquid form, the volume on the drug label must be expressed per smallest package unit.

c) Package inserts:

- The name and strength, weight or concentration of each component of pharmaceutical substance, medicinal material in the formulation by the smallest unit dose or package unit with the wording "Pharmaceutical substance composition" or "Active ingredient composition" preceding the name of the pharmaceutical substances, medicinal materials must be presented;

- The excipient components of the formulation with the wording "Excipient composition:" preceding the name of the excipients must be presented. It is not mandatory to list the excipient components already evaporated or dissipated during the manufaturing process nor the weight, volume, strength or concentration of each excipient component;

- For vaccines: The active ingredient composition per smallest unit dose must be specified;

- For biologics: The strength of biologics should be expressed in units of weight,units of biological activity units or international units per biologic;

- For traditional drugs, medicinal material drugs: Each medicinal material shall be presented in its Vietnamese name, immediately followed in parentheses by its scientific name printed in italics;

- In particular for traditional drugs belonging to Ministry of Health's List of state secrets and intergenerational family drugs, omission of certain medicinal material components, and their respective strength, weight, volume in the formulation is allowed. In this case, the statement "Formulation of the drug is state secret" or "Formulation of the drug is intergenerational family secret" must be printed in the place of formulation.

2. Format for presenting medicinal material names, excipient names:

a) The name of the pharmaceutical substances, excipients shall be presented according to their international non proprietary name or scientific name;

b) The name of pharmaceutical substances, excipients does not require translation into Vietnamese.

3. Format for presenting names of medicinal materials, traditional medicinals:

a) Vietnamese name:

- The name of medicinal materials, traditional medicinals shall be presented according to the Vietnamese naming convention of Vietnam pharmacopoiea or as listed on the Ministry of Health's list of drugs, drug raw materials;

- If the medicinal material's Vietnamese name is not featured in Vietnam pharmacopoeia or nor in the Ministry of Health's published list of drugs, drug raw materials: use the Vietnamese names in the book " Medicinal plants and medicinals of Vietnam" authoored by Do Tat Loi; the book "1000 Medicinal plants and animals" by the Institute of Medicinal Materials; In this case, the name to be used must be approved by the Minister of Health upon advice from the Ministry of Heath's consultative committee for certificate of marketing registration.

- Where the name of an imported medicinal material cannot be translated into Vietnamese, the name used in the exporting country should be used, along with the scientific name of the medicinal material;

- Where different parts of a medicinal material, traditional medicinal are used in the manufacture of different drugs, the specific part used or the name of such specific part must be indicated. E.g., lotus seed centers, meadowsweet, honeysuckle.

b) Scientific name (Latin name):

- The scienfitic name of the medicinal material, traditional medicinal from Vietnam pharmacopoeia, the Minister of Health’s list of medicinal materials, traditional medicinals shall be used, printed in italics;

- If the scientific name of the medicinal material, traditional medicinal is not featured in Vietnam pharmacopoeia or Ministrer of Health’s lists the respective name from foreign pharmacopoeias should be used.

4. Format for presenting medicinal material extracts, extract types and formulation:

a) Presentation of medicinal material extracts:

- Name, type of the extract and composition, concentration, strength or weight of medicinal material components must be fully presented;

- Trade name of the extract may be used if available, and the name of each medicinal component of the extract should also be presented in accordance with the provision of clause 3 of this Article;

- If the extract does not have a trade name, the word “extract” (in the case of single medicinal material component extract) or “medicinal material mixture extract” (in the case of multiple component extracts) should be printed before the components’ names.

b) Format for presenting types of extract:

- Extract types must be specified according to the 3 types: liquid extract, solid extract or dry extract according with Vietnam pharmacopoeia;

- If the types of extract is not specified, the moisture content must be indicated along with the name of the medicinal material extract name or the proportion of extract relative to the starting medicinal material quantity.

c) Format for presenting formulation of extracts:

- If there are quantitative criteria for the potency of the medicinal material or mixture of medicinal materials indicated in the respective monograph of Vietnam pharmacopoeia monograph or Ministry of Health's recognized foreign pharmacopoeias, the medicinal material extract should be presented along with its potency in % terms of the quantitated drug substance or individual substances of the mixure;

- If there are no quantitative criteria for the potency of the medicinal material or mixture of medicinal materials indicated in the respective monograph of Vietnam pharmacopoeia or Ministry of Heath's recognized pharmacopoeias, the medicinal material extract should be presented along with the respective starting medicinal material weight or the proportion of the extract relative to the starting medicinal materials (of drug manufacture standards);

- When a solvent is used to extract medicinal materials for production of extracts, unless the solvent is ethanol, water or a combination of ethanol and water, the name of the extracting solvent must be included along with the medicinal extract's name.

5. Format for presenting names of medicinal materials (other than medicinal material extracts) in drug formulation:

a) Name of semi finished medicinal material and composition, concentration, strength or weight of each medicinal material component of the semini finished product must be fully presented;

b) Format for presenting names of semi finished medicinal materials:

- Trade name of the semi finished product should be used if available and the name of each medicinal component of the semi finished medicinal material shall also be presented in accordance with the provision of clause 3 of this Article;

- If the semi finished medicinal material does not have a trade name, the medicinal material's name must be presented according to the provisions of clause 2 of this Article (in the case of single component semi finished medicinal material or "medicinal material mixture" (in the case of multiple component semi finished medicinal material), and the type of the semi finished medicinal material (e.g.: powder, granule)specified before the name of the medicinal material or before the wording "medicinal material mixture".

c) Format for presenting names of semi finished medicinal materials:

- If there are quantitative criteria for the potency of the medicinal material or mixture of medicinal materials indicated in the respective monograph of Vietnam pharmacopoeia monograph or Ministry of Health's recognized foreign pharmacopoeias, the medicinal material extract should be presented along with its potency in % terms of the quantitative drug substance or individual substances of the mixure;

