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

APAC PMRE Task Force

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Abbreviation

Abbreviation	Description
ACTD	ASEAN Common Technical Document
ADR	Adverse Drug Reaction
AE	Adverse Event
API	Active Pharmaceutical Ingredient
ASEAN	Association of South-East Asian Nations
ASTT	Administration of Science, Technology and Training
AVG	ASEAN Variation Guideline
B.E.	Buddha Era
BA	Bioavailability
BE	Bioequivalence
BLA	Biologics License Application
BP	British Pharmacopoeia
BPOM	Badan Pengawas Obat dan Makanan (Indonesian national agency of drug and food control)
BSE	Bridging Study Evaluation (Taiwan)
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)
CECA	Comprehensive Economic Cooperation Agreement (Singapore)
CEP	Certification of suitability to the monographs of the European Pharmacopoeia
CFDA	China Food and Drug Administration
CFDI	Center for Food and Drug Inspection
ChP	Chinese Pharmacopoeia
CIOMS-I	Suspect Adverse Reaction Report Form (CIOMS Form I)
CIRB	Centralised Institutional Review Board (Taiwan)
CMC	Chemistry, Manufacturing and Control
CMO	Contract Manufacturing Organization
CoA/COA/CA	Certificate Of Analysis
CoI	Co-principal Investigator
CPO	Contract Pharmaceutical Organization.
CPP	Certificate of Pharmaceutical Product
CRC	Clinical Research Centre
CREC	Central Research Ethics Committee (Thailand)
CRF	Case Report Form
CRM	Clinical Research Materials Notification
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
CUHK	Chinese University of Hong Kong
CV	Curriculum Vitae
DAL	Drug Administlation Law
DAV	The Drug Administration Department of Vietnam
DCA	Drug Control Authority (Malaysia)
DCGI	Drugs Controller General India
DLP	Data Lock Point
DMF	Drug Master File
DMP	Data Management Plan
DNA	Deoxyribonucleic Acid
DOH	Department of Health
DP	Drug Product
DRGD	Drug Registration Guidance Document （Malaysia）
DRR	Drug Registlation Regulations (China)
DS	Drug Substance
EC	Ethical/Ethics Committee

Abbreviation	Description
EC-MOPH	Ethics Committee - Ministry of Public Health
EFTA	European Free Trade Association
EMEA/EMA	European Medicines Agency
EP	European Pharmacopoeia
EPW	Empowered Procurement Wing (India)
ERB/ERC	Ethical Review Board/Committee (Philippines)
ETP	Economic Transformation Program（Malaysia）
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/F2F/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
GQCE	Generic Quality Consistency Evaluation （China）
GS1	Global Standard One
GTIN	Global Trade Item Number
HA	Health Authorities
HGRAC	Human Genetic Resource Administration of China
HIV	Human Immunodeficiency Virus
HKD	Hong Kong Dollar
HKU	University of Hong Kong
HSA	Health Sciences Authority (Singapore)
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 E2A	ICH E2A Clinical safety data management: (definitions and standards for expedited reporting)
ICH E2B (R2)	Maintenance of the ICH Guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports
ICH E2B (R3)	ICH guideline E2B (R3) on electronic transmission of individual case safety reports (ICSRs) -
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)
ICH M3	Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals
ICH M4	M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals
ICH Q12	Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management
ICSR	Individual Case Safety Report (Philippines)
IDR	Indonesia Rupiah
IEC	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
KACRC	Korean Association of Clinical Research Coordinator
KGMP	Korea Good Manufacturing Practice
KOL	Key Opinion Leader
KOMNAS	The Indonesian Human Rights National Commission (Komnas HAM)
KoNECT	The Korea National Enterprise for Clinical Trials
KRW	Korea Won
LOA	Letter of Authorization

Abbreviation	Description
LTO	License to Operate
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
MAV	Major Variation Application
MedDRA	Medical Dictionary for Regulatory Activities
MF	Master File (Japan)
MFDS	Ministry of Food & Drug Safety (Korea)
MFR	Manufacturer
MHLW	Ministry of Health, Labour and Welfare (Japan)
MHRA	Medicines and Healthcare Products Regulatory Agency
MIDR	Million Indonesia Rupiah
MIIT	Ministry of Industry and Information Technology (China)
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 (China)
MRCT	Multi-Regional Clinical Trials
MREC	Medical Research & Ethics Committee (Malaysia)
MTA	Material TransferAagreement
NADFC	National Agency for Drug and Food Control (Indonesia)
NATCM	National Administration of Traditional Chinese Medicine (China)
NBE	New Biological Entity
NCE	New Chemical Entity
NCO	New Combination
ND	New Delivery system
NDA	New Drug Application
NDOS	New Dosage form of Approved New Drug
NF	National Formulary
NHC	National Health Commission (China)
NI	New Indication
NIBIO	National Institute of Biomedical Innovation, Health and Nutrition (Japan)
NIFDC	National Institutes for Food and Drug Control (China)
NME	New Molecular Entity
NMPA	National Medical Producyts Adominstration (China)
NMRR	National Medical Research Register (Malaysia)
NOC	No Objection Certificate
NPRA	National Pharmaceutical Regulatory Agency (Malaysia)
NR	New Route of administration
NS	New Strength of Approved New Drug
NSAE	Non Serious Adverse Event
ODD	Orphan Drug Designation (Taiwan)
OECD	Organisation for Economic Cooperation and Development
OTC	Over-The-Counter
PBRER	Periodic Benefit Risk Evaluation Report
PD	Pharmacodynamics
PHREB	Philippine Health Research Ethics Board
PI	Principal Investigator
PI	Package Insert
PIC	Pharmaceutical Inspection Convention
PIC/S or PIC/s	Pharmaceutical Inspection Co-operation Scheme
PK	Pharmacokinetics
PMD Act	Pharmaceuticals, Medical Devices and Other Therapeutic Products Act (Japan)
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PMF	Plant Master File
PMS	Post-Marketing Surveillance/Study
PRC	People's Republic of China
PRH	Product Registration Holders (Malaysia)
PSM	Pre-submission Meeting (Malaysia)
PSUR	Periodic Safety Update Report
PvPI	Pharmacovigilance Program of India
QC	Qquality Control
QOS	Quality Overall Summary
QP	Qualified Person
R&D	Research and Development
RA	Regulation & Approval (RA-EWG)

Abbreviation	Description
RCT	Randomized Controlled Trial
r-DNA	recombinant DNA
REMS	Risk Evaluation and Mitigation Strategy
RMB	renminbi = CNY (CHINESE YUAN)
RMP	Risk Management Plan
RTF	Refuse-To-File (Taiwan)
S&E	Safety & Efficacy
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAKIGAKE	"Breakthrough Therapy"-type priority review system (Japan)
SAP	Statistical Analysis Plan
SAR	Serious Advance Reaction
SAR	Statistical Analysis Report
SAS	Special Access Scheme
SEC	Subject Expert Committee
SMF	Site Master File
SMP	Safety Monitoring Program (Thailand)
SMPC/SmPC	Summary Product Characteristics
sNDA	supplemental New Drug Application
SOP	Standard Operating Procedure
SRA	Stringent Regulatory Authorities
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
TOC	Table of Contents
TOX	Toxicology
TPI	Taiwan Package Insert
US	United States
USFDA	US Food and Drug Administration
USP	United States Pharmacopoeia
VN	Vietnam
WD	Working Day
WHO	World Health Organization

EXECUTIVE SUMMARY 2020

China	RDPAC/PhIRDA	· To regulate the communication and exchange between applicant and Center for Drug Evaluation of NMPA, Regulations on Communication and Exchange for Drug R&D and Technical Review and Approval (NMPA No.74 [2018]) were released on September 30th, 2018 by NMPA. These regulations are applicable for drug registration. (See details in page 6 of the table) · To encourage innovation, accelerate new drug R&D, meet the needs of public drug demand and implement R&D primary responsibility of the applicant, the Announcement on Adjusting Review and Approval Procedures for Drug Clinical Trial (NMPA No. 50 [2018]) was released by NMPA on July 27th, 2018. This announcement is applicable for clinical trial protocol application. (See details in page 6 of the table) · To adjust the range of application of imported drug registration administration, including MRCT clinical trial application in China, clinical trial registration and marketing application of innovative chemical and biological drugs, the government released the Decision on Issued Concerning on Adjusting the Registration of Imported Drugs on June 20th , 2017. (See details in page 12 of the table) · To guide the service of re-registration application of imported drugs, Guideline for Imported Drugs Re-registration and Approval Service were released on December 1st, 2016. The guideline is applicable for application and transact of re-registration of imported drugs. (See details in page 12 of the table) · To strengthen the administration on drug registration, accelerate the R&D and marketing process of innovative and generic drugs with clinical value to meet the urgent medical needs and solve the contradictory problems on backlog of drug registration applications, the former CFDA released Opinions on Encouraging Priority Review and Approval for Innovative Drugs on December 28th, 2018. The opinions are applicable for the registration of drugs with obvious clinical value and advantages. (See details in page 21 of the table) · To raise the physicians and publics' attention to rare diseases, create terminal demand, and promote the application and popularization of gene sequencing on rare disease screening from top to bottom. China's First List of Rare Diseases was issued by NHC, MOST, MIIT, NMPA and NATCM on May 22nd, 2018. (See details in page 22 of the table) · To strengthen the drug administration, ensure drug quality, secure the safety of drug using and legitimate rights of public, protect and promote public health, the revised Drug Administration Law of PRC was adopted and implemented on December 1st, 2019. The law is applicable for all R&D, manufacture, sales, utilization, supervision and administration activities in China. (See details in page 24 of the table) · To establish a scientific, strict drug administration system and implement the Drug Administration Law of the People's Republic of China effectively, the government solicit public opinions on Provisions for Drug Registration (Draft for Comment), Provisions for Supervision of Drug Manufacture (Revised Draft for Comment), Provisions for Supervision of Drug Distribution (Draft for Comment). (See details in page 24 of the table) · To strengthen the administration of non-clinical study quality management practices certification, the NMPA released Regulation on the certification of GLP for Non-Clinical Laboratory Studies (Draft for Comment) on November 21st, 2018, the regulation is applicable for China's GLP Certification Administration. (See details in page 24 of the table) · To further clarify the associate review, approval and supervision of APIs, pharmaceutical excipients, packaging materials and containers with pharmaceutical preparations. Announcement on Improvement of Associated Evaluation and Approval of Drug (NMPA No. 56 [2019]) was released on August 15th, 2019. The announcement is applicable by applicants or Marketing Authorization Holder (MAH). (See details in page 35 of the table) · To regulate drug insert sheets and labels in accordance with the Drug Administration Law of PRC, the former CFDA released Provisions for Drug Insert Sheets and Labels (CFDA No. 24) on March 15th, 2006, the provisions are applicable for all drugs approved and marketing in China. (See details in page 36 of the table) · To guide and standardize the research and management of the change of approved chemical and biological medicine, NMPA issued 3 draft guidelines, including Guideline for Post-approval Changes Study of Chemical Drug Products, Guideline for Post-approval Changes Study of Biological Drug Products, and Guideline for Post-approval Changes to Clinical Trial of Drugs on November 8th, 2019 for public comments. (See details in page 41 of the table) · As showed in the table of the RA report, to promote the technical standard of harmonization with ICH, the guidelines of M4, E5 (R1), E2E, E2A, and E2B (R3) were adopted by NMPA. · To promote the technical standard of harmonization with ICH, the guidelines of E1, E2F, E3, E3 Q&As (R1), E4, E5(R1), E5 Q&As (R1), E17, E7, E7 Q&As E8, E9, E10, E11(R1), E12A, E15, E16, S1A, S1B, S1C(R2), S3A , S3A Q&As, S3B , S4, S6(R1), S7A, S7B, S8, S9, S9 Q&As, S10 were adopted and implemented in stages by NMPA. http://www.nmpa.gov.cn/WS04/CL2138/360014.html http://www.nmpa.gov.cn/WS04/CL2138/360015.html Note: After the cut-off date of PMRE ver. 2020, Drug Registration Regulation / Provisions for Drug Registration (Decree of the State Administration for Market Regulation No. 27) was issued on March 30th. It will be effective from July 1st 2020. http://gkml.samr.gov.cn/nsjg/fgs/202003/t20200330_313670.html
Hong Kong	HKAPI	In 2019, the drug registration timeline has been improved and now only 5 months processing time is needed as Hong Kong is a secondary review system, approve drug registration with 2 CPPs.
India	OPPI	No change from 2019 version
Indonesia	IPMG	· To support investment in Indonesia for drug sector, BPOM made several transformation through BPOM Regulation No.15 year 2019 as amendment to Regulation of Head BPOM No 24 . These are including simplification program for drug registration process, eg. enhancement of electronic drug registration, deletion of mechanism approvable letter, determine reference countries for reliance pathway, reducing reference countries from 3 (three) countries to 1 (one) countries and also acceleration on drug registration by shortening drug registration timeline, etc. (See details in below tables).
Japan	JPMA	The amendment of the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act (the PMD Act) was enacted in December 2019, and will be gradually implemented from FY2020. The main changes are the legislation of the conditional early approval system and the SAKIGAKE designation system, which were in operation, and the legislation of the access system for special-use drugs. In addition, due to legal clarification of the sponsor's responsibilities regarding the treatment of unapproved drugs used in clinical trials, changes will be made in clinical trial procedures such as the clinical trial notification and reporting of adverse drug reactions. The timing of enforcement is not yet determined.
Korea	KPBMA/KRPIA	· In order to reinforce safety management of imported drugs, the registration system of overseas manufacturing site of imported drugs was implemented (December 12, 2019). Accordingly, the target and procedures for registration, change registration and change notification were established, and other matters necessary for its implementation (procedures and methods for access, inspection, and suspension of imports, etc.) were prepared. · Improve the deficiencies in the operation of the existing system. (enforced Dec. 30, 2019) e.g. - Regarding the data requirements for IND, Non-clinical study data from non-OECD countries should be recognized if the results of the inspection from OECD member countries meet the GLP criteria. - Establish the inspection basis for overseas non-clinical trialing institutions for the quality assurance of submitted materials, etc.
Malaysia	PhAMA	The National Pharmaceutical Regulatory Agency (NPRA) restructured their organization on 2nd December 2019. Guidance notes for Pre-submission Meeting (PSM) is being finalized to provide regulatory advice (with regards to quality, safety and efficacy aspects) to applicants prior to the submission of an application to register a product. The "Guidelines on Facilitated Registration Pathway: Abbreviated and Verification review" was made effective for applications submitted from 01 April 2019 for NCEs and Biologics. The NPRA had initiated publication on the NPRA website of the Approved label and Package Insert (PI) for all approved products containing scheduled poison as part of the efforts to improve transparency.
Philippines	PHAP	· Not much has changed with in the regulatory policies of FDA. In May 2019, a new guideline was issued for Clinical Trials (FDA Circular No. 2012-007-A), streamlining the process of application. · The requirement to do Phase IV Clinical Trials in lieu of PSURs is still in place, where applicants are required to submit Phase IV Clinical Trial Protocol together with the NDA submission. Discussions have begun between the FDA and the industry to amend this policy, but so far no formal policy amendment has been issued.
Singapore	SAPI	In 2019 Singapore HSA enhanced the regulatory process and implemented several initiatives in areas such as post-approval changes by implementing a new "Do and Tell" option for a list of specified post-approval minor variations which allows companies the flexibility to make specified administrative changes without prior-approval, re-categorization of post-approval variations, revision of site-specific stability data requirement involving primary packagers, turnaround screening time of 50-day turnaround time was published and e-labelling guideline was published
Taiwan	IRPMA	No major updates are provided.
Thailand	PReMA	The key updates on Thailand regulatory environment in 2019 is the new Drug Act (No. 6) B.E. 2562 published in the Government Gazette on April 16, 2019. The key changes are: ·New Drug Registration must provide "Documents that show the number of patent or petty patent application which went through the publication process according to patent law" (Section 9). ·The certificate of drug formula registration shall be valid for seven years from the date it was issued and need renewal. (Section 11). ·New section added on procedure, regulations and conditions of drug research (Section 8) and the penalty fee (Section 12). ·All fees in Drug Act 1967 has been replaced (Section 14).
Vietnam	PG	· Circular 32/2018/TT-BYT, coming into effect since 1 September 2019, guiding drug registration have removed the 5-year of existing authorization in other markets, enabling drugs, vaccines, and biologics to register in Vietnam as soon as they are approved by stringent regulatory authorities, and introduced changes to optimize the process for drug registration. This is a major improvement in accelerating patient access to high quality, innovative pharmaceuticals. · With the efforts to ensure quality and traceability of all medicines circulating in Vietnam, additional specific information, which are not in line with global practice, for content of Certificate of Pharmaceutical Products for Marketing Authorization in Vietnam has been introduced in Circular 32. This is an administrative challenge that requires continued dialogue and discussion between health authorities and Vietnam Ministry of Health to ensure the harmonization with international practice, and identify optimal measures that enhance quality management.