- If there are no quantitative criteria for the potency of the medicinal material or mixture of medicinal materials indicated in the respective monograph of Vietnam pharmacopoeia or Ministry of Heath's recognized pharmacopoeias, the semi finished medicinal material should be presented along with the respective starting medicinal material weight or the proportion of the semi finished medicinal material relative to the starting medicinal materials (of drug manufacture standards);

6. Format for presenting names of semi finished drugs (other than semi finished medicinal material) in drug formulation:

a) Name of semi finished drugs and composition, concentration, strength or weight of pharmaceutical substance components must be fully presented;

b) Format for presenting names of semi finished drugs:

- Trade name of semi finished product should be used if available and the name of each pharmaceutical substance component of the semi finished product specified in accordance with the provision of clause 2 of this Article;
- If the semi finished drug does not have a trade name, the pharmaceutical substance's name must be presented according to the provisions of clause 2 of this Article (in the case of single pharmaceutical sustance semi finished product) or as "pharmaceutical substance mixture" (in the case of multiple pharmaceutical substance semi finished product), and the type of semi finished drug product specified (e.g.: powder, granule) before the pharmaceutical substance's name or before the wording "pharmaceutical substance mixture".

c) Format for presenting formulation of semi finished drugs: follow the provisions regarding semi finished drugs in clause 1 of this Article.

7. Units of strength, concentration, weight, volume:

The strength, concentration, weight, volume should be expressed in terms of units of strength, units of concentration, units of weigtht, units of volume, units of activity or other common units, as follows

a) Unit of weight: gram (abbreviated as g), miligram (abbreviated as mg), microgam (abbreviated as µg or mcg) or kilogram (abbreviated as kg). If the weight is less than 1 mg it should be expressed in decimal number (e.g.: 0,25mg);

b) Unit of volume: mililíter (abbreviated as ml), microlíter (abbreviated as µl or mcl), or liter (abbreviated as l or L). If the volume of the drug is smaller than 1 ml it should expressed in decimal numbers (e.g.: 0,5ml);

c) Other measuring units:

- Units of activity may be used according to international convention for certain special pharmaceutical substances;
- Measuring units internationalized and commonly used in healthcare sector such as IU and other units of activity according to international convention for certain special pharmaceutical substances and when translated in to Vietamese may cause confusion should be kept as originally presented, not required to be translated into Vietnamese.

d) If a pharmaceutical substance used in the formulation is in a form different from the form used for dosage calculation, the substance's strength, concentration, weight must be converted into dosage units of the outer package label and package insert. Pharmaceutical substance forms in use include base form, salt form, hydrated form or others.

Article 17. Dosage forms

1. Dosage forms shall be specified as: tablet, pill, hard capsule, injection solution, powder for solution for injection, suppository (placement position indicated), powder, granule or other dosage forms according to Viettnam pharmacopoeia or other commonly used International pharmacopoeias.
2. Package insert, in addition to the contents stipulated in clause 1 of this Article, must also include the following:

a) Description of the drug appearance in terms of color, size, volume, physical shape or (any) other particulars;

b) Scored tablet must be indicated whether it is intended to be breakable by half or not;

c) Information about pH and osmolarity (if applicable) must be indicated.

Article 18. Indications

The indications of a drug must be consistent with its uses, dosage form, route of administration. Information regarding indications must be clear, specific and contain the following:

1. Use of the drug: the uses of the drug, such as treatment, treatment adjuvant, prophylaxy (prevention), symptom reduction must be specified.
2. Intended users (if any): indications or indication limits on specific patient groups; which can be categorized by age groups or age ranges or specific age limits.
3. Additional conditions for safe, effective use of the drug (if any).

E.g., concomitant administration of other drugs or therapeutic methods to improve treatment effectiveness and reduce undesirable effects of a drug.

Article 19. Dosage and administration

1. Dosage:

a) Dosage must be specified for each route of administration or/and each indication.

- The timing and time intervals between uses in a day, method of administration to optimize effectiveness (e.g., taken with a lot of water, taken before meals) should be specified;

- The recommended total minimum dose, the total maximum dose, limits on duration of use (if applicable) should be indicated.

b) Dosage and administration for adults, for children (if applicable) should be specified. Dosage for children should be indicated by age groups or by bodyweight;

c) Cases requiring of special patient groups requiring dose adjustment (if applicable) such as children, elderly people, patients with kidney failure, patients with liver failure or other cases should be indicated .

2. Administration:

a) Route of administration, administration timing and method of administration to optimize effectiveness must be indicated:

- For injectable drugs, instructions on how to prepare, reconstitute the drug for injection and how to inject: intramuscular injection, intravenous injection, intravenous infusion, subcutaneous injection, deep subcutaneous or deep intramuscular injection and other ways; speed of injection or infusion should be specified (as necessary);

- Usage instructions for special patient groups requiring precautions referred to in point d clause 1 of Article 15 of this Circular must be provided;

- For concoctions: instructions on how the drug should be used, taken (water used in, tools for, concoction, concoction method, tincture preparation method, temperature and time duration required), what to avoid and other precautions while taking the drug.

b) For prescription drugs:

Apart from the provisions of point a clause 2 of this Article, the following information on administration in children, special patient groups and other precautions (as neccessary) must be provided:

- Dosage must be specified by age groups. Dosing should be by bodyweight or body surface area (mg/kg or mg/m2) or by corresponding dose intervals. For the drugs that can be used in children for the same indications with adults, dosage and admistration method must be specified.

- With regard to drugs that do not come in dosage forms intended for children, manufacturer's recommendations on ways to make the drug suitable for the consumption of children from a certain age must be provided;

- With regard to drugs that do not have indications intended for children of one or all age groups, dosage and administration method of the drug must be presented using one of the following wording:

+ Safety and effectiveness of the drug on children of certain age (by months or years), or other relevant patient groups) e.g., by sex, body weight) have not been established;

+ It is not recommended to use the drug in children of certain age (by months or years), or other relevant patient groups (e.g., sex, body weight) due to issues of safety and effectiveness of the drug;

+ The drug should not be used for certain indications in children of certain age (by months or years) (or other relevant patient groups, e.g. by sex, body weight).