Item	Contents	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/CTA	Requirements to be the IND/CTA applicant	Sponsor (Companies) or regulatory agency (CRO) or institute	CRO or 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. CROs are able to submit the Clinical Trial Notification (CTN) if they serve as the in-country caretaker.	Companies, CRO and doctors who can follow standards of GCP, can be IND holders.	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. [Malaysian Guideline for Application of Clinical Trial Import Licence (CTIL) and Clinical Trial Exemption (CTX) §4.1]	FDA-licensed Sponsors and Contract Research Organizations (CROs) A license to operate (LTO) is required for a CRO and its Sponsor, prior to the conduct of clinical trial. (Administrative Order No. 2014-0034 and FDA Circular No. 2015-003)	Yes, CRO is possible, however the sponsor should be a locally registered business entity registered with the Accounting and Corporate Regulatory Authority (ACRA) in Singapore.	The applicant is the pharmaceutical license owner or local legal entity with sponsor's delegation in Taiwan. CRO can be an applicant if the company also has been 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 If consultation system exists, input "yes" and describe the details such as consultation timing or procedures.	Yes. Applicants can apply for communication and exchange on innovative drugs, improved new drugs, biosimilar drugs, complex generic drugs and GQCE products during R&D process and registration applications. For detailed requirements, may refer to Communication and Exchange of Drug R&D and Technical Evaluation Procedure (No.74 of 2018) and NMPA Announcement of China National Drug Administration on Adjusting Review and Approval Procedures for Drug Clinical Trial (No. 50 of 2018), of which article 1&2 is specific for clinical trial.	No	Non-formal consultation is possible. Pre-screening of the application is done at DCGI (Drug Controller General of India)/CDSCO (Central Drugs Standard Control Organization 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.	Yes The consultation with Head of evaluator & Assistant Director by email and appointment before discussed.	Yes Various clinical trial consultations are offered by PMDA on new drugs and biological products (e.g., pre-PhI/ Pre-PhIIa/Pre-PhIIb/End of PhII study, Pre-application, Quality, Safety, etc.).	Yes Pre-IND/CTA consultations are offered by IND/CTA applicants throughout medical product development phases of chemical and biological products. The primary review opinions will be returned or face-to-face meeting instead of the review opinion can be will be held within 20 days after pre-IND consultation requests. The IND/CTA applicants can also request the face-to-face meeting. The final review opinions will be returned within 30 working days after application by MFDS if there isn't any argument.	NPRA is finalizing guidance notes for Pre-submission Meeting (PSM). The main objective of PSM is to provide regulatory advice (with regards to quality, safety and efficacy aspects) to applicants prior to the submission of an application to register a product.	Yes Consultation is done through official letters. Currently, there is no provision for face-to-face consultation with FDA.	No, but company can always write in to HSA to request for a meeting.	Yes Regulation consultation service is available for all phases of product development. In 2018 the reasonable consultation fee will be charged to the applicant and the consultation result would be recognized as formal record during NDA review. For more detailed information, please refer to the following website. http://www.cde.org.tw/eng/consultation_services/assistance_explain?id=14	Yes Can consult at FDA (Such as direct contact, telephone)	No 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.

Item	Contents	China	Hong Kong	India	Indonesia	Japan	Korea	Malaysia	Philippines	Singapore	Taiwan	Thailand	Vietnam
		RDPAC/PhIRDA	HKAPI	OPPI	IPMG	JPMA	KPBMA/KRPIA	PhAMA	PHAP	SAPI	IRPMA	PReMA	PG
IND/CTA	Flow of clinical trial notification, IND application and IRB permission	-Communication and exchange meeting is mandatory before 1st IND submission, except some special conditions which listed in the guidance of No. 50 of 2018. -No mandatory requirement to complete IRB review prior IND submission -IRB review should have been completed before clinical trial started. -When IND submission accepted by CDE, if no comments from CDE after 60 WD, clinical trial can be started.	Parallel submission to Department of Health and Ethics Committee. Both approvals needed.	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 only start after EC approval	Refer to BPOM regulation No. 21 Year 2015 about Procedure of Clinical Trial Approval, annex II and annex III	A clinical trial is conducted based on the notification, and not based on an application. Contracts with clinical sites should be signed after 30 days from the date of clinical trial notification (14 days from the second trial onwards).	IRB approval is required before or after MFDS approval. In addition, parallel application is allowed. Clinical trials can be initiated after both of MFDS and IRB approvals.	A CTIL from the Drug Control Authority (DCA) authorising the licensee to import a product for purposes of clinical trials is required. All the clinical trials that require CTIL/ CTX must be registered with NMRR (National Medical Research Register). NPRA will only accept favorable opinion/ approval issued by EC that is registered with the DCA. [Malaysia Guideline for Application of CTIL and CTX §5.1]	In May 2019, FDA issued a streamlined process in obtaining approval for Clinical trials. In the new process, FDA reviews for completeness, forwards it to outside technical reviewers, then decides based on the reviewers' recommendations. Ethical review approval from the institution's ethics committee is no longer a prerequisite for FDA application, and may be done in parallel with FDA review. (FDA Circular No. 2012-007-A)	Under the Health Products Act and its subsidiary legislation, the Health Products (Clinical Trials) Regulations, and require either Clinical Trial Authorization (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 Authorization (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 Authorization (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.	IRB submission in parallel with TFDA's review of an IND application and c-IRB (jointed IRB review) system has been adopted since 2013.	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 31 May 2018 Submission fee applied: rate as of 24 Dec 2018 Initial review fee: 1,000 THB Expert review fee: 4,000 THB Consultant fee: 2,000 THB	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 MOH 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) if it is announced.	Implied permission system for clinical trial: -If no comments from CDE since IND submission accepted in 60WDs, clinical trial can be started. -If any queries from CDE, response should be submitted within 5WDs. Or else, If IND submission was hold another round of 60WDs is needed.	120 calendar days.	IND review: 6-8 months EC review: 2-4 months As per actual experience	Timeline for evaluation is 20 working days for protocol & amendment of clinical trial after NADFC stated the protocol & amendment complete	The "after 30 days from the first clinical trial notification" rule applies for drugs containing new active ingredients, new ethical combination drugs and drugs with a new administrative route. Clinical trials can be started 14-days after the clinical trial notification from the second trial onwards (for the same product).	IND application official timeline 30 working days Queries can be given by MFDS up to 2 times. In case of query given, it would take 2-3 months or more. IND approval by MFDS and IRB review can be got 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: Main product categories: 45 working days For Others: 30 working days [Malaysia Guideline for Application of CTIL and CTX §5.2] The IRB/IEC should review a proposed clinical trial within a reasonable time. [Malaysian GCP§3.1.2] IRB/IEC approval: Complete submission without queries can be approved within 4 to 8 weeks. Generally, MREC approval takes 50 working days. [http://www.crc.gov.my/general-clinical-trial/ Item 15]	According to the FDA: Application process – not more than 15 days Review – not more than 45 days Decision – not more than 15 days However, there are instances where actual processing timelines including queue time is between 100 to 200 days.	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	For the case of standard IND application, the review timeline is 45 calendar days after submission. For the protocol with same protocol number is submitted in A10 countries simultaneously, accelerate review(Fast track system is not applicable for First in Human Study) is available and the review timeline is15 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 Amendment - 20 WD IRB: (each study site or EC of MOPH) - Institute EC 2-3 months - Central EC CREC 5-6 months EC-MOPH 7-8 months.	Registering a clinical trial: -5 working days for ASTT to verify legality of application -60 days for applicant to respond if needed to further complete application -5 working days after receipt of eligible application, for ASTT to grant written approval Approving a clinical trial: -5 working days for ASTT to verify legality of application -60 days for applicant to respond if needed to further complete application -25 days after receipt of eligible application, ASTT to meet with National Biomedical Ethics Committee and a record on clinical trial outline assessment shall be made -5 working days after receipt of record by National Biomedical Ethics Committee, ASTT submits complete application to MOH Minister for approval (if clinical trial needs correcting, applicant has 90 days)

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IND/CTA application materials	Application form If application form is needed, input "Yes" and describe country specific requirements (if any) and its language	Yes (in Chinese)	Application form for Certificate for Clinical Trial.	Yes (Form 44, in English)	Yes There is a checklist requirement Refer to BPOM regulation No.21 Year 2015 about Procedure of Clinical Trial Approval, annex I	Yes Clinical trial notification form (in Japanese)	Yes IND application can be made through nedrug web site. The format of Application form should be written in Korean.	Yes Application form must be filled in English or Bahasa Melayu. (The documentation/ requirements details are provided in the Malaysian Guideline for Application of CTIL and CTX.)	Yes Form is available in the FDA website. It is in English.	Application for Clinical Trial Authorisation, Clinical Trial Notification or Clinical Trial Certificate to HSA through PRISM.	Yes The official format of application is in Chinese. The applicant can write in by English.	Yes Local form (in Thai)	Yes, in Vietnamese
	A statement regarding the reason why the sponsoring of the proposed clinical trial is scientifically justified	Yes (in Chinese)	Not required	Yes (in English)	Yes Refer to BPOM regulation No. 21 Year 2015 about Procedure of Clinical Trial Approval Using Indonesian or English language	Yes (in Japanese)	Yes (in Korean)	Yes (in English or Bahasa Melayu)	Yes in English	No	Yes The official letter to indicate the sponsoring of proposed clinical trial is needed.	Yes Cover letter (have template in Thai)	No
	Protocol If protocol submission is needed, input "Yes" and describe its language	Yes (in Chinese) Protocol or draft protocol is needed for new drug Phase I IND submission.	Yes, in English	Yes (in English)	Yes Refer to BPOM regulation No. 21 Year 2015 about Procedure of Clinical Trial Approval Using Indonesian or English language	Yes (in Japanese)	Yes The protocol must be written in Korean. The protocol written in English, however, is acceptable in case of phase 1 study.	Yes (in English or Bahasa Melayu)	Yes in English	Yes, in English	Yes Either Chinese or English version is acceptable. The Chinese synopsis is requested.	Yes See detail in guideline, can be in Thai or English	Yes Protocol is mandatory in VNM and ENG. MOH EC members refer to ENG version to verify information.
	IB f IB is needed in the CTA/IND application, input "Yes" and describe its language	Yes (in Chinese)	Yes (in English) For Phase IV trials, HK registered pack insert can be used.	Yes (in English)	Yes, (in Indonesian or English) Refer to BPOM regulation No. 21 Year 2015 about Procedure of Clinical Trial Approval	Yes (in Japanese)	Yes. (in Korean) In case of foreign language, Korean document should be attached to the original document.	Yes (in English or Bahasa Melayu)	Yes in English	Yes, in English	Yes Either Chinese or English version is acceptable.	Yes See detail in guideline (for unregistered drug in Thailand)	Yes In Vietnamese; Or in English accompanied by a summary in Vietnamese
	CRF (sample) if CRF template (blank form) is needed in CTA/IND application, input "Yes" and describe its language	No	Yes (in English)	Yes (in English)	Yes, (in Indonesian or English) Refer to BPOM regulation No. 21 Year 2015 about Procedure of Clinical Trial Approval	Yes (in Japanese)	No CRF template is not necessary for MFDS IND approval.	Yes (in English or Bahasa Melayu)	Yes in English	Yes, in English	Yes Either Chinese or English version is acceptable.	No No requirement	Yes In Vietnamese or in English
	Informed Consent Form (ICF) If sample of Informed Consent Form is needed in the CTA/IND application, input "Yes" and describe its language	Yes (in Chinese)	Either in both English and Chinese, or in Chinese only.	Yes- ENGLISH to be submitted to DCGI. ICF in local regional/vernacular languages has to be submitted to EC for approval. ICF must be in a language that is non-technical and understandable by the study subject. Some EC insist for back translation and translation certificate(s) as well.	Yes, (in Indonesian or English) Refer to BPOM regulation No. 21 Year 2015 about Procedure of Clinical Trial Approval	Yes (in Japanese)	Yes. ICF template must be written in Korean. For foreign subjects, ICF templates written in foreign languages can be used.	Yes (in English or Bahasa Melayu)	Yes in English and Filipino; IC in regional/vernacular language required as applicable	Yes, in English	Yes ICF should be in Chinese and there is a template for CIRB. TFDA announced on 3-Nov-2018 that TFDA authorizes 35 IRBs for ICF amendment review and approval of drug clinical trial from 2018/11/6 to 2020/12/31. Thus, the ICF amendment is no need to submit TFDA for approval for these 35 IRBs.	Yes Yes, in Thai	Yes, in Vietnamese and English (both are mandatory)
	Investigator's CV	No	English CV of PI.	Yes (in English)	Yes, (in Indonesian or English) Refer to BPOM regulation No. 21 Year 2015 about Procedure of Clinical Trial Approval	No	No Information of investigational sites, investigators is required. But, CV itself is not necessary.	Yes (in English or Bahasa Melayu)	Yes in English	CV of PI, in English	Yes For both PI and Co-I, either Chinese or English version is acceptable. TFDA regulated necessary training hours needed for GCP and ethical then qualified to conduct clinical trial.	No No requirement	Yes, in Vietnamese or English