- Cases requiring precautions regarding dosage and administration (if applicable):

+ When discontinuing the use of the drug, missing a dose, taking the drug with food and water, resuming the use of the drug after a treatment course;

+ Adjusting dosage when using with other coadministered drugs, adjusting dosage to suit patients' conditions (dose adjusting based on clinical signs and symptoms and/or test results of renal function, liver function);

+ Preventive measures against specific adverse events (e.g., taking antiemetic medication prior to the use of cancer treatment drugs), non serious adverse reactions that are common with initial doses;

+ Special recommendations for healthcare personnel or patients regarding the handling and administration of the drug (if applicable), information on other delivery methods, especially the gastrointestinal intubation (subject to information availability) for parenteral drugs, information on the rate of drug injection or infusion should be clearly stated.

3. Special handling precautions before and after use

Additional instructions should be provided for drugs requiring handling before and after use, namely:

a) Handling before use (if applicable):

- Specify how to prepare the drug before use (reconstitution or dilution);

- Describe protective measures for persons preparing the drug;

- Specify the external appearance of the drug before reconstitution or dilution, characteristics of the drug after reconstitution in the case of drugs requiing reconstitution before use.

b) Handling after use (if applicable):

- Precautions regarding the disposal of the drug after use in special cases such as cytotoxic drugs, preparations containing living organisms and other specifically regulated cases;

- If there are special instructions or handling precautions required of healthcare personnel, the statement "No special handling precautions required after use" should be added.

Article 20. Contraindications

1. For drugs with contraindications cases in which the drug cannot be used must be specified.
2. With regard to drugs that are contraindicated in children, the children’s age ranges (by months or years) or other relevant patient groups (e.g. by sex, body weight) must be specified for each of the contraindications.

Article 21. Warnings and precautions

1. Preventive steps, precautions for use, special recommendations for use in children, patients with chronic conditions must be indicated (subject to information availability).

2. Situations warranting precautions:

a) Test results or clinical conditions of patients that require evaluation before administering the drug, measures necessary to reduce risk of adverse reactions during use;

b) Serious adverse events that warrant warnings to healthcare personnel;

c) Measures for prevention and early detection of symptoms of serious adverse reactions;

d) Risks associated with starting or stopping treatment;

đ) Patients with predisposing risks of adverse reactions to the drug class (often serious and commonly occuring reactions);

e) Clinical signs, symptoms or tests requiring monitoring during treatment. Interference with laboratory tests by use of the drug.;

g) Warnings and precautions for children patients regarding safety associated with prolonged duration of use (e.g., impacts on the child's development, neuropsychological , sexual development and others);

h) Warnings regarding known adverse effects associated with excipients or residual substances in the drug. Warning statements relating to excipients must be provided under this section or under the section on warnings and precautions for use of the drug;

i) Warnings regarding the ethanol component in the drug formulation;

k) Hazards associated with potential errors during use of the drug.

3. Biosimilars:

Warnings regarding the risks involved in the replacement, substitution between reference biologics and biosimilars during treatment.

Article 22. Use in pregnant and breastfeeding women

1. Use of the drug in pregnant women:

a) Information on the risks associated with the use of the drug in pregnant women should be included. If there is not enough information on the effects of the drug on pregnant women, the statement "There is no data on use in pregnant women, the drug should only be used if the benefits clearly outweigh any possible risks." must be included.

b) Recommendations for use in pregnant women should include the use in women who are likely to become pregnant or are using contraception, at different stages of pregnancy;

c) Additional information on the effects of the drug on the fetus, covering main possible impacts on the fetus. If there is no information on fetal toxicity, it must be clearly stated;

d) Recommendations for monitoring the fetus and neonate if the mother is using the drug during pregnancy (subject to information availability).

2. Use of the drug in breastfeeding women:

Description of specific scenarios such as stopping or continuing breastfeeding, stopping or continuing treatment (subject to information availability) should be provided.

Article 23. Effects on ability to drive, operate machinery

1. The effects of the drug on the ability to drive, operate machinery should be described using one of the following wordings: no effect or negligible effects, mild effects, moderate effects, severe effects.

If there is no evidence of drug effect on the ability to drive or operate machinery, the statement "There is no evidence of drug effects on the ability to drive or operate machinery." must be added.

2. Additional important information (if any) such as time the effects are expected to abate and absorptivity of the drug with continuing use should be provided.

Article 24. Drug interaction, drug incompability

1. Drug Interactions:

a) Information on interactions of drugs with other drugs and other types of interaction (e.g., alcohol, food, feed) that may affect the therapeutic action and effectiveness of the drug should be provided, such as:

- Drug interactions of clinically significance based on pharmacodynamic and pharmacokinetic studies on the drug;
- Consequences of drug interactions: clinical manifestations (if any), effects of drug interactions on drug concentration level in blood, pharmacokinetic parameters of active ingredients or active metabolites, effects of drug interactions on test results. Indicate how to handle the consequences of the interactions;
- Description of the mechanism of interaction if it is known. If there are no studies on drug interactions, it should be noted in this section;
- Other serious drug interactions such as drug adsorption into packaging, infusion kit.

b) For medicinal material drugs, traditional drugs, incompability of use (if any) must be clearly stated. e.g., avoid raw cold good when taking drug of heat preserving properties; If the drug is of cold reducing properties, avoid spicy stimulating food.

2. Drug compability:

a) Information on chemical and physical compatibility of the drug with other drugs when mixed or concomitantly administered, especially with reconstituted or diluted drugs prior to intravenous administration should be provided.

b) If there is no information on drug compatibility the statement: "Because there are no studies on drug compability, do not mix this drug with other drugs." should be added.