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IND/CTA application materials	Overall requirement on content if "list of content" or "check list" form is needed in the application, input "Yes"	Yes (in Chinese) Adopt to ICH M4 Module1	No		Yes Refer to BPOM regulation No. 21 Year 2015 about Procedure of Clinical Trial Approval Using Indonesian or English language	No	No List of content or checklist form is not required.	Yes (in English or Bahasa Melayu)	No	No	Yes The check list form for required documents is provided in Chinese.	No No requirement	No Application for approval for clinical trial consists of: a) Application form b) Documents containing information about the drug for clinical trial: - Drug trial documents: composition, manufacturing process, quality standard and drug test report (in the case of a modern drug, herbal drug or traditional drug, it is required to have a drug test report of the state-owned drug-testing facility that complies with GLP or provider of drug/medicinal ingredient testing services that complies with GLP within its scope of operation or of the manufacture that complies with GMP; in the case of a vaccine, it is required to have a quality test report of the National Institute for Control of Vaccine and Biologicals or Certification of analysis in the case of a batch of vaccines and biologicals); - Documents about pre-clinical trial of the drug that needs to be tested: reports on pharmacological effects, toxicity, safety, proposed dose, administration route and directions for use; - Documents about the clinical trial in previous phases (if the trial facility applies for permission for clinical trial in the next phases and the drug is not exempt from clinical trial in previous phases). c) Legal documents about the drug for clinical trial: - A copy of the written approval for registration of the clinical trial granted by the Administration of Science Technology and Training, the Ministry of Health. - A certified true copy or a copy bearing the seal of the trial facility, produced together with the original for comparison of the application fom for permission for phase 4 clinical trial submitted by the competent pharmacy authority if the drug is requested to undergo phase 4 clinical trial; - Package insert of the drug licensed for free sale if the drug is requested to undergo phase 4 clinical trial; - A certified true copy or a copy bearing the seal of the trial facility, produced together with the original for comparison of the trial facility's certificate of eligibility for pharmacy business; - A confirmation of participation provided by the trial centers if a multicenter trial is conducted in Vietnam; - A certified true copy or a copy bearing the seal of the trial facility, produced together with the original for comparison of the written approval for participation in the trial granted by the People's Committee of the province or central-affiliated city if a field trial is conducted; - A clinical trial agreement between the organization/individual that has the drug for clinical trial and the provider of clinical trial services; between the organization/individual that has the drug for clinical trial and the trial assistance organization (if any). d) A clinical trial outline and its description: - A description of the clinical trial outline - A Case Report Form (CRF); dd) Principal investigator's academic résumé and copy of the certificate of completion of GCP training course which is issued by the Ministry of Health or GCP training institution; e) Participant information sheet and volunteer letter g) A record on scientific and ethical assessment prepared by the internal Biomedical Ethics Committee; h) Label of the drug

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IND/CTA application materials	Non-clinical summary if non-clinical reports are needed in the IND/CTA, input "Yes"	Yes (in Chinese)	No	Yes (in English)	Yes, (in Indonesian or English) Refer to BPOM regulation No. 21 Year 2015 about Procedure of Clinical Trial Approval Using Indonesian or English language	No Non-clinical information is included in the IB.	Yes. (in Korean) In case of foreign language, Korean document should be attached to the original document.	Yes Non-clinical information is required in the Investigator's brochure, in English or Bahasa Malaysia	Yes in English	No	No No separate document is required. Referred to IB.	No including in IB	No Not applicable (often included in IB) If provided, Vietnamese/English
	Non-clinical report	Yes (in Chinese)	No	Yes (in English)	Yes, (in Indonesian or English) Refer to BPOM regulation No. 21 Year 2015 about Procedure of Clinical Trial Approval Using Indonesian or English language	Yes In the case of First-in-Human, submit the final non-clinical reports of the studies on which the IB was prepared. Language is in English or Japanese.	No If necessary, full report (English or Korean) can be requested by MFDS.	No	Yes in English	No	No No separate document is required. Referred to IB.	No including in IB	No Not applicable (often included in IB) If provided, Vietnamese/ English
	Clinical summary If clinical summary is needed, input "Yes" and describe its language	Yes (in Chinese), if there was any clinical data.	Not required	Yes (in English)	Yes, (in Indonesian or English) Refer to BPOM regulation No. 21 Year 2015 about Procedure of Clinical Trial Approval Using Indonesian or English language	No Clinical information is included in the IB.	Yes. (in Korean) In case of foreign language, Korean document should be attached to the original document.	Yes (in English or Bahasa Melayu)	Yes in English	No	No No separate document is required. Referred to IB.	No including in IB	No NA If provided, Vietnamese/ English Clinical summary is often included in Protocol and IB.
	Clinical report	Yes (in Chinese) If there was any previous clinical date, or conduct clinical trial in other countries or the products has been marketed, the applicant should provide the whole clinical trial date, including the original and Chinese translation materials. After being approved to conduct clinical trials of drugs, the applicant shall submit regularly updated reports on safety during the period of clinical research to CDE.	Not required	Yes (in English)	Yes, (in Indonesian or English) Refer to BPOM regulation No. 21 Year 2015 about Procedure of Clinical Trial Approval Using Indonesian or English language	No	No Clinical full report (English or Korean) can be requested by MFDS.	No	Yes in English	No (for HSA, every 6 monthly, status report of the trial to be submitted; for IRB usually annually)	Yes Either Chinese or English version are acceptable.	No including in IB	No NA. it is often included in IB
	CMC summary	Yes (in Chinese)	Not required	Yes (in English)	Yes, (in Indonesian or English) Refer to BPOM regulation No. 21 Year 2015 about Procedure of Clinical Trial Approval	No	Yes. (in Korean) In case of foreign language, Korean document should be attached to the original document.	Yes (in English or Bahasa Melayu)	Yes in English	No	No However CMC data is required either in English or Chinese.	Yes See detail in guideline (for NCE)	Yes (IMPD, CoA, SmPC, label…) English/Vietnam
	CMC report	Yes (in Chinese)	Not required	Yes (in English)	Yes, (in Indonesian or English) Refer to BPOM regulation No. 21 Year 2015 about Procedure of Clinical Trial Approval	No	Yes. (in Korean) In case of foreign language, Korean document should be attached to the original document.	Yes (in English or Bahasa Melayu)	Yes in English	No	Yes CMC data is required either in English or Chinese.	Yes See detail in guideline (for NCE)	Same as CMC summary
	GMP certificate of the investigational drug	For IND of IMCT which import drug isn't marketed abroad, GMP certificate is not required, GMP statement is acceptable. For CTA of 5.1 category of import drug, CPP and GMP statement is required. For IND of China standalone study, GMP certificate is required	Yes	Yes	Yes Necessary	No	Yes GMP certificate is necessary. If GMP certificate is not acquired or available, QP declaration letter should be submitted instead of GMP certificate.	Yes (in English or Bahasa Melayu)	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.	Yes Necessary	Yes Necessary
	Sample of the investigational drug (for IND review) if the sample of the investigational drug is needed in the IND/CTA application, input "Yes"	Not mandatory requirement, depends on if CDE has further requirements of sample testing	Sample not required, but a sample certificate of analysis of the drug is required.	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 normally 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 Pharmacopoeia commission Laboratory). The Applicant needs to submit the samples in the quantity sufficient for three fold analysis	No Product Information of investigational drug, CoA of investigational drug, Summary Batch protocol (Three consecutive batch)□ only for Vaccine, Lot release only special for vaccine.	No	No The sample of investigational product is not required.	No Sample NOT required, but a sample certificate of the analysis of the drug is required.	No	No	No Sample NOT required.	No Not required	No. Minimal required is label mockup. Dossier still can be submitted without pictures.

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NDA	Requirement for MAH, applicant for import drugs	According to new issued Drug Administration Law, -Drug Marketing Authorization Holder (MAH) refers to enterprises or R&D institutions which hold a drug approval license. -Where the MAH is an overseas enterprise, the enterprise legal person within the territory of the People's Republic of China shall be designated to fulfill the obligations of the MAH and assume the joint liability of the MAH together.	The local subsidiary can be the MAH, while foreign company cannot be the MAH.		Multi- National company and domestic pharmaceutical company having manufacturing license can register Imported drug that will be registered as NDA in Indonesia is prioritized for national health program, new active substance and drug which can't be produced locally	Only the marketing authorization applicant (MAA) / holder (MAH) of pharmaceutical products may submit an NDA.	To strengthen the safety management of imported drugs, overseas manufacturing site registry will be implemented and local inspections will be carried out. The results of which will lead to the suspension, etc. of import of the drugs concerned. The MAH must be a locally incorporated company, corporate or legal entity in Korea.	The Product Registration Holder (PRH) must be a locally incorporated company, corporate or legal entity, with permanent address and registered with Companies Commission of Malaysia (with the scope of business related to the health/ pharmaceutical product). [DRGD §3.1]	FDA-licensed Drug Manufacturers, Traders, Distributors Under Republic Act No. 3720, as amended, any establishment that intends to import, distribute, sell or offer for sale any imported drug product must first secure a License to Operate (LTO) as Drug Importer. The requirements for securing an LTO is provided under Administrative Order No. 2016-0003.	MAH holder must be a Company which is based and registered in Singapore.	Required	The local subsidiary can be the MAH and a foreign company cannot be the MAH. (Drug Act, B.E. 2510 Section 14)	The following entities may register drugs/medicinal ingredients: a) Any establishment manufacturing, wholesaling, exporting, importing drugs/medicinal ingredients in Vietnam; b) Any foreign establishment having a license for manufacturing, wholesaling, exporting, or importing drugs/medicinal ingredients in local country and having a representative office in Vietnam.
	Acceptance of CTD format	ICH CTD format is mandatory for NDA application of chemical drug cat.1 and 5.1 and therapeutic biological products category 1 and preventive biological products category 1 since Feb. 1st 2018	Not specified. CTD can be accepted.	ICH-CTD is acceptable. However, it is not indicated in document issued by HA. Currently applications need to be submitted through online SUGAM portal and CTD sections can be uploaded as per the checklist.	ACTD (article 27 Drug Registration Guideline No. 24 year 2017) In practical, Both ICH-CTD format and ASEAN CTD format are acceptable by BPOM.	ICH-CTD format	For new drugs and drugs requiring data submission and drugs requiring pharmaceutical equivalence testing (except for orphan drugs, high pressure gas for medical use, radiopharmaceuticals, export-only pharmaceuticals, and other products that are not directly applied to humans) among prescription drugs, shall be prepared in CTD format. For items beyond items stated above, the CTD format may be used, if the drug manufacturer so chooses.	The online product registration application is based on the ASEAN CTD format. ICH format accepted with some reformatting for uploading into the online system which is structured in ACTD format (presently no change of title/numbering required)	FDA accepts NDAs following ASEAN and ICH CTD format, (Administrative Order No. 2013-0021)	ACTD or ICH-CTD	All new drug applications including generic application should be submitted in ICH CTD format after 1-July-2014. (no change comparing current regulation).	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. Others can be submitted via eCTD or hard copy and either CTD or ACTD format.	ACTD and ICH-CTD format

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NDA	Category of NDA	For Chemical New Drugs -New Drug Application (NDA) -Supplemental New Drug Application (sNDA) For Generic Drugs -Generic Drug Application For new indication of imported drugs marketed abroad, the registration category is 5.1 (NDA) instead of supplementary application. For new indication of the drugs marketed in China, the registration category is 2.4 (NDA) instead of supplementary application. For biological products registration category still refer to No. 28 2007.	Three categories: 1. New Chemical Entity (NCE) 2. Generic (i.e. drug substance already registered at Department of Health (DOH) 3. Biosimilar	New Drug: 1) New Chemical Entity (NCE), 2) Modified or new claims namely, new indications, dosage, dosage form (including sustained release dosage form) and route of administration 3) Fixed Dose Combination (FDC) (See 122E of the Drugs and Cosmetics Rule,1945) Note: all vaccines and Recombinant DNA (r-DNA) derived drugs shall be new drugs unless certified otherwise by the Licensing Authority. A 'New Drugs' continues to be considered a new drug for a period of 4 years from the date of first approval in India.	Article 5 ,Drug registration Guideline No.24 year 2017: New Registration consist of : a. Category 1: New Drug and Biological Product registration including Biosimilar Product. b. Category 2: branded generic / generic product. c. Category 3: Registration of other dosage form with special technology, example transdermal patch, implant and beads.	For New Drugs: New Drug Application (NDA) and supplemental New Drug Application (sNDA), Generic drug application.	<Chemical> (1) New Drug 1) New chemical structure (NCE) 2) Combination drug including NCE 3) The radiopharmaceuticals that fall under 1) and 2) (2) Data requiring drug (Drug for supplementary data submission) 1) Drug with new salt, isomer or ester, 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) (3) Generics <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 (3) Cell therapy products (4) Gene therapy products	1) New Drug Products a) New NCE b) Hybrid NCE 2) Biologics 3) Generics 4) Health Supplements 5) Natural Products [DRGD §5.1.1]	New drugs include: • new chemical entities - those not previously authorized for marketing for any pharmaceutical use in the country, including those ➢ With a new indication ➢ With a new mode of administration ➢ in a new dosage form ➢ a new fixed-dose formulation ➢ new dosage ➢ follow-on biologicals • Generic Prescription Drugs • Biologics • Traditional Medicines • Herbal Drugs • OTC Drugs • Household Remedies • Medical Gases • Veterinary Drugs • Stem Cell Products	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 and biological 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 strengths of the generic chemical product.	New Drug I: (1) New chemical entity (2) New therapeutic area (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 Product	1.New drug: drugs containing new pharmaceutical substances, medicinal materials, which for the first time are used for drug manufacture in Vietnam; drugs involving a new combination of pharmaceutical substances that have been marketed or medicinal materials that have been already used in drug manufacture in Vietnam. 2.Extension Visa 3.Variation, supplementation 4.Generic 5.Biosimilar 6.Vaccines Acc.to Law No 105/2016/QH13 and Decree 54/2017 and Decree 155/2018

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NDA	Requirement of CPP	Yes 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. For biological products registration category still refer to No. 28 2007.	To be submitted at the time of application No. of CPP required: NCE: 2 ICH countries (including source country) Generic: 1 (source country only) Biosimilar: 2 country approval from the 5 referenced countries.	CPP or Free sale certificate (FSC) issued by country of origin is required at NDA. The CPP and FSC should be notarized and apostilled or legalized.	Yes. Copy of CPP for pre-registration and registration is accepted since currently NDA registration is performed by online electronic registration. Annex, Drug Registration Guideline No. 15 year 2019 One CPP could be utilized as supporting docs for Path 120 WD (reliance) and 300 WD. For Path 120 WD (reliance), BPOM refer to reference countries : EU, US, Australia, Canada, England & Japan. Applicant can choose 1 country as reference. Several requirements are necessary, eg. unredacted assessment report from reference countries, same quality document with reference country, etc.	No	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. For pharmaceuticals except new drugs that are manufactured at sites that were not assessed as qualified for the KGMP by the Minister of the MFDS, certificate of manufacture that describes the name and location of manufacturer, etc. and which those that prove they are appropriately manufactured in the county of manufacturing of the relevant items. Drugs listed in the compendiums of the US, Japan, UK, Germany, France, Italia, Swiss 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.)	Yes The CPP should be submitted at the time of registration application. CPP is only required for imported product. 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.)	Yes 1 CPP is required to be submitted from the source or any reference country. Must indicate that it is registered and freely sold in that country	No Submission of CPP is not compulsory as a form of proof of approval. The proof of approval must come in the form of an official approval letter or equivalent document (e.g. CPP) issued by the National Medicine Regulatory Authority which certifies the registration status of the product (not provincial/ territory/ or state agencies). CPPs that indicate that the product is not licensed in the exporting country (including the scenario where the product is licensed "solely for export only") are not acceptable proof of approval.	Yes CPP(s) are required before drug license collection. The detail is as the same as 2019. Amendments this year of "Regulations for Registration of Medicinal Products" for CPP legalization exemption.	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.	Yes **New drugs & imported biologics**: - 1 CPP issued by the manufacturing country; AND - 1 CPP issued by one of the SRA – Stringent Regulatory Authorities containing language certifying that the drug is licensed for marketing and is actually marketed **New imported vaccines** - 1 CPP issued by the manufacturing country; AND - 1 CPP issued by one of the reference regulatory authorities containing language certifying that the vaccine is licensed for marketing and is actually marketed **Requirements for CPP:** a) CPP must bear the signature, name of the signing person, issue date and the seal of the CPP issuing authority; b) CPP must be issued by the national-level competent pharmaceutical regulatory authority. Where the CPP is issued by a pharmaceutical regulatory authority but not a national-level one: The registrant must provide legal papers proving that this issuing agency is the competent authority for the purpose and that the national-level pharmaceutical regulatory authority of such country does not issue CPP as a matter of law of the country. c) The signature, the name of the signing person and the seal of the CPP-issuing authority must be authenticated by the competent authority; Where this authenticating verbiage is not in English language, a Vietnamese or English notarized translation must be provided; d) The content of CPP must cover all the information required in Form 7/TT enclosed with this Circular and the following information: - Formulation of the drug, of which the name, composition, concentration, strength of each of the active ingredients, medicinal materials, excipients are indicated; with regard to soft capsule, hard capsule dosage forms information about the formulation composition of the capsule shell must also be provided; - Specifications of finished product, of pharmaceutical substances, of medicinal materials, name, address of manufacturer of pharmaceutical substances, medicinal materials; - Where a drug the manufacture of which involves several different manufacturing establishments, the name, the address, the role each performs, must be clearly indicated on CPP; - Where a CPP does not contain information about manufacturer's GMP conformity status, the registrant must submit in addition the GMP certificate of all manufacturing establishments [involved], in conformance with the requirements of clause 1, 2, 3 of this Article; - Annexes to the CPP (if any) must be certified by the CPP issuing authority. **Reference regulatory authority:** - *Reference regulatory authorities* include: European medicines agency (EMA), US, Japan, France, Germany, Sweden, the UK, Switzerland, Australia, Canada, Belgium, Austria, Ireland, Denmark and the Netherland ['s regulatory authorities]. - *The SRA – Stringent Regulatory Authorities* are pharmaceutical regulatory authorities which are classified by World Health Organization (WHO) as belonging to the SRA list, comprising: a) Member of the ICH before 23 October 2015, comprising: US Food and Drug Administration (FDA), the pharmaceutical regulatory authorities of member countries of European Commission (EC), the UK Medicines and Healthcare products Regulatory Agency (MHRA) Japan Pharmaceuticals and Medical Devices Agency ((PMDA) b) Observer members of ICH before 23 Oct 2015, comprising pharmaceutical regulatory authorities of European Free Trade Association (EFTA) and Swiss regulatory authority (Swiss medic), and Canada Health Ministry (Health Canada). c) Regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement before 23 Oct 2015, comprising Australia, Iceland, Liechtenstein and Norway.

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NDA	Acceptance of foreign clinical trial data. (Can approval be obtained by utilizing foreign clinical trial data?)	Yes -For innovative drugs, clinical trial data obtained overseas of simultaneous development in China and overseas is acceptable. -For generic drugs, integrated BE study data obtained overseas can be used for registration application in China. Data should incudes bioavailability/BE study, PK/PD study, safety and efficiency data in accordance with ICH E5, should meet ICH GCP and China registration requirement. Acceptance includes, 1) Completely acceptable 2) Partial acceptable: Supplemental trial required after communication with CDE. -For serious diseases, rare diseases and pediatric diseases lacking of effective treatment, if the data can be partially accepted after evaluation, post-marketing study for efficiency and safety is required. 3) Not acceptable.	The overseas clinical trial data is acceptable. Bridging data are not required.	Clinical data in Indian population is required except few lifesaving therapeutic categories /orphan drugs which is at the discretion of the regulatory agency. Current scenario, Indian Regulatory Agency (DCGI/CDSCO) is insisting local clinical trial data for every new drug and it is mandatory.	Yes 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	Yes The data from overseas clinical trial is accepted in accordance with ICH E5. The drugs approved using a bridging strategy or global clinical trial data have increased. However, the Japanese PK data is indispensable.	Only for New Drugs, bridging data is needed additionally. Of the new drugs 3) OTC drugs with sufficient experiential use in Korea and overseas, they will be reviewed by the individual drug.	Yes 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.	Yes There is no requirement for local clinical trial data (Phases I-III) for registration.	Yes Overseas clinical trial data is acceptable.	Yes. BSE is mandatory for NDA and BLA such as gene-engineering drugs, vaccines, new molecular of plasma preparations and allergenic preparations.	Yes	Yes The clinical trials on drugs, the clinical data included in clinical documents must be in line with guidelines of ICH, Vietnam Ministry of Health or other organizations recognized by Vietnam If clinical trials are conducted before above-mentioned regulations on drug development become available, the data from such trials shall be acceptable for the purpose of dossier evaluation. (Registration Circular 32/2018/TT-BYT, coming into effect on 1 September 2019)