Article 25. Unwanted side effects

1. Information on discontinuation of use, possible adverse reactions warranting reporting to physicians, pharmacist or to Center for Drug Information and Monitoring of drug adverse reactions should be provided.

2. Apart from the contents stipulated in clause 1 of this Article, information on adverse reactions according to prescribed summary table of adverse reactions (if any) must be added:

a) Summary of adverse reactions by frequency: Very common (ADR $\geq$ 1/10), common (1/100 $\leq$ ADR <1/10), rare (1/1000 $\leq$ ADR <1/100), rare (1/1000 $\leq$ ADR <1/10000) and very rare (ADR <1/10000);

For medicinal material drugs, traditional drugs: listing possible adverse reactions should suffice, characterizing by frequency not required.

b) For pediatric patients, description must be specified for age-related characteristics and extent of adverse responses on pediatric population (if any); clinically significant differences between adults and children (or specific age groups) in regard to drug safety (if any). If the information has been mentioned elsewhere in the package insert, a cross reference should be made;

c) Any clinically significant differences (frequency of response, severity, recovery, and need for follow-up) in special populations (eg, the elderly , patients with liver failure, kidney failure, patients with other conditions should be clearly stated.

3. If there is no reporting or no evidence of adverse adverse reactions, the statement "No adverse reactions has been reported" and "Notify doctor immediately or pharmacist's immediately of adverse reactions occurred during use." should be added.

Article 26. Overdosage and management

1. Overdosage:

a) Description of symptoms and manifestations of overdose: specific symptoms and signs of acute poisoning, disability causing potential (if any);

b) If there is no information on overdose of the drug the statement "There is no data on overdose of the drug, do not exceed the dosing indicated of the drug" should be added.

2. Management:

a) Specific steps or ways to manage odversage, including monitoring, using agonist, antagonist drugs, detoxification,acceleration of drug elimination from the body. If there is no or not sufficient information, the statement "Actively monitor for timely response" should be added;

b) Information specific to special patient groups such as the elderly people, pregnant and breastfeeding women, children, people with liver impairment, kidney impairment, patients with comorbid chronic diseases (if available) should be provided.

Artile 27. Pharmacology, clinical information

1. Pharmacodynamics : covering the following:

a) pharmacological group and ATC code;

b)Description of mechanism of action for each of the approved indications;

2. Pharmacokinetics: covering the following

a) pharmacokinetic properties (absorption, distribution, metabolism, elimination and others) for each of the recommended dosage, concentration and dosage form of the drug;

b) Description of differences across elements (e.g., age, gender, weight, smoking status, patients with liver impairment, kidney impairment) affecting pharmacokinetic parameters. If such effects are clinically significant, they must be clearly presented in quantifiable parameters;

c) The correlation between dosage, concentration, pharmacodynamics parameters (including primary and secondary assessment criteria) and characteristics of patient population under study;

d) For pediatric patients: a summary of results from pharmacokinetic research in children of different age groups and in comparison with adults (if applicable). Dosage forms used in pharmacokinetic studies in children, uncertainties due to limitations of restricted use in pediatric patients should be noted.

3. Data from clinical trials, non-clinical trials (if applicable):

a) Summary of key findings from major clinical trials that support the approved indications of the drug (if applicable), including at least the following:

- Description of the main characteristics of the sample;
- Main evaluation criteria;
- Additional evaluation criteria (if any);
- Findings of the trials in relation to main criteria.

b) Information related to non-clinical trials (if applicable).

Article 28. Smallest packaging unit, packaging specification

1. The smallest packaging unit is normally specified as follows:

a) For dosage form being tablet, the smallest unit is the tablet. In small packages, the smallest packaging unit is a package, bottle, vial or bag;

b) For liquid dosage forms, the smallest packaging units are ampoule, bottle, vials, syringe and pre-filled syringe;

c) For dosage forms being powder for solution for injection, the smallest packaging units are ampoule, bottle, vial, syringe and pre-filled syringe;

d) For dosage forms being powder, granule for oral solution, the smallest packaging units are sachet, vial, bag;

đ) For dosage forms being cream, ointment, gel for external use, the smallest packaging units are tube, vial, bag;

e) For dosage forms being patch, the smallest packaging unit is patch;

g) For dosage forms being sprays or aerosols, the smallest packaging units are spray can, spray bottle, spray canister, unit dose spray or container for aerosol dispensers;

h) For dosage form being combination kit the smallest packaging unit is kit;

i) For dosage forms being formulation for concoction, the smallest packaging units are bag, package or box;

k) For medicine materials, the smallest packaging units are bag, pack, package, carton, box, bottle, jar.

2. Format for presenting packaging specification:

a) Packing specifications should be presented using natural numbers to indicate quantity, weight, volume of the drug contained in the commercial packaging;

b) If a commercial packaging encloses multiple packaging units the quantity of each packaging unit and the total quantity enclosed must be indicated;

c) Other components accompanying the drug, such as needles, syringes, measuring spoons, measuring cups, aerosol devices and other supporting devices (if any) included in the commercial packaging must be specified.

3. With regard to drugs belonging to the list of controlled drugs, in particular narcotics, psychotropics, drugs containing drug precursors, the outer packaging must not enclose than 100 smallest packaging units.

Article 29. Lot number manufacturing date, expiry date

1. Lot number:

Lot number should be printed in full as “Lot number” or worded in abbreviated form as follows: “So lo SX”, “LSX” or “SLSX” along with lot number code. Information content and construction of lot number identifier is for the manufacturer to decide on.