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NDA	Application fees	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)	Application fee: HKD 1100 License fee: HKD 1370 Renewal fee (every 5 years): HKD 575	Vide GSR1193(E) dated December 12, 2018, the fee structure has been revised. Current application fees is as below Application fees. NDA: INR 250,000 (include MAA fee) Import License: INR 10,000 and at the rate of INR 1000/- for additional drug. Registration Certificate (for import drug): 10,000 USD for one manufacturing site or its equivalent in Indian currency and 5,000 USD 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: 1,800 USD 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 twenty 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 licenses for test and analysis of a drug has been kept INR 5,000 for a single drug and at the rate of INR 300/- for each additional drug	Annex, President Regulation No. 32 year 2017 on type & tariff for drug registration: 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 On site Inspection IDR 50 Mio (excluding transportation & accommodation of inspector)	The application fee was revised on Apr. 1, 2019. Application fees for drugs containing new active ingredients (in case of non-orphan drug) are: 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, and overseas 3,717,600 yen +travel expenses for GMP inspection: domestic 875,000 yen, and overseas 1,104,200 yen + travel expenses.	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.	New drug application for NCEs is PhP40,000.00 plus Php 500.00 for brand name clearance New drug application for other categories depend on existence of brand names: • Branded: PhP15,000.00 plus Php 500.00 for brand name clearance • Unbranded: PhP10,000.00	Registering a product – NDA & GDA a) Screening (Payable upon submission) (i) Abridged/Verification evaluation route (NDA & GDA) $565 (ii) Full evaluation route (NDA) $2,830 b) Evaluation (Payable upon acceptance) (i) NDA Abridged evaluation route - NDA-1 & NDA-2 $11,200 - NDA-3 $5,665 (ii) NDA Verification evaluation route - NDA-1 & NDA-2 $16,700 - NDA-3 $5,665 (iii) NDA-1,2,and 3: Full evaluation route $82,700 (iv) GDA Abridged evaluation route - GDA-1 $3,965 - GDA-2 $2,265 (v) GDA Verification evaluation route - GDA-1 $10,200 - GDA-2 $5,150 (vi) GDA Verification evaluation route (CECA Scheme) - GDA-1 $10,200 - GDA-2 $5,150 C) Annual retention fee (per registered product) - NDA & GDA $309 HSA website: https://www.hsa.gov.sg/therapeutic-products/fees	Application fees (”Fee-Charging Standards for the Registration of Western Medicines and Medical Devices”)	Effective 4 Aug, 2017, new fee is applied to all types of applications except A)a new drug that is researched, developed and manufactured locally for national security as notification of the Minister of Public Health B)an orphan drug that has items in accordance with the Notification of the Food and Drug Administration C)a drug registered and needs revision as the Ministry of Public Health or the Food and Drug Administration stipulates regarding quality and safety problems	NDA: 250 USD
	Other requirements	N/A Risk Management Plan should be submitted for innovative drugs NDA.		Application for Import License is required after marketing approval and Registration Certificate.	Specific country requirement on product labeling on product package, example: font type and size of the generic name, retail price, symbol of prescription drug, the name of importer. Site Master File, Established Inspection Report within 2 years, GMP certificate and Manufacturing License are 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, stem cell therapeutics 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. - Drugs for which the Minister of the MFDS deems it necessary to submit risk management plans due to occurrence of serious side effects following marketing (e.g. valproic acid, isotretinoin, alitretinoin-contained drugs, etc.), Risk Management Plans shall be submitted. - Drugs for which applicants deem it necessary to submit RMP, RMP shall be submitted.	Other requirements are as noted in the DRGD.	• Reference Standard Sample (at least 300 mg; subject to FDA advise when to submit) • Compliance to foreign GMP requirements (before submitting NDA, applicants must first secure a Certificate of GMP Compliance from FDA for each foreign manufacturing site involved in the final product under Administrative Order No. 2013-0022 and FDA Circular No. 2014-016) • Local generic labeling requirements under Administrative Order No. 2016-0008 Registration sample/s mocked-up in the proposed commercial and sample labeling presentations, including the corresponding Certificate of Analysis (subject to FDA advise when to submit)	For GDA, the reference product must be the registered product with Singapore HSA Batch numbering system is required for registration of generics and branded innovators Singapore-Specific Annex is required for submission of risk management plan in support of NDA, GDA and MAV applications.			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	Yes (in Chinese)	For NCE/Biosimilar only (document in English).	Yes, in English	Yes (in Indonesian or English as in part II Quality) Refer to regulation BPOM No.24 Year 2017 regarding the Criteria and Procedure of Drug Registration, annex VII	Yes Only Japanese as M2.3 in CTD	Yes M2 in CTD: Korean Tables, etc. may be written in English.	Yes (Part 2 in ACTD) - in English or Bahasa Malaysia	Yes ACTD Part II in English	Yes (in English)	Yes (In English as M2.3 in CTD)	Yes 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 at least 2 batches from API manufacturer and DP manufacturer).	Yes QOS of DS, DP Vietnamese or English
	CMC report/body of data	Yes (in Chinese)	For NCE/Biosimilar only (document in English).	Yes (English is acceptable as M3 in CTD)	Yes (in Indonesian or English as in part II Quality) Refer to regulation BPOM No.24 Year 2017 regarding the Criteria and Procedure of Drug Registration, annex VII	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-pharmacopeia spec. should be prepared in Korean in Application package.	Yes (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)	Yes 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 at least 2 batches from API manufacturer and DP manufacturer).	Yes 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	Yes (in Chinese)	For NCE/Biosimilar only (document in English).	Yes, in English	Yes (in Indonesian or English as in part III Non Clinical Data) Refer to regulation BPOM No.24 Year 2017 regarding the Criteria and Procedure of Drug Registration, annex VIII	Yes Only Japanese as M2.4, M2.6 in CTD	Yes M2 in CTD: Korean Tables, etc. may be written in English.	Yes (Part 3 in ACTD) - in English or Bahasa Malaysia	Yes ACTD Part III in English	Only for full dossier, in English	Yes (In English as M2 in CTD)	Yes ACTD on Non-Clinic Part III or ICH CTD Module 2	Yes Vietnamese or English The non-clinical document shall be prepared in conformance with the guidelines of ACTD - Part III or Module 4-ICH-CTD.
	Non-clinical report	Yes (in Chinese)	For NCE/Biosimilar only (document in English).	Yes, (English is acceptable as M4 in CTD)	Yes (in Indonesian or English as in part III Non Clinical Data) Refer to regulation BPOM No.24 Year 2017 regarding the Criteria and Procedure of Drug Registration, annex VIII	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 III in English	Only for full dossier, in English	Yes (In English as M4 in CTD)	Yes ACTD on Non-Clinic Part III or ICH CTD Module 4	Yes (optional) 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 Pharmacodynamics 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	Yes (in Chinese)	For NCE/Biosimilar only (document in English).	Yes, in English	Yes (in Indonesian or English as in part IV Clinical Data) Refer to regulation BPOM No.24 Year 2017 regarding the Criteria and Procedure of Drug Registration, annex IX	Yes Only Japanese as M2.5, M2.7 in CTD	Yes M2 in CTD: Korean Tables, etc. may be written in English.	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)	Yes ACTD on Clinic Part IV or ICH CTD Module 2	Yes The clinical document shall be prepared in conformance with Letter 72/QLD-DK
	Clinical report	Yes (in Chinese)	For NCE/Biosimilar 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 Refer to regulation BPOM No.24 Year 2017 regarding the Criteria and Procedure of Drug Registration, annex IX	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)	Yes ACTD on Clinic Part IV or ICH CTD Module 5	Yes (optional) 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 Pharmacodynamics (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	CTD Part I (Module 1) in Chinese Regional requirements of CMC such as chromatography, batch record, draft version of manufacturing and testing specification etc. Module 5 appendix (SAP,SAR, DMP,DMR, clinical site summary report)	All documents in English. General requirements: 1.An authorization letter from the overseas manufacturer for the applicant; 2.Soft copy of the business registration certificate; 3.Soft copy and certified true copy of the manufacturer's license; 4.Methods, standards and conditions of the manufacture of the pharmaceutical product, manufacturing and quality control facilities, technical personnel, etc.; 5.Soft copy and certified true copy of GMP certificate which meets PIC/S GMP standards; 6.Soft copy and original or certified true copy of CPP from the country of origin; 7.One set of prototype sales pack for each pack size, complying with the labelling requirements; For NCE or biological entity: 8.Soft copy and original or certified true copies of CPP from 2 or more of the "acceptable" countries; 9. Expert evaluation reports on the safety, efficacy and quality of the product. CV of the expert and the expert's signature on the corresponding reports are required; 10. EU-RMP and or FDA REMS. Information on whether any of the risk management plan activities and mitigation strategies will be implemented in HK; 11. Proposed package insert of the product. Where the package insert is in the form of a patient information leaflet, a prescribing information leaflet for healthcare professionals for use in HK should also be submitted. The following document(s) to support the proposed indication(s), dosage, route of administration and other contents of the package insert (if any); 12.A copy of reputable reference; 13.Documentary evidence showing that the package insert has been approved by one of the listed countries; 14. Master formula (Batch formula not accepted) - Non-proprietary names of ingredients, colour Index number or E-number for all colourants used should be provided; 15. Finished product specifications; 16. Method of analysis 17. COA of a representative batch 18. Stability data 19. 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. 20. Safety documents for ingredients with animal origins About Biosimilar guideline, please refer "Guidance Notes for Registration of Biosimilar Products" (2019/Dec)	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 regulation BPOM No. 15 year 2019 on amendment to regulation of Head BPOM no.24 year 2017.	CTD M1 and M2 are acceptable only in Japanese. CTD M1: 1.1 Table of Contents 1.2 Approval application (copy) 1.3 Various certificates 1.4 Patent information 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 similar 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 toxic 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 & 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	Aside from the abovementioned country-specific requirements, the documentary requirements of FDA are aligned with the ACTD requirements.	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	New NDA RTF checklist was announced on 20-Aug-2019 due to patent linkage officially announced by TFDA on the same date.	E-Submission for NCE and new biologics / Vaccine for human use.	CoPP, GMP, Label mockup, Manufacturing profile including Plant Master File following Decree 54/2017/ND-CP 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 (names of "review organization", "decision organization", "advice committee" etc)	Review: CDE (Center for Drug Evaluation) Decision: NMPA (Notional Medical Products Administration) Inspection: CFDI of NMPA(Center for Food and Drug Inspection) Registration Testing: NIFDC (National Institutes for Food and Drug Control)	Review: Drug Office, DOH Approval: Pharmacy and Poisons Board	NDA approval organization in CDSCO consists the following members and committee. 1.CDSCO staff review 2.Subject expert committee review. 3.Technical committee review. 4.APEX committee review Based on the recommendations of above, DCGI will approve the NDA.	BPOM regulation No. 15 year 2019 on Amendment to regulation of Head BPOM No. 24 year 2017 article 45 and article 49 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. Committee of Quality Evaluation with the task of evaluating the quality aspect. 3. 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, Labor and Welfare) Advice CDFS (Council on Drug and Food Sanitation)	Review NIFDS, Regional Office of MFDS (generic drugs) GMP review MFDS Pharmaceutical Quality Reception, Pre-review, approval and approval overall management MFDS Approval generalization Team (Since 2019) Separate Pre Review (on application) NIFDS Drug Review Management Division	Review: National Pharmaceutical Regulatory Agency (NPRA) Advice: NPRA's Review Committee Decision: DCA (Drug Control Authority)	Review and Decision The Center for Drug Regulation and Research (CDRR) of the Food and Drug Administration (FDA) Advice The FDA may hire external consultants for data requiring specific expertise (e.g. clinical and non-clinical data, abortifacient properties, etc)	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.	Review Thai FDA Decision Thai FDA Advice Drug Committee	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	All staffs: about 800 <2020 personnel plan> CDE: 1600 in total	Undisclosed	No detailed/updated information available	No information on amount of reviewer in regulation for each section committee.	All staff: 936 Review Dept.: 561 Safety Dept.: 224 (as of Apr. 1, 2019)	MFDS Chemical Administration - Approval generalization Team: 44(Overall Approval management) - Fusion Technology Policy Team: 10 - Pharmaceutical Policy Division: 33 - Pharmaceutical Management Division: 19 - Narcotics Policy Division: 12 - Narcotics Management Division: 14 - Pharmaceutical Quality Division: 20(GMP review) - Clinical Trials Management Division: 22 - Pharmaceutical Approval and Patent Management Division: 8 - Pharmaceutical Safety Evaluation Division: 18(Related to PMS, safety data) Bio Administration - Biopharmaceutical Policy Division: 17 - Biopharmaceutical Quality Management Division: 17 NiFDS Drug Evaluation Department(Clinical, non-clinical, CMC review) - Drug Review Management Division: 23 - Pharmaceutical Standardization Division: 21 - Cardiovascular and Neurology Products Division: 21 - Oncology and Antimicrobial Products Division: 35 - Gastroenterology and Metabolism Products Division: 18 - Bioequivalence Evaluation Division: 17 Biopharmaceuticals and Herbal Medicine Evaluation Department - Bio Review Management Division: 9 - Biologics Division: 19 - Recombinant Protein Products Division: 13 - Cell and Gene Therapy Products Division: 11	Effective from 2nd Dec 2019, NPRA has been restructured into 4 Centres, i.e. 1.Regulatory Coordination & Strategic Planning 2.Product & Cosmetic Evaluation 3.Compliance & Quality Control 4.Administration Reviewers are mainly in Centre 2; and also Centre 3 for evaluation of Analytical data.	As of December 2019, The CDRR has around 100 employees, half of which are technical evaluators for registration.	unknown	CDE is responsible for drug registration review and consultation service, there are around 270 staffs including non-reviewers. Among these manpower, about 220 staffs are responsible for drug review, including Clinical, Non-clinical, CMC, PK/PD, Phar,/Tox and statistical.	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/flow	Review framework is disclosed. See http://www.cde.org.cn/personal.jsp	Undisclosed	1.DCGI accept the application in Form 44 and then following steps are followed. 2.CDSCO staff review Subject expert committee review. 3.Technical committee review. 4.APEX committee review 5.Based on the recommendations of above, DCGI will approve the NDA	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 Approved Registration Number Currently all registration process are performed in e-reg (New Aero system). Master data registration is necessary to be completed for API, all excipients, API manufacturer , excipients manufacturer & drug product manufacturer prior apply in electronic registration system. According to BPOM regulation No. 15 Year 2019, Approvable letter was removed. Approvable letter would be issued only for drug that has not yet produced in commercial scale. Note: * Only NCE/Biological Product New Additional Indication and Posology - 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.		Disclosed	Disclosed. See DRGD Section B- 8. Flow of Registration Process (Figure 4):			RTF (refuse to file) notification will be issued on Day 42 when a new drug application (NDA) or biologics license application (BLA) is deemed incomplete by the TFDA, the agency can decide not to review the application since 20-Aug 2019. New RTF checklist (Refuse to File) for NCE and Biological products (including Biosimilar) became effective since 20-Aug 2019.	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	Official timeline of BLA/NDA of import drug for review in DRR 2007: 150 working days. Special review: 120 working days	NCE: 5-7 months Generic: 9-12 months	New drugs manufactured in India: 12 months New drugs imported to India: 1.NDA: 12 months 2.Form-41: 6-9 months 3.Form-10: 2 months	Refer to BPOM regulation No. 15 Year 2019, Timeline of pre-registration 40 working days after completed documents for category 1,2,3. Timeline of registration export-only drugs: 7 working days Timeline of renewal registration: 8 hour (unwritten regulation) Timeline of minor variation registration: 40 working days Timeline of first registration of new drug developed by Industry that perform investment in Indonesia: 50 working days Timeline of first registration of first generic drug that perform investment in Indonesia and variation registration of new drug and biological product related quality that has been approved in (at least) 1 reference country: 75 working days Timeline of registration 100 working days: a. New Drug & Biological Product that are indicated for the treatment of serious life-threatening human or infection disease b. New Drug & Biological Product are indicated for treatment of serious and rare diseases (Orphan drug), c. New drug, biological product, generic drug and branded generic drug for public health program d. New drug & Biological product by Pharmaceutical industry that perform investment in Indonesia e. New drug & Biological product which development by Pharmaceutical industry / research institution in Indonesia through at least 1 clinical trial in Indonesia f. New generic drug that has same formula, source of materials, drug specification, quality, packaging specification, production process, production facility as those the approved branded generic drug g. Registration of major variation with new indication/posology for the drug as referred to point a to e. h. Registration of major variation in respect of quality and product information. Timeline of registration 120 working days for a New Drug, Biological Product, major variation (new indication/ posology which has been approved in at least 1 (one) countries with known good evaluation Timeline of registration 150 working days for New Registration of Generic and Branded Generic drug not covered by the evaluation procedure provided in registration 100 working days. Timeline of registration of 300 working days after completed documents for a New Drug, Biological Product, major variation (new indication /posology) not covered by the evaluation procedures provided in registration 100 and 120 working days.	Review time change (80 percentile value) Priority review: 8.6 months (FY2018) Standard review: 11.9 months (FY2018)	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.	The committed turnaround time for NDA is 254 calendar days. However, current applications are processed in 2-4 years. Note that FDA is now working with the Anti-Red Tape Authority on the review and revision of the processing timelines vis-à-vis alignment with the Ease of Doing Business Act. Meanwhile, processing timelines remain unpredictable.	Reference to GUIDANCE ON THERAPEUTIC PRODUCT REGISTRATION IN SINGAPORE January 2019, TPB-GN-005-005 – TARGET PROCESSING TIMELINES. APPENDIX 5 TARGET PROCESSING TIMELINES Screening: 50 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 Abbreviated review: 180 days/120 days For the non-NCE NDA with efficacy & safety clinical data, the review timeline in TFDA/CDE is 300 days. For the non-NCE NDA without efficacy & safety clinical data, the review timeline in TFDA/CDE is 200 days.	Timeframe for approval of new drug (NCE) and biologics is 220 working days*; Vaccine 280 working days*; * Referred to FDA notification on May 2018 Biosimilar: 230 working days; Generic: 135 working days	within 12 months under normal scheme