2. Manufacturing date, expiry date (or use by date):

a) Manufacturing date, expiry date (or use by date) shall be written in full as “Manufacturing date”, “Expiry date or Use by date” or in abbreviated form in capital letters as “NSX” (“Mfg Date”), “HD or HSD” (“Exp. Date or UBD”) , followed by the date the drug is manufactured, and its expiry date.

b) Manufacturing date, expiry date should be written in order of day, month, and year of the calendar year with each value represented in 2 characters, and only the year value may be represented in 4 characters.

The numeric characters indicating the date, month, year of a date in time should be printed on the same line and separated by a slash "/" date/month/year)", a period "." (date.month.year), a hyphen "-" (date-month-year), a space (day month year), or contiguously;

c) If the outer packaging encloses ampoules, solvent vials or other components accompanying the drug, the outer packaging label must be presented as follows:

- If manufacturing date, the expiry date of all the components is the same, the same one manufacturing date, expiry date should be printed on the outer packaging label;

- If the components having different manufacturing dates, different expiry dates, either the expiry date of the nearest expiring component or the expiry dates of each of the respective components of the kit should be printed on the outer packaging label.

3. Format for presenting manufacturing date, expiry date (or use by date), lot number::

a) Where manufacturing date, expiry date, lot number are printed in a foreign language on the original label:

- The following information must be printed on the supplementary label: manufacturing (NSX), expiry date (HD/HSD), lot number (LSX/SLSX) see original label for manufacturing date, expiry date, lot number in foreign language.

E.g., NSX, HD, SLSX see "Mfg Date", "Exp Date", "Lot.No." printed on packaging.

- If expiry date is printed by "month/year" on primary packaging label, in full by "date/month/year" on the outer packaging label, the date printed on the outer packaging label should be counted as expiry date;

Expiry dates are printed by “month/year” on both the primary packaging label and outer packaging label but manufacturing date is printed as follows:

+ If manufacturing date is printed in full by “date/month/year” on the original label, the expiry date printed on supplementary label should be counted basing on the manufacturing date of the original label;

+ If manufacturing date is printed by “month/year” on the original label, the expiration date should be counted as the last date of the expiring month, and the statement “expiry date is the last date of the expiring month” must be printed on the supplementary label.

b) If the size of the primary packaging label does not allow for fitting lot number, expiry date and corresponding symbols of "So lo SX" and "HD" according to the provisions of clause 1 clause 2 of this Article a sequence of numeric characters depicting lot number, manufacturing date, expiry date may be printed on the primary packaging label but the information must be presented in full on the outer packaging label as required.

c) Format for presenting shelf life on package inserts:

- Shelf life in terms of time interval from manufacturing date should be specified;
- Shelf life after first opening the primary packaging for multidose types of drug such as eye drop or nose drop, ear drop, ointment, gel for multiple uses and oral multidose liquid form drugs or bottled tablets, large containers (if any);
- Shelf life after preparation for use in the case of powder, granule requiring dilution into solution or suspension before use such as powder, granule for suspension or solution for injection or oral consumption.

Article 30. Changing expiry dates printed on drug label for reasons of national defense, security, epidemic prevention and combatting, mitigation of consequences of natural disasters, calamities

Due to reasons of national defense, security, prevention and combating epidemics, mitigation of consequences of natural disasters, calamities, the Minister of Health shall decide on changing expiry dates printed on drug labels and regulate the presentation of expiry date on a case by case basis subject to the drug's quality, weighing benefits and risks or the serious shortage in domestic supply.

Article 31. Format for presenting storage conditions for drugs, drug raw materials, quality specifications

1. Labels of drugs, drug raw materials, package inserts:

Storage conditions in terms of temperature (in Celsius unit abbreviated as °C and a specific number) should be indicated. Humidity, lighting or other special conditions in storage or in transit (if applicable) to ensure quality integrity should be noted.

2. Package inserts should include storage conditions for the cases stipulated in item 2 and 3 point c clause 3 Article 29 of this Circular.
3. Format for presenting quality specifications:

Quality specification of the drug, drug raw materials must be presented on the outer packaging label and package insert, specifically as follows:
a) For the drugs, drug raw materials following quality specifications of Vietnam pharmacopoeia or Ministry of Health's recognized foreign pharmacopoeias: quality specification should be presented by pharmacopoeial name in full in Vietnamese or by Vietnamese abbreviated name of Vietnam pharmacopoeia or in English abbreviated name of foreign pharmacopoeia. Edition or publishing year of the pharmacopoeia is not required to be included;
b) For the drugs, drug raw materials following manufacturer's quality specifications, the wording "Manufacturer's specification" or , in abbreviated form "TCCS" should be printed.

Article 32. Number of certificate of marketing registration, number of import license

1. Number of certificate of registration for marketing in Vietnam

The wording "Number of certificate of registration for marketing:" or, in abbreviated form "SĐK:" should be printed, followed by a blank space upon submission of marketing registration dossier. Before the drug being placed on the market, the certificate identifier number granted by Ministry of Health must be added.

2. Number of import license:

The wording "Number of import license:" or, in abbreviated form, "GPNK:" should be printed on the label, followed by a blank space upon submission of application dossier for import license. Before the drug being placed on the market, the import license number granted by Ministry of Health for drugs, drug raw materials not yet licensed for marketing in Vietnam, must be added.

Article 33. Name, address of manufacturing, compounding, processing, importing establishments and other establishment relevant to the drug (if applicable)

1. General provisions on format for presenting names, addresses of manufacturers, importers on labels, package inserts:

a) Outer packaging label of drugs, drug raw materials:

- For domestically manufactured drugs: print in full the role, name, address of manufacturer;

- For domestically manufactured or imported drug raw materials: print in full the name and address of manufacturer;

- For imported drugs: print in full role, name and address of manufacturer; name and address of importer.

b) Primary packaging label: Manufacturer name may be presented under full legal name or trade name provided it is identifiable.