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NDA Approval review	Priority review system	Yes For detailed requirements of priority review, may refer to CFDA Doc.(2017) No.126, CFDA's Comments on Encouraging Priority Review and Approval for Innovator Drugs Updated version of this document was issued by CDE on Nov.8 2019 for public comments currently.	Usually no; except the following situations, 1. official request from Hospital Authority upon urgent situation. 2. there is a local unmet medical need of the product for communicable diseases or matters of public health importance (e.g. vaccine of recent epidemic outbreak)	There is no formal priority review system. Depends on therapeutic area and unmet requirement.	Reliance system with 120 working days Refer to BPOM regulation No. 15 Year 2019.	A priority review system exists. Orphan drugs receive priority review automatically. New drugs not designated as orphan drugs that target other serious diseases, and are likely to contribute to the improvement of quality of healthcare may be designated as "non-orphan priority review product" based on overall evaluation of the seriousness of the target disease and medical usefulness of the drug. Designation is assigned based on the opinion of external experts if an application is submitted with an application for marketing approval. Early conditional approval system became effective on Oct. 20,2017. Trial of SAKIGAKE (Japanese "Breakthrough Therapy"-type priority review system) was started from 2015. Legislation of "Early Conditional Approval System", SAKIGAKE designation and 'Early access for special-use drugs' were enacted in Dec 2019.	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 5) Drugs for which prevention or treatment effects against the prevalence of biological terrorism-induced infectious diseases and other infectious diseases may be expected. 6) Drugs used to treat or prevent serious diseases or those that are life-threatening or terminal and incurable diseases, and have markedly improved their safety or efficacy compared to existing drugs or treatment options	Yes Priority Review Conditions, Product categories and Timelines as given in DRGD 8.4.2 Priority Review	Yes 1. Products to be manufactured exclusively for export 2. New drug products considered to be a major therapeutic advance 3. First five products of newly-licensed establishments 4. Products for government projects 5. Imported pre-qualified vaccines. Applicant must make a request for priority review, to be approved by FDA. When granted, there is no explicit mention of reduction in processing timelines. (CDRR Memorandum No. 0003, s. 2013)	Priority review system or pathway is only applicable to product 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.	Yes To improve the new drug accessibility to public and accelerate the new drug review and efficient utilize the review resource, TFDA announced or amend the several designations for sponsor utilization since Nov 2019 which include: 1. Designation Request of Medications for Pediatric Population or the Minority Patients with Serious Diseases 2. Streamlined review designation 3. Priority review designation 4. Accelerated Approval 5. Breakthrough Designation Reference: https://www.fda.gov.tw/TC/siteListContent.aspx?sid=2984&id=32228	Yes Priority Review: for product in need e.g. anti-HIV, anti- cancer or product in need as per endorsed from Thai FDA. Abridged Evaluation (not all are priority reviews): 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.	Yes **Cases eligible for dossier evaluation under fast track evaluation scheme** 1. Drugs on the list of orphan drugs issued by the Minister of Health. 2. Drugs to support emergency requirements in national defense, security, prevention and combatting epidemics, mitigating consequences of natural disasters, calamities. 3. Drugs produced domestically on new GMP-conforming manufacturing lines or on upgraded GMP-EU, GMP-PIC/S conforming or equivalent manufacturing lines within 18 months from the GMP certification date; 4. Vaccines that are prequalified by World Health Organization, vaccines used in national expanded immunization programs; 5. Special therapeutic drugs with special dosage form to which there are no more than 02 (two) similar drugs (of the same active ingredients, the same dosage form, the same strength, same concentration) with a certificate of marketing registration still valid at the time of dossier submission, comprising: a) Drugs for cancer treatment; b) New generation of antivirals; c) New generation of antimicrobials; d) Drugs for the treatment of dengue fever, tuberculosis, malaria. 6. Drugs produced domestically, comprising: a) Drugs produced under contract manufacturing or technology transfer arrangements being drugs for cancer treatment, vaccines, biologics, new generation of antivirals, new generation of antimicrobials. b) Medicinal material drugs that are outcomes of satisfactory evaluated national, ministerial-level or provincial-level scientific and technology research grant, that are manufactured entirely from WHO-GACP domestically cultivated and harvested medicinal material sources. c) New drugs produced domestically on which a clinical trial in Vietnam has been completed; 7. New drugs (for cancer treatment, new generation antivirals, new generation antimicrobials), biologics; 8. Brand name drugs produced under contract manufacturing or technology transfer arrangements in Vietnam. **Cases eligible for dossier evaluation under simplified evaluation scheme** Drug registration dossiers shall be evaluated under simplified evaluation scheme when simultaneously satisfying the following conditions: 1. Drugs manufactured at facilities that are periodically assessed by Drug Administration for GMP conformity. 2. Drugs on the List of non-prescription drugs. 3. Drugs that are not of modified release dosage form 4. Drugs that are not for use directly on the eyes.

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NDA Approval review	Orphan drug system	Yes First "List of Orphan Drug" was issued by NHC/MOST/MIIT/NMPA/NATCM on May of 2018, including 121 rare diseases. The list will be updated at least every 2 years in principle. There is no specific orphan drug review pathway but priority review pathway or special pathway. -Priority review pathway: Please refer to previous article "Priority review system". -Special pathway: For new drugs that have been approved in US/EU/JP in recent 10 years, may apply for special pathway as imported new drug in urgent clinical needs. If included in the designated list, review and approval of orphan drugs will be completed within 3 months.	No	The orphan drug system does not exist. But accepts US/EU orphan drug approval. There is a proposal for providing for quick/expeditious review process for approval of an orphan drug after clinical development in India.	Drugs for rare disease will be evaluated within 100 working days. No regulation establishing	Yes An 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 outstanding and significantly greater than those of the existing drugs. Possibility of development -There is a theoretical ground for using the drug for the target disease 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 (for non-clinical trial phases, occasions where evidence is available for the possibility of the drug to advance to clinical trials are included) in Korea	Yes As described in DRGD section 5.1.5 Registration of Orphan. (Management of Orphan Drugs including criteria for designation is pending finalization of the "Malaysian Guideline for the Management of Orphan Drugs" and the List of Malaysian Rare Diseases.)	The Philippines has already passed its Orphan Drug Law, where FDA shall: ·Prioritize the registration of orphan drugs ·Facilitate the issuance of Compassionate Special Permit for the restricted use of orphan drugs We are yet to see the implementation of this law.	No orphan drug designation available	Yes 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.	No 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 with the incentive of exemption of registration fee	Yes The Ministry of Health already issued Circular 26/2019/TT-BYT on Orphan drug list, with following criteria: 1. A drug is considered to be included in the orphan drug list for prevention, diagnosis and treatment of a rare disease when it meets any of the following requirements: a) The drug is for or prevention, diagnosis and treatment of a rare disease as stipulated by Minister of Health; b) The drugs is indicated and classified as an orphan drug by one of the reference medical authorities. 2. A drug is considered to be included in the list of drugs not readily available is one for which in the Vietnam market there are no readily available other drugs that can substitute it, or one with documents proving significant quality, safety and efficacy benefits over other substitutable drugs in the local and international markets and falls under any of the following cases: a) A drug for prevention, diagnosis and treatment of diseases with low prevalence rate in a population at any point in time not exceeding 0.05% of the population and which is any of the following: a genetic, congenital, cancer, autoimmune, communicable, tropical infectious, or any other disease as decided by Minister of Health upon advice by the Professional Board formed by Minister of Health; b) Any vaccine, drug for diagnosis or prevention with estimated usage not exceeding 8,000 cases every year in Vietnam; c) A radioactive drug; a marker; d) A drug for which business activities do not generate sufficient profit to cover investment and marketing of the same in Vietnam market.
	approval matters	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 for chemical product; Manufacturing and testing specification for biologics ·labeling and artwork ·packaging insert Approval date and valid date	Current Certificate of Drug/ product registration form, the following information is described. · Company name/address · Name of Drug/product · Expiry date of the certificate	·Generic 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	Refer to BPOM regulation No 24 year 2017 article 27, 28 & 29 : All submitted information in the electronic registration system are binding and subject to approval by the authority. Those are followings: 1.Information as master data 2.Administrative Documents 3.Quality Documents 4.Non-Clinical Documents 5.Clinical Documents 6.Product Information & Labelling	·Non-proprietary Name ·Brand name ·Ingredients 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/Accreditation 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.	All registration particulars. (Re: DRGD)	Brand Name Labels Priority Review FDA GMP Clearance	·Non-proprietary Name ·Brand name ·Ingredients 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/Accreditation Category ·Forensic status of drug	TFDA will issue approval letter with draft TPI after complete NDA review. TFDA will issue notification letter after TPI finalized within 15-30 days after approval letter issued. Applicants can prepare printed TPI and packaging material samples to collect the drug license after receiving License Collection Notification within 3 months. Drug product can be manufactured/imported after License collected.	Any changes require variation submission and approval is required.	MA covers the following information, ·Brand name ·Active substance and Contents ·Dosage form ·Package size ·Specification ·Shelf-life ·Name & address of applicant ·Name & address of manufacturer

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NDA Approval review	Other information concerning approval review	Revised Drug Administration Law (DAL) of China has been published by NPC on Aug. 26th and formally enforced on Dec. 1st. Draft revised Drug Registration Regulation (DRR) was issued on Sep. 30th and Oct. 15th and under revision currently after soliciting public comments.	N/A	None	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.				There is separate review team and processing timelines for New Drug Applications of Biological products.		Patent Linkage TFDA announced that newly added one column as “data exclusivity for new addition” according to Article 40-3 of Pharmaceutical Affairs Act was implemented in TFDA license system; so this information can be searched in TFDA license system since Sep 16, 2019. The Implementation Rules of Patent Linkage of Drugs” was announced on 1-July-2019.; the effective date is Aug 20th, 2019 after announced.		
NDA Pre-approval inspection	GCP inspection	Not mandatory. After the centralized acceptance since Dec.1st 2017, CDE entrust CFDI to conduct GCP on-site inspection during NDA review per CDE review needs. It is applicable for both domestic drug and import drug.	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 for 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).	Yes for local clinical studies. Details given in the Malaysian Guideline for Good Clinical Practice (GCP) Inspection.	GCP inspection for local clinical studies (if ever conducted) is not routinely done, but may be done by FDA	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 (GUIDANCE ON GCP COMPLIANCE INSPECTION FRAMEWORK GN-CTB-3-001A-001 (2 May 2017) page 7)	TFDA issued announcement about GCP inspection process on 22-Jan-2020, and it will be implemented one year later. https://www.fda.gov.tw/TC/newsContent.aspx?cid=3&id=25880.	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	1) For local drugs, pre-approval on-site inspection will be conducted based on the review needs before approval. 2) For import drugs, usually site inspection combined with GMP system inspection after license approval based on risk and some special cause	For manufacturer with PIC/S GMP: Document inspection only, CPP/GMP certificate from source country accepted. For manufacturer without PIC/S GMP: DOH would conduct PIC/S inspection to the facilities before its product would be considered for registration in HK.	GMP inspection of Indian manufacturing units will be arranged before granting the manufacturing license and periodic review of the manufacturing 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 manufacturing units outside India on need basis.	Regulation of NADFC No. 7 year 2019: For imported product: Based on evaluation of Site Master File, if necessary desk inspection and GMP inspection site will be request by NAFDC. GMP Inspection Report from PIC/S country will be evaluated and can be considered for waiving on inspection	GMP compliance inspections are mandatory requirements prior to seeking marketing approval. Application for GMP compliance inspections for all manufacturing sites listed in the application for marketing approval must be submitted to the GMP compliance inspection authority (PMDA or respective 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). For non-sterile products, inspections may be exempted if an inspection report prepared by a PIC/s member was submitted Even in case of on-site inspection waiver, GMP documents should be submitted	On-site inspection (both local and oversea) required unless exempted. (Details given in Guidance Document Foreign GMP Inspection)	Before submitting an NDA, applicants must first secure a foreign GMP certificate from FDA for each manufacturer involved in the final product. This is obtained either through desktop review (if PIC/S-GMP certified), or through on-site inspection (for non-PIC/S) For locally manufactured product, GMP certificate is issued through actual inspection	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.	TFDA website for PMF for reference: https://www.fda.gov.tw/TC/siteListContent.aspx?sid=301&id=417	Require GMP clearance for all manufacturing flow in P3 except Quality testing site. Site inspection might be required in case submitted document is insufficient.	- 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. - Mutual recognition, acceptance of inspection, 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	The revised China GLP (draft) was issued for public comments on Nov.21st 2018.	GLP inspection and PV inspection are not required.	GLP audit shall be the part of GMP audit.	In the GMP inspection site, the Laboratory is inspected by NAFDC. The Laboratory inspected following GLP requirements.	"Paper-based compliance inspections" are executed by PMDA to confirm whether the data attached to the NDA application accurately reflects the results of clinical trials, and other studies, and whether those were conducted 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.	Laboratory should get the GLP certification if applicable, and GLP inspection will be conducted if necessary.	On-site inspection is conducted for all local establishments following appropriate standards.	None	Business undertakings engaged in wholesaling, importing and exporting pharmaceuticals, shall meet the standard of Western Pharmaceuticals Good Distribution Practice (GDP) 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 trials	Necessary procedures to start clinical trials	IRB approval isn't mandatorily required by CDE before IND submission but should before starting the clinical trial. IND permission/IRB approval => HGRAC approval => start clinical trial	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 EC approval. Trials should also be registered with CTRI (Clinical Trial Registry of India; Indian Registry) before screening patients.	After receiving Clinical Trial Approval Letter from NAFDC, the Clinical Study can be started. Refer to BPOM regulation No. 21 Year 2015 about Procedure of Clinical Trial Approval	Notice of claimed investigational new drug exemption to PMDA. Contracts with clinical sites should be signed after 30 days from the date of clinical trial notification (or 14 days from the start of the second trial).	Regulatory approval: MFDS IND approval is required. Import investigational drug; It is necessary to be approved by MFDS in order to initiate the clinical trials. IRB approval is required at each investigational site.	CTIL/CTX application => NPRA => DCA Application => MREC DCA & MREC approvals => start of clinical trial	1.Secure a License to Operate (LTO) for CRO and/or Sponsor 2.Secure Clinical Trial Approval and Import License (from FDA) 3.In parallel secure IRB/EC from institution	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), 2 May 2017 (GN-CTB-2-001A-002) Guidance on Regulatory Requirements for New Applications and Subsequent Submissions, 2 May 2017(GN-CTB-2-003A-002)	1.TFDA approval and Import permit of IMP 2.IRB approval (IND in TFDA and IRB can be submitted parallel) 3.CTA signed with site 4.1st payment done to medical institution IMP shipment to site	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.	Procedures for registering a clinical trial 1. The owner of the drug for clinical trial shall submit an application for permission for clinical trial to the Administration of Science Technology and Training, the Ministry of Health, whether directly or by post. 2. The Administration of Science Technology and Training, the Ministry of Health shall verify legality of the application within 05 working days from the receipt of the application. If the application is not satisfactory, the applicant shall be instructed in writing to complete the application until it is satisfactory. 3. The applicant shall cooperate with the Administration of Science Technology and Training, the Ministry of Health in completing the application within 60 days from the date on which it is instructed in writing. After the aforementioned deadline, the application will be rejected. 4. Within 05 working days from the receipt of the satisfactory application, the Director of the Administration of Science Technology and Training, the Ministry of Health shall grant a written approval for clinical trial according to the Form No. 13 in the Appendix III hereof. If the application is rejected, it is required to respond and provide explanation in writing.
	Required data/ documents/ brochures to start clinical trials Are there any local requirements of specific data other than ICH-M3 or S6, for initiation of clinical trials?	No All the toxicity data is included in the IB.	For additional requirements per individual scenarios, please refer to Appendix I of the guidelines (Guidance Notes on the Application for Certificate for Clinical Trial/Medicinal Test version Feb 2019), p.8-10.	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). Refer to BPOM regulation No. 21 Year 2015 about Procedure of Clinical Trial Approval	No. Generally necessary data and or documents are followed as per ICH requirements. In some instances, additional reproductive toxicity tests are requested prior to clinical trials.	There is no additional requirement other than ICH-M3	Yes CTIL/CTX Application: The necessary data / documents are covered in the latest edition of the Malaysian Guideline for Application of CTIL and CTX. Regulatory submissions are made in parallel with IRB submissions. IRB/IEC Application: Details of documents required for submission are available, eg for The Medical Research and Ethics Committee (MREC), the relevant information is available under the User Manual/Documents section in NMRR website (https://www.nmrr.gov.my).	FDA follows ICH Safety and Efficacy Guidelines as its requirements	The sponsor should submit the supporting documents (listed in Table 1) to HSA for CTA, CTN and CTC applications.	Yes Investigator Brochure is required for clinical trial approval.	ICH E6	An application for permission for clinical trial consists of: a) An application form b) Documents containing information about the drug (general information about the drug for clinical trial: name, ingredients, indications, physical and chemical properties, dosage form and other relevant information); pre-clinical trial documents; documents about the clinical trial in previous phases), prepared in Vietnamese or English language and accompanied by a summary made in Vietnamese language.