If there are several establishments involved in the manufacture of a drug, either of the following two formats may be used:

- List all establishments participating in the manufacture of the finished drug product;

- Print the name of the establishment responsible for batch release.

c) With regard to traditional drugs stipulated under clause 1 and clause 2 Article 70 of Pharmaceutical law and labeling of drugs manufactured, compounded at medical service establishments stipulated under clause 2 and clause 3 Article 85 of Pharmaceutical law:

- Outer packaging labels: print in full name and address of the medical service establishment processing, formulating, compounding, manufacturing the drug;

- Primary packaging labels: print full legal name or trade name of the medical service establishment.

d) Labels of drugs compounded and sold per prescription at drugstores stipulated under point b clause 1 Article 47 of Pharmaceutical law: print in full name and address of the drugstore compounding the drug;

đ) Package inserts: print in full role, name address of manufacturing establishments involved. For imported drugs the manufacturing country's name must be translated into Vietnamese, unless it has no meaning when translated or cannot be translated;

e) Apart from manufacturing establishments, importers, role, name, address of other establishments relevant to the drug may also be added on the label and package insert (such as registrant, distributor, trademark owner company, product owner and others).

2. Format for presenting roles of establishments relevant to the drug in front of the establishment's name, specifically:

a) For manufacturing establishments:

- If there is only one establishment participating in manufacturing the drug: the role should be indicated as "Manufacturer":".

- If there are several establishments participating in manufacturing process: the role of each establishment should be indicated, such as: "Semi finished product manufacturing establishment" "Primary packaging establishment"; "Batch release responsible establishment";

- The name of manufacturing establishments of the drug, drug raw material presented should be the name recorded in Certificate of satisfaction of conditions for pharmaceutical business issued by the competent authority relevant to the business operations they perform.

b) For importers: the role should be indicated as "Importing enterprise";

c) For other establishments: the role "Distributor", "Product's owner", "Trademark's owner" and other roles relevant to the drug (if applicable) should be indicated).

3. Format for presenting name and address of manufacturing establishments:

a) With regard to drugs the manufacture of which involved the participation of different manufacturing establishments, the name of all such establishments along with the address of the respective manufacturing sites should be presented according to the prescribed format. The names of participating manufacturing establishments must be of the same type size and printed on the same face sheet (same plane) of the label;

b) For contract manufactured drugs: Print "Manufactured at: (name, address of the contract receiving party) under contract with: (name, address of the contract giving party)". The names and addresses of the contract receiving party and the contract giving party must be of the same type size and printed on the same face sheet (same plane) of the label;

c) Drugs contract under technology transfer agreements: Print "Manufactured at: (name, address of the technology transferee party) under technology transferred from: (name, address of the technology transferring party)". The names and addresses of the technology transferer party and the technology transferee party must be of the same type size and printed on the same face sheet (same plane) of the label.

4. Format for presenting name and address of importer: one of the following formats should be followed:

a) Print in full "Importing enterprise: name, address of the importer of the drug, drug raw material" on the label;

b) Print in abbreviated form "DNNK: full name, address of the importer".

The wording "Importing enterprise:" or "DNNK:" should be printed followed by a blank space which must be filled in with importer's full name and address before the drug being placed on the market.

5. Format for presenting name, address:

a) Format for present establishments' name:

- Name of domestic establishments: print the name as recorded in Certificate of satisfaction of conditions for pharmaceutical business, Certificate of business registration or Certificate of investment, issued by the competent authority;

For medical service establishments in particular: print the name as recorded on the establishment's Operating license in accordance with the Law on medical examination and treatment.

- Name of foreign establishments: print the name as recorded in Certificate of pharmaceutical product or Certificate of good manufacturing practice for pharmaceutical products, issued by the competent authority of the respective foreign country or as recorded on other pertinent certificates.

b) Format for presenting establishments' address:

- Address of domestic manufacturing establishments: The domestic manufacturing establishment's address printed should be the address of the place of business recorded in the relevant Certificate of satisfaction of conditions for pharmaceutical business, in addition, the address of the enterprise's head office may also be included;

- Address of manufacturing establishment: Print the number, street (village, hamlet), commune (ward, township), district (urban district, provincial town, city), province (centrally affiliated city);;

For the address of medical service establishments in particular: print the address of the drug manufacturing site of the medical service establishment as recorded on its Operating license in accordance with the Law on medical examination and treatment.

- With regard to imported drugs:

The manufacturer's address printed should be the address of the manufacturing site as recorded in Certificate of pharmaceutical product or Certificate of good manufacturing practice issued by the competent authority of the exporting country.

c) Name, address, logo (if any) of organizations, individuals relevant to the drug referred to in this clause that are printed on the label or package insert must be of a type size not larger than that of the manufacturing establishments' name, address or logo unless the former can demonstrate that they are the product's owner;

d) If the importer's name, address, logo are printed on the label, they should not be of a type size larger than those of the manufacturing establishments;

đ) . If the manufacturing establishment of a drug is a member or an affiliate of an organization such as a corporation, general corporation, group, association and other organizations, the establishment shall be allowed to print on the drug's label the name or the name and address, trademark, brand of such organization if the latter so permits

E.g., a drug manufactured at a company's branch facility in address A, affiliated to company B, the label may be printed with "Company B, Branch, manufactured at address A".

Article 34. Origin of drugs, drug raw materials

1. Determining the origin of drugs, drug raw materials:

a) The origin of a drug, drug raw material shall be determined in accordance of the provisions of Commercial law, its guiding documents regarding origins of goods and related legal normative documents;

b) Organizations, individuals responsible for the labeling of drugs stipulated under Article 6 of this Circular shall themselves determine and record the origin of their drugs, drug raw materials but must ensure the integrity, accuracy, conformity with legislative provisions on origins of goods or Treaties to which Vietnam is a signatory, of the determination.