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Clinical trials	Required data/ documents/ brochures to start clinical trials Are there any local requirements of documents/brochures outside IND/CTA dossier?	Yes -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.	For additional requirements per individual scenarios, please refer to Appendix I of the guidelines (Guidance Notes on the Application for Certificate for Clinical Trial/Medicinal Test version Feb 2019), p.8-10.	As per Schedule Y. Registration of clinical trial is mandatory in the CTRI prior to initiation of the trial.	Informed Consent to the patient Refer to BPOM regulation No. 21 Year 2015 about Procedure of Clinical Trial Approval	Yes Explanatory materials and consent form used for obtaining informed consent	GMP certificate is necessary. If GMP certificate is not acquired or available, QP declaration letter and GMP dossier should be submitted instead of GMP certificate. Insurance certificate may be required in the individual investigational sites.	Yes The Malaysian Guideline for Application of CTIL and CTX covers all the main requirements including Informed Consent Form. Other key guidelines for conducting clinical trials in Malaysia are: ·Malaysian Guideline for Good Clinical Practice ·Malaysian Guideline for Safety Reporting of Investigational Products ·Guidelines for Good Clinical Practice (GCP) Inspection ·Malaysian Guideline for Bioequivalence Inspection	As per FDA Circular No. 2012-007, Application for clinical trial approval requires the submission of a dossier containing the following parts: •Part A: Clinical Trial Protocol •Pharmaceutical Data •Investigator's Brochure Other documents such as clinical trial agreements/contracts are not part of the dossier	Yes •Informed Consent Form •Principal Investigator's CV •List of overseas sites (if applicable) •GMP certificates •COA for study batches of investigational product	Yes For bio-sample needed to send out overseas, the statement from central lab and the export permit are required. For the case authorized to CRO, the authorization letter from sponsor is required.	Material Transfer Agreement	Yes a) An application form b) Documents containing information about the drug for clinical trial: - Drug trial documents: composition, manufacturing process, quality standard and drug test report (in the case of a modern drug, herbal drug or traditional drug, it is required to have a drug test report of the state-owned drug-testing facility that complies with GLP or provider of drug/medicinal ingredient testing services that complies with GLP within its scope of operation or of the manufacture that complies with GMP; in the case of a vaccine, it is required to have a quality test report of the National Institute for Control of Vaccine and Biologicals or Certification of analysis in the case of a batch of vaccines and biologicals); - Documents about pre-clinical trial of the drug that needs to be tested: reports on pharmacological effects, toxicity, safety, proposed dose, administration route and directions for use; - Documents about the clinical trial in previous phases (if the trial facility applies for permission for clinical trial in the next phases and the drug is not exempt from clinical trial in previous phases). c) Legal documents about the drug for clinical trial: - A copy of the written approval for registration of the clinical trial granted by the Administration of Science Technology and Training, the Ministry of Health. - A certified true copy or a copy bearing the seal of the trial facility, produced together with the original for comparison of the application form for permission for phase 4 clinical trial submitted by the competent pharmacy authority if the drug is requested to undergo phase 4 clinical trial; - Package insert of the drug licensed for free sale if the drug is requested to undergo phase 4 clinical trial; - A certified true copy or a copy bearing the seal of the trial facility, produced together with the original for comparison of the trial facility's certificate of eligibility for pharmacy business; - A confirmation of participation provided by the trial centers if a multicenter trial is conducted in Vietnam; - A certified true copy or a copy bearing the seal of the trial facility, produced together with the original for comparison of the written approval for participation in the trial granted by the People's Committee of the province or central-affiliated city if a field trial is conducted; - A clinical trial agreement between the organization/individual that has the drug for clinical trial and the provider of clinical trial services; between the organization/individual that has the drug for clinical trial and the trial assistance organization (if any). d) A clinical trial outline and its description: - A description of the clinical trial outline (Form No. 08 in the Appendix III hereof); - A Case Report Form (CRF); dd) Principal investigator's academic résumé and copy of the certificate of completion of GCP training course which is issued by the Ministry of Health or GCP training institution; e) Participant information sheet and volunteer letter (Form No. 09 in the Appendix III hereof); g) A record on scientific and ethical assessment prepared by the internal Biomedical Ethics Committee; h) Label of the drug prescribed in the Circular No. 01/2018/TT-BYT dated January 18, 2018 of the Minister of Health.
	Required data/ documents/ brochures to start clinical trials Document Language and acceptability of English documents	In Chinese	Documents in English. Patient information and patients consent form in both English and Chinese or in Chinese only.	English (all documents) ICF: necessary to translated into local language to particular area.	Indonesian or English	In principle, all documents must be in Japanese language.	Protocol and consent form should be translated into Korean. However, the protocol written in English is acceptable in case of phase 1 study. Other documents or plans written in English can be acceptable.	Documents in English or Bahasa Melayu.	English. For those intended for study subjects, English and/or vernacular language	English	Only protocol synopsis and documents to subjects should be in Chinese.	Thai and/or English	Vietnamese or English language

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Clinical trials	Acceptability of overseas clinical data, and requirements of additional local clinical studies for domestic NDA application when foreign data is to be used. Are there any conditional requirements to accept foreign data, for example proof of the similarity in PK/PD?	Yes Overseas clinical trial data should meet ICH GCP and support the evaluation of efficacy and safety of target indications If no ethnic sensitivity factors that influence the efficacy and safety based on PK/PD study, overseas clinical trial can be accepted.	Yes (for NCE products). Not required for generic products.	Subject to the above, Foreign Clinical data can be a supportive document, however Indian data (Phase III) is mandatory.	Yes Acceptable, if the clinical data following GCP and the result based on evaluation of safety and efficacy is good.	Yes Acceptable if the similarity in PK/PD is indicated.	Yes Foreign clinical data are acceptable if the similarity in PK/PD is indicated.	No	Yes Acceptable if the similarity in PK/PD is indicated.	Yes	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, If the clinical trials on drugs, the clinical data included in clinical documents must be in line with guidelines of ICH, Vietnam Ministry of Health or other organizations recognized by Vietnam (including guidelines of international organizations of which Vietnam is a member, guidelines of the reference regulatory authorities). If the clinical trials are conducted before above-mentioned regulations on drug development become available, the data from such trials shall be acceptable for the purpose of dossier evaluation. Clinical data (except for biologics similar to reference biologics and vaccines similar to the vaccines already licensed for marketing in Vietnam) shall cover information adequate for the analysis, the explanation of Asian ethnic factors on the safety and efficacy of the drug to allow extrapolation of the clinical data on Asian population according to the guidelines stipulated above or there must be data of bridging studies according to ICH-E5 for the extrapolation of clinical data on Asian population
	Acceptability of overseas clinical data, and requirements of additional local clinical studies for domestic NDA application when foreign data is to be used. Please comment whether there are any requirements of local clinical study data for NDA application and local clinical study is necessary or not, especially for necessity of PK / healthy sbj. data and/or patient data in the country.	Chinese PK data is required by CDE to support China NDA/BLA, which can be generated prior or in parallel with phase 3 depending on the situation. Usually China joins global/regional MRCT, which indicates the consistency in drug response (i.e. efficacy and safety) between Chinese and overall population. If conditional approval is agreed by CDE, limited Chinese data can be used to support NDA/BLA and post-marketing commitment is required.	Not necessary.	Necessary waiver for clinical trial in Indian population for approval of new drugs, which have already approved outside India can be considered only in cases of national emergency, extreme urgency, 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) Further, as per the provisos to Rule 122A(2) & Rule 122B(3) of the Drugs & Cosmetics Rules, 1945, the requirement of submitting the results of local clinical trials may not be necessary if the drug is of such a nature that the licensing authority may, in public interest decide to grant such permission on the basis of data available from other countries. Further, the submission of requirements relating to animal toxicology data may also be modified or relaxed under the DCR in case of new drugs approved and marketed for several years in other countries and adequate published evidence regarding the safety of the drug is available.	Generally, Indonesian patient's data requested which indicates similarity in drug response (i.e. Efficacy and safety) with foreign data for drug which is used for family planning programme and other drugs based on request from Authorized body, for example public health programme for TB, etc	In principle, PK in healthy Japanese sbj and P2b data in Japanese patients are requested.	Foreign data is acceptable. In principle, similarity in PK/PD between Korean and foreign data should be indicated. If there isn't, bridging study is requested by MFDS for bridging data in Korean.	Not necessary	Local clinical trials for NDA approval of imported products are not mandatory. However, there is a requirement to conduct local Phase IV Clinical trials, in lieu of submitting PSURs. The protocol for the Phase IV trial is submitted together with the NDA Dossier. (FDA Circular No. 2018-012)	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 If the clinical trials are conducted before above-mentioned regulations on drug development become available, the data from such trials shall be acceptable for the purpose of dossier evaluation. Clinical data (except for biologics similar to reference biologics and vaccines similar to the vaccines already licensed for marketing in Vietnam) shall cover information adequate for the analysis, the explanation of Asian ethnic factors on the safety and efficacy of the drug to allow extrapolation of the clinical data on Asian population according to the guidelines stipulated above or there must be data of bridging studies according to ICH-E5 for the extrapolation of clinical data on Asian population

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Clinical trials	Acceptability of overseas clinical data, and requirements of additional local clinical studies for domestic NDA application when foreign data is to be used. When requirement of the local subject data exists, please specify the required number (or rate) of local subjects in the pivotal clinical studies for NDA approval	In general, sample size needs to discuss with CDE at pre-IND communication. The total subjects' number depends on the trial design and the needs of statistics, of which Chinese subject number should meet the consistency evaluation with overall population in drug response. CDE may have requirement on the fixed percentage (e.g. more than 15%) of Chinese subjects in overall population, considering different disease prevalence and overall development plan.	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) Currently 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) 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.	Not specified. Evidence of consistency in drug responses among Japanese and foreign patients in multi-regional clinical trials based on ICH E17 is requested.	Not specified. Authority often requests statistically meaningful number of patients to be included even in the local study.	N/A	There is no required number of local subjects in clinical trials for NDA approval.	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
	Environment for conducting clinical trials Practical number of clinical centers or sites in the country. Please comment if there is any license system for clinical study site.	According to revised China DAL (Article 19), drug clinical trial institutions shall be subject to record administration; detailed measures shall be formulated by the drug administrative department of the State Council jointly with the competent health administrative department of the State Council.	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 is around 50 clinical center.	Clinical trial can be initiated in many study sites. No license system for clinical study site.	All investigational sites must be certified by MFDS, there are 196 sites (JAN 2020) Since 25OCT2018, all samples in clinical trials should be tested in certified labs by MFDS.	The ICR (Institute of Clinical Research) functions as the clinical research arm of the MoH. It has 33 branches located at major MOH hospitals (Hospital CRC) and National Cancer Institute.	Clinical trial can be initiated in any study site so long that a Philippine Health Research Ethics Board (PHREB)-accredited ethics committee exist in the site (or on-going accreditation).	There are 13 public hospitals and 16 private hospitals which can conduct clinical trials.	All medical centers or teaching hospitals and specialized hospital are qualified to conduct clinical trials in Taiwan. It's around 128 centers/teaching hospitals	21 officially recognized sites (IRB/EC sites)	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.
	Environment for conducting clinical trials Installation of IRB system for clinical trials. Is there National IRB?	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 All EC needs to be registered at CDSCO (Indian Regulatory Authority) and there is periodic renewal of registration (e.g. every three years)	There is National IRB system.	Institutional IRB.	IRB should be installed in each investigational site. There is no national IRB.	No But a Central Ethics Committee, called the Medical Research and Ethics Committee (MREC), reviews and approves all clinical trials to be conducted at all MOH hospitals as well as institutions without a Local Ethics Committee.	Ethics committee of a clinical trial site should be accredited by PHREB.	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 (jointed IRB review) system led by the TFDA has been adopted since 2013. Systems to reduce review periods and to prevent the duplication of inquiries and inconsistencies between IRBs have been adopted. Deliberations are carried out in turn by the 7 major facilities. After c-IRB, the sponsor can receive abbreviated review by each IRB using the results of the c-IRB.	Increasing number of IRB that adopt National IRB submission. Previously, it can submit directly to local IRB.	Yes There are EC both at the Site and on the health authority level