2. Format for presenting the origin of imported drugs, drug raw materials:

The origin of drugs , drug raw materials shall be printed on the outer packaging as follows:

a) Print the group words “origin:” ,“manufactured in:” or “manufactured by:” along with the name of the country or territory where the drug, drug raw material is manufactured;

The name of the manufacturing country or territory should not be printed in abbreviated form.

b) If the origin of a drug, drug raw material is the same with the manufacturing country or territory, only the manufacturing country’s name is required to be printed, in Vietnamese or in English if it has no meaning when translated into Vietnamese or cannot be translated;

c) If the origin of a drug, drug raw material is different from the manufacturing country or territory, information on the origin must be presented in full in accordance with the provision of point a clause 2 of this Article.

3. With regard to drugs, drug raw materials manufactured in Vietnam for domestic circulation on which the manufacturing site’s address has been printed, it is not required to print the origin of such drugs, drug materials on the label.

Article 35. Other contents to be presented on drug labels

1. Apart from the mandatory contents stipulated in this Circular, additional contents may be added to samples of label and package insert of drug registration dossiers, import license application dossiers for drugs having no marketing registration certificate or the labels of drugs categorized under clause 1 and clause 2 Article 11 of this Circular, provided that the provisions of clause 3 of this Article are complied with.

2. Apart from the mandatory contents stipulated in this Circular, before placing a drug on the market, organizations, individuals responsible for the drug shall be allowed to add to the label, package insert contents other than those approved by the competent authority without having to inform or obtain approval from the latter provided they are in compliance with the provisions of clause 3 of this Article, but the establishment responsible for labeling must take responsibility for the accuracy of the additional information printed, covering:

a) Adding or revising anti counterfeiting stamps and contents of product security, anti counterfeiting nature on the drug’s label for the purpose of combatting counterfeiting or product authentication;

b) Changing the format, color of package insert; changing the size of outer packaging label or primary packaging label of the drug, drug raw material;

c) Adding or revising telephone number, region code, webpage address, email address of establishments relevant to the drug; of the trademark’s owner establishment;

d) Adding or revising the symbol ® after the drug name, company logo; changing the logo of a company relevant to the drug;

đ) Changing the location of printing number of certificate of marketing registration or number of import license, location of affixing supplementary labels, location of printing lot number, expiry date, manufacturing date on the label;

e) Contents in other languages translated from Vietnamese text that was approved by Ministry of Health in the drug registration dossier or import license application dossiers for drug having no marketing registration certificate.

36. Other contents to be presented on drug labels:

a) Additional contents presented should not be in contravention of the laws, not of advertising character and be truthful, accurate, reflecting the true nature and uses of the drug, not overcasting , not distorting the mandatory contents on the label and must ensure the integrity of the mandatory contents as approved by Ministry of Health’s competent agencies;

b) The following information, images shall not be used:

- Information, images prohibited from use in advertising stipulated under Article 8 of Advertising law;

- Contents stipulated in clause 2, 3, 4, 5, 6, 10, 11, 12, 13, 14, 15 and 16 Article 126 Decree no 54/2017/NĐ-CP;

- Contents, images stipulated under clause 2 Article 18 Decree 43/2017/NĐ-CP.

- Information, images to the effect that a biosimilar is bioequivalent or clinical equivalent to a reference biologic.

c) The contents in other languages referred to in point e clause 2 of this Article must match and be as complete as the Vietnamese version from which they are translated. The size of the alphabetic characters, numeric characters printed in other languages should not overcast, not larger than, the Vietnamese ones;

d) The labels, package inserts of drugs, drug raw materials manufactured for exportation shall be allowed to be printed in other languages according to the sales and purchase contract with the importing country but the contents of such labels, package inserts must not distort information on and the nature of the drugs, drug raw materials.

Chapter IV
IMPLEMENTATION PROISIONS

Article 36. Entry into force

1. This Circular shall take effect from 01 June 2018.
2. Circular no 06/2016/TT-BYT dated 08 Mar 2016 of the Minister of Health regulating drug labeling shall be repealed on the date this Circular takes effect, except for the provisions regulating the labeling of invitro diagnostic biologics, which shall remain in force until there is another legal normative document replacing it.

Article 37. Transitional provisions

1. Drugs, drug raw materials for which a certificate of marketing registration or import license was issued before the effective date of this Circular shall be treated as follows:

a) Allowed to continue to be marketed, using the samples of labels, package inserts approved by Ministry of Health, until expiry date of the lots of drugs, drug raw materials that were manufactured or imported within the validity period of Certificate of marketing license or import license issued before the effective date of this Circular, except for the cases referred to in point b clause 1 of this Circular.

b) With regard to the drugs, drug raw materials belonging to the List of hazardous drugs and hazardous drug raw materials promulgated under the Minister of Health's Circular no 06/2017/TT-BYT of 03 May 2017; the drugs belonging to the Minister of Health's List of non prescription drugs promulgated under Circular no 23/2014/TT-BYT of 30 Jun 2014, but not belonging to the List of non prescription drugs promulgated under the Minister of Health's Circular no 07/2017/TT-BYT of 03 May 05 2017, the registrants, the importers must sort the drugs, drug raw materials out, update, supplement [labeling] information resulted from the sorting as follows:

- Drugs, drug raw materials manufactured before the effective date of this Circular: the provision of point a clause 1 of this Article shall apply;
- Drugs, drug raw materials manufactured from the date this Circular takes effect: the establishments must themselves update information on the labels and package inserts of the drugs, drug raw materials resulting from the sorting , in accordance with the provisions of this Circular before placing them on the market, within 12 months from the effective date of this Circular without having to inform Ministry of Health, unless they wish to proceed with formalities for

registration of changes, supplementations to the existing Certificate of marketing registration of the drugs pertaining to package inserts according to the provisions of Ministry of Health's Circular regulating the registration of drugs, drug raw materials.

2. Drug registration dossiers or import license application dossiers for drugs having no certificate of marketing registration that were submitted to Ministry of Health's competent authorities before the effective date of this Circular pending the issuance of the respective certificate or license, other than those categorized under clause 3 of this Article, shall be treated as follows:

a) The registrants, the importers of the drugs shall be allowed to submit dossier supplementations to Ministry of Health requesting to update information on labels and package inserts according to the provisions of this Circular in order for the updated dossiers to be evaluated and certificates of marketing registration or import licenses be issued accordingly;

b) If the registrants, the importers do not submit dossier supplementations according to the provision of point a of this clause, Ministry of Health shall evaluate the labels' and package inserts' contents according to the provisions of the Minister of Health's Circular no 06/2016/TT-BYT of 08 Mar 2016 regulating drug labeling, except for the cases referred to in point b clause 1 of this Article;

Within 06 (six months) from the date a certificate of marketing registration is issued, the establishments responsible for drug labeling shall be responsible for updating the contents of labels, package inserts in accordance with the provisions of this Circular by way of registering changes, supplementations to the existing Certificate of marketing registration according the provisions of Ministry of Health's Circular regulating the registration of drugs, drug raw materials, except for the cases referred to in point b clause 3 Article 6 of Circular no 07/2017/TT-BYT.

3. Registration dossiers of drugs, drug raw materials that were submitted before the effective date of this Circular to Ministry of Health's competent authorities under the form of registration of changes , supplementations to Certificate of marketing registration pertaining to label samples, package insert samples previously submitted but have not been approved must be supplemented with [revised] samples of labels, package inserts according to the provisions of this Circular.

Article 38. Publicizing contents of package inserts

1. Drug Administration shall be responsible for reviewing, updating and publicizing on its web page package inserts of drugs already licensed for marketing belonging to the Minister of Health's issued list of originators, reference biologics to serve as references for drug manufacturers, drug registrants in their preparation of registration dossiers for similar generics, biosimilars.

2. If there are changes or supplementations made to a package insert of a drug belonging to the List of originators, reference biologics in the course of marketing, the updated version must be announced and published on Drug Administration's web page within 45 days from the date the official letter approving the changes, supplementations is issued.

3. Drug registrants, drug manufacturers shall be responsible for keeping package inserts of generics, biosimilars updated in line with contents of those of the respective originators, reference biologics of the List of originators, reference biologics, published on Drug Administration's web page as per the following:

a) Package inserts of generics, biosimilars must be consistent with those of the respective drugs on the List of originators, reference biologics of the same concentration, strength, active ingredient, dosage form, route of administration, except for the information that are inherently different (such as shelf life, excipient composition, quality specification, bioavailability

parameters, pharmacodynamics data, unwanted side effects, clinical trials' results). Information regarding unwanted side effects in package inserts of generics, biosimilars should not be fewer than that of the respective originators, reference biologics, except for the side effects of originators, reference biologics that are attributed to excipient components not present in the formulation of the generics, biosimilars;

b) Within 12 months from the date Drug Administration announces and publishes the package insert of an originator, reference biologic on its web page according to the provision of clause 1, clause 2 of this Article, manufacturers, importers of generics, biosimilars shall be responsible to themselves update the label, package insert of the relevant generic, biosimilar to render them consistent, with regard to the information referred to under clause 2 of this Article, with the published package insert without having to inform Ministry of Health, unless otherwise requested by Ministry of Health.

Article 39. Provisions on references

Where the legal normative documents referred to in this Circular are revised, supplemented or replaced, the updated version of the documents shall prevail.

Article 40. Execution responsibility

Drug Administration, Administration of Traditional medicine and units under Ministry of Health, Health Departments of provinces, central-affiliated cities, Vietnam Pharmaceutical Corporation - JSC , domestic and foreign manufacturers, registrants, importers, exporters of drugs, drug raw materials, medical service establishments and establishments providing extemporaneous compounding shall be responsible for the implementation of this Circular.

Organizations, individuals involved should promptly report to Ministry of Health (Drug Administration, Traditional medicine Administration) any issues encountered during the course of implementation for the latter's consideration, resolution./.

PP. THE MINISTER
VICE MINISTER

(signed)

Truong Quoc Cuong

Recipients:
- Gov's Office (Officla Gazettem Gov web portal);
- The Minister of Health;
- MoH Vice Ministers;
- Ministries: Justice (Legal document control Dpt); Science and Technology (Legal Dpt); Trade and Industry; Finance (General Dpt of Customs); Public Security (Health Adm), National Defense (Military Health Adm); Transporti (Health Adm);
- Health Dpts of provinces, central affiliated cities;
- MoH's affiated Divisions, Adinistration, General Dpts, Ministry Office, Inspectorate;
- Vietnam pharmaceutical business associations; Vietnam Pharmaceutical Corporation- JSC;
- Drug manufacturers, registrants of Vietnam;
- MoH's web portal;
- File: VT, PC, QLD (12b).

[emblem]

The Announcement of Food and Drug Administration

Title: Guidance for Market Authorization Holders on Post-Marketing Safety Reporting for Human Drugs, Narcotics, and Medicinal Neuropsychotropic Substances

In order to provide the single direction and standard as well as the definite working procedure of post-marketing adverse events reporting and monitoring related to health products to Market Authorization Holders consequence to their compliance and optimizing the pharmacovigilance effectiveness, therefore Food and Drug Administration of Thailand has been issued the announcement entitled “Guidance for Market Authorization Holders on Post-Marketing Safety Reporting for Human Drugs, Narcotics, and Medicinal Neuropsychotropic Substances” as detail enclosed.

Hence, this will be effective from now on.

The announcement on 18 December 2015

[signature]

(Mr. Boonchai Somboonsook)

General Secretary of Food and Drug Administration

The enclosure of

the Announcement of Food and Drug Administration

Title

Guidance for Market Authorization Holders on

Post-Marketing Safety Reporting for

Human Drugs, Narcotics, and Medicinal Neuropsychotropic Substances

Dated 18 December 2015

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