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Clinical trials	Environment for conducting clinical trials How is the actual subject enrollment situation? Are there any supportive system for patient enrollment, such as clinical trial network?	There is intensely competitive between different clinical trials for subject enrollment. Some regional clinical trial networks are established spontaneously by researchers.	The government's policy is to recommend the implementation of clinical trials regardless of the phases from the perspective of industrial development. There are 2 major clinical research centers under the umbrellas of 2 large medical universities, and they are participating in more than 1,000 multinational clinical trials. The Phase 1 Clinical Trial Centre of CUHK and the Phase 1 Clinical Trial Centre of HKU started operations in December 2013 and the 1st quarter of 2014, respectively. Data from clinical trials implemented in accordance with CFDA standards is accepted by the CFDA at trial implementing facilities certified by the CFDA (Prince of Wales Hospital, Queen Mary Hospital, the Hong Kong Eye Hospital and Hong Kong Sanatorium and Hospital's oncology department).	Clinical trials can be carried out upon approval by the Drug Controller General of India (DCGI). In 2013, the government decided to demand stricter requirements for conducting the clinical trials due to ethical problems, etc., the number of clinical trials decreased significantly with the proclamation of new regulations.	Unknown	While the environment of clinical trial is improving, the number of the patients enrolled per institute still remains low, and, therefore, the relatively high clinical trial cost in Japan is noteworthy. Clinical trial networks have been established to improve patient enrollment. However, except for the pediatric or rare disease areas, the general engagement and utility of such networks are minimal.	It depends on the situations of target diseases or investigational sites. In general, the subjects are recruited in good manner.	Patient enrollment can be enhanced further. Clinical Research Malaysia supports clinical research in Malaysia.	Clinical trials in the country must be conducted following ICH GCP guidelines.	HSA has set up an Innovation Office in April 2018 to provide a conducive regulatory environment that supports the development of the biomedical sector, by providing scientific and regulatory advice for early stage clinical development of innovative therapeutic products intended for product registration in Singapore.	There are 14 TCTC. Th enrolment per site varied by PI and site. There are less referral among the study and non-study sites	In most cases, participations in multinational clinical trials are from Phase3. Inter-facility clinical trial network has been established	Participations in multinational clinical trials are possible. Local regulations are referring to the guidelines of ICH, Vietnam Ministry of Health or other organizations recognized by Vietnam (Source: Article 24 Circular 29/2018/TT-BYT)
	Environment for conducting 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 Authority often conduct an inspection of site to verify compliance to GCP	GCP is observed in all clinical study sites. (GCP is required 100% clinical site in Malaysia). Authority conducts site inspections to verify compliance to GCP.	GCP is observed in all clinical sites. Part of the licensing requirements for CROs and Sponsors is compliance to GCP. This is verified during inspection. Likewise, inspection of sites during clinical trials is conducted to verify compliance to GCP.	GCP is observed in all clinical studies	GCP implementation in all clinical trials is mandatory since 1997. TFDA has officially become the Regulatory Member of ICH on June, 2018.	A must	Regulated entities of GCP principles 1 Every trial facility shall conduct the clinical trial according to the approved clinical trial outline and GCP guidelines. 2. DAV shall inspect the site and classify GCP compliance of the local trial facility. MoH shall publish on its portal the GCP-certified trial facilities (Source: Article 7& 11; Circular 29/2018/TT-BYT)
	Environment for conducting clinical trials Number of investigators who will conduct or participate in the clinical studies.	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	Large number of physicians in Japan	Uncountable, lots of investigators in Korea. Mandatory educational systems exist in Korea.	More than 9000 medical professionals certified with Good Clinical Practice (GCP)	Under Part A of the CTA dossier, companies are required to submit the Resumes of the principal and all other investigators involved in the clinical trial.	No info	No data for the number of investigators. The physician who is working on qualified clinical site would be able to conduct/participate in the clinical studies. However, all investigator should meet TFDA's qualification, including required GCP & Ethical training etc.	No information (Beware of USFDA blacklist)	All investigators must possess appropriate qualifications, training, and experience. All investigators involved in the trial must have had formal training in good clinical practices (GCPs), and submit proof that a GCPs course has been completed. Principal investigator's academic résumé and copy of the certificate of completion of GCP training course which is issued by the Ministry of Health or GCP training institution shall be submitted in the application for permission for clinical trial. (Source: Article 19.2.dd. of Circular 29/2018/TT-BYT)

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Clinical trials	Investigational drug Condition of customs procedure.	As IND approval system changed to implied permission system, clinical trial notice letter is issued by CDE instead of CTA approval letter, which can be used 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.		After receiving IND approval from the Ministry of Food and Drug Safety, a standard customs clearance report should be completed and approved by the Korea Pharmaceutical Traders Association.	Clinical trial import license and proper clearance required.	For the importation of each investigational drug product and ancillary materials, an import permit is required. This is issued by FDA together with the clinical trial approval. (FDA Circular No. 2012-007)	Reference to Guidance on Clinical Research Materials, 2 May 2017	The import permit is issued by TFDA and 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	MOH's DAV is responsible for authorizing the import and export of drugs in Vietnam. According to these sources, IPs for use in clinical trials are categorized as finished drugs without registration numbers. Once the MOH approves the clinical trial dossier, an import permit application must be submitted to the MOH's DAV for approval of the IP in the quantity specified in the clinical protocol. The import permit is valid for one (1) year. (Source: Article 94.1 of Pharmaceutical Law#105)
	Investigational drug Requirements of Investigational drug labeling and its language.	Yes (in Chinese) Requirements include: 1) Indicate "only used for clinical trial". 2) For investigational drugs used in IMCT, 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. need to be indicated in the label.	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.	Yes, Investigational drug label written by Japanese is needed	Yes. Korean investigational drug label is required and detailed contents are followed; 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. 10. Name of Investigator (if necessary) 11. directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product)	Yes The labelling requirements should be in accordance to Malaysian Guideline for Application of CTIL & CTX, Appendix E (Labelling Requirements). Language in Bahasa Melayu or English.	Yes In English. Note that importation of investigational drug product requires an import permit.	Reference to Guidance on Labelling of Therapeutic Products and Medicinal Products Used in Clinical Trials, 31 Jan 2018, GN-CTB-2-003D-003 https://www.hsa.gov.sg/content/dam/HSA/HPRG/Clinical_Trials/Guidance/HSA_CTB_Guidance_Labelling_MP_TP_31Jan2018.pdf Please see page 10. In English	Yes Label has to be prepared in traditional Chinese under PIC/S GMP regulation.	Yes 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-administration 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	Yes IP must be clearly labeled with the wording: "Products used for clinical trials. Use for other purposes is prohibited." A sample IP with the label in the smallest packed unit must also be included in the clinical trial dossier. Label of the drug shall be according to the Labelling Circular No. 01/2018/TT-BYT (Source: Article 19.2.h. Circular 29/2018/TT-BYT)

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Clinical trials	Investigational drug Acceptability of the use of domestically unapproved drug as comparator.	Yes For biologics, branded biologics that marketed abroad and IND approved domestically are acceptable to be one-time imported and used as comparator.	Not specified.	Not allowed/accepted	We can't use domestically unapproved drug as comparator. Comparator can be imported using special access scheme (SAS) path	Use of domestically unapproved drugs as a comparison in some cases may be permitted, especially in multi-regional clinical trials (MRCT). However, the Authority often requests complex procedures to report SAE etc. Simplification of operating procedures is now under discussion for the use of domestically unapproved drugs in the MRCT.	It is possible to use if the unapproved drug is the international standard drug. It is recommended to have a Consultation with the MFDS in advance.	Yes Details given in Malaysian Guideline for Application of Clinical Trial Import Licence and Clinical Trial Exemption.	Yes the guideline does not define restrictions on the comparator drugs. For instance, the issued List of Comparator/ Reference Drug Products for BA/BE studies include unregistered drugs.	The unapproved drug can be used as a comparator as long as its protocol and CTC/CTA/CTN have been approved. Guidelines: GN-CTB-2-001C-001 https://www.hsa.gov.sg/content/dam/HSA/HPRG/Clinical_Trials/Guidance/HSA_CTB_Guidance_CRM_2May2017.pdf	Yes It is possible to use as IMP	No Not accept.	Yes For use as reference standards/comparator drug in bioequivalence studies; if it 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. (Source: Article 73.1.b of Decree54)
	Availability of the support from multi-national CRO	Yes 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. Indian origin multinational CROs are also available.	Multi-national CRO is available in Indonesian	Yes Multi-regional CRO is available in Japan	Yes Multi-national CRO is available and local CROs are also available to support the clinical trials.	Yes International CROs include: · Quintiles · PAREXEL · INC (formerly MDS) · Covance · Pharmanet · PPDi · The George Institute for International Health · Novotech Locally incorporated CROs include Info Kinetics Sdn Bhd	Yes Multi-national CROs are present in the country.	Yes Available	Yes There are around 34 CRO in Taiwan and over 12 multi-national CRO established branch office in Taiwan. There are less local CROs in Taiwan.	Yes There are many international CRO in Thailand.	Yes
	Export of biological sample derived from subjects	According to the regulation, if export biological samples, getting the permission from IRB, HGRAC's approval is required as per based on "Human Genetic Resource Interim Management Measures" In practice, need to have sufficient rationale to get HGRAC's approval to export biological sample.	It is possible to export biological samples.	It is possible to export biological samples with proper approval and justification.	There are restrictions on the export of biological samples from subjects (No. 657/MenKes/Per/VIII/2009). Application for the export of biological samples must be made to the Ministry of Health.	Yes It is possible to export biological samples, if it is included in the signed informed consent document.	Yes It is possible to export biological samples, if it is included in the signed informed consent document.	Yes It is possible to export biological samples.	Yes It is possible to export biological samples.	Yes It is possible to export biological samples if the importing country's conditions are met. Meeting the conditions of the importing country is the responsibility of the applicant.	Yes It is possible (okay) to export biological samples and required to apply for export permit	Yes It is possible to export MTA may be required by IRB.	Yes It is possible to export.

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Clinical trials	Adverse reaction reporting during clinical trial	Adopt to ICH E2A, E2B(R3) -SUSAR occurred during the clinical trial in China and outside of China should be reported to CDE. -For fatal or life-threatening SUSAR, sponsor needs to report to CDE within 7 days after initial receiving SUSAR; for non-fatal or life-threatening SUSAR, sponsor can report to CDE within 15 days after initial receiving SUSAR. -If Chinese translation can't be prepared well, sponsor can submit the English report to CDE firstly, then Chinese report can be submitted in the next 15 days.	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	New Gazette 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.	Additional information: Sponsor should report serious adverse event in clinical trial which have life threatening within 7 working days start from the first time known the event, and following 8 working days to complete the report.	Cases of death by unknown, adverse events have to be reported to PMDA within 7 days. Cases of death by known adverse event and unknown serious adverse event have to be reported within 15 days.	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	Death or possibly leading to death SAEs within 7 days, other SAEs within 15 days.	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 For expected ADRs, reporting is part of the regular progress report. (FDA Circular No. 2012-007)	Fatal or life-threatening unexpected ADRs: within 7 calendar days. All other serious unexpected ADRs: within 15 calendar days. (See EXPEDITED SAFETY REPORTING REQUIREMENTS FOR THERAPEUTIC PRODUCTS AND MEDICINAL PRODUCTS USED IN CLINICAL TRIALS) https://www.hsa.gov.sg/docs/default-source/clinical-trials/hsa_ctb_guidance_expedited_safety_reporting_2may2017.pdf	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 CIOMS 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	Yes Clinical trial inspection was conducted based on the review needs. There are local institutes have been inspected by FDA already.	Accredited to the sites by separate parties.	Yes	Yes NAFDC will do GCP site inspection during clinical trial	Yes After NDA, PMDA inspects the applicant and 2-4 medical institutions based on GCP.	Yes, by the MFDS	Yes	Yes The authority inspects the applicant and medical institutions based on GCP, but is rarely conducted.	Yes Will be conducted by the HSA Clinical Trial Branch, on locally conducted clinical trials.	Yes TFDA request GCP on site inspection 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	Specifications and test methods are set according to Chinese Pharmacopeia and product own specification	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 set according to pharmacopeia, or by companies supported with appropriate validation documents	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 and provide i serial sealing label on the individual products.	Both compendial and non-compendial method are acceptable	Yes. With regard to vaccines, antibody containing sera, blood derivatives and plasma from human: The registrant must collect samples for quality control testing at the National institute for control of vaccines and biologics. The registrant must submit Test certificate, test standard and method, certified by the National institute for control of vaccines and biologics as part of the registration dossier
	Pharmacopeia	All import drugs and domestic drugs should follow ChP2015.	BP, USP, EP and JP. In-house specification for NCE is also 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	The FDA recognizes USP-NF, official Homeopathic Pharmacopoeia of the United States, Philippine Pharmacopoeia, official Philippine National Drug Formulary (PNDF), BP, EP, JP, Indian Pharmacopoeia, and any national compendium or any supplement to any of them	Pharmacopeias accepted by HSA are Ph. Eur., USP, BP, and JP	USP/NF, EP, JP, BP and ChP. are all acceptable.	Standard Pharmacopoeia: USP 39/ NF 34 and supplements, BP 2016 volume 1-5, the fifth edition of IP and supplements, the eighth edition of EP and supplements plus updated revision, JP 17th edition*, and Thai-pharmacopoeia II volume I part 1 and supplements. In addition, the updated version of standard pharmacopoeia as announced is accepted. * effective in February 2020	Standard: Vietnam Pharmacopoeia Reference (USP/NF, JP, EP, BP, USP, Ph.Eur.) Pharmacy business establishments and drug preparing facilities can apply Vietnam's pharmacopeia or one of the following reference pharmacopeias: European, British, United States, International, and Japanese; (Source: Article 4 Circular #11/2018/TT-BYT)
	GMP system What is current GMP requirements?	-Chinese GMP 2010 version (MOH order 79) -According to revised China DAL, there will be no GMP certificating and relevant requirements will be included in the qualification of drug manufacturing license.	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 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.	PIC/S	PIC/S GMP (Administrative Order No. 2012-0008)	PIC/S GMP requirements	Amendments of PIC/S GMP for Medicinal Products (Part 1) on May 13th. Please refer to TFDA website.(https://www.fda.gov.tw/TC/lawContent.aspx?cid=68&scid=180&id=3155)	Thai FDA is PIC/s country member effective from 1 Aug 2016.	Local manufacturers follow WHO-GMP, or EU GMP standards issued by SRA countries in order to be granted certificate of eligibility for drug manufacturing. (Source: Article 3 Circular #35/2018/TT-BYT,) For foreign manufacturers having drugs registered for marketing in Vietnam: must submit GMP from origin country. 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. b) Manufacturers belonging to ICH member countries, Australia and that are inspected and assessed as in conformity with GMP by USFDA, EMA, Australia TGA, Japan PMDA or Canada. (Source: Article 96; Decree #54)

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Manu -facturing	GMP system Please describe GMP evaluation process by the authorities.	1) For local drugs, GMP system inspection will be conducted combined with pre-approval on-site inspection according to the draft Administration of Drug Registration (for public comments now). 2) For import drugs, GMP inspection conducted after license approval, usually combined with on-site inspection except some special cases.	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 or manufacturer without PIC/S GMP certification, 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 manufacturing units outside India on need basis.	Additional information BPOM Regulation No. 7 year 2019 on the assessment on GMP compliance of imported drug manufacturing facilities. 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 orrequest a desktop inspection 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 a pre-requisite for obtaining Product Marketing Approval in Japan (see Pre-approval inspection, GMP). GMP inspection of a licensed manufacturer is performed every five years either as an on-site inspection or by inspecting the documents.	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	Manufacturers are subject to GMP conformity assessments through acceptable GMP evidence or GMP inspection.	As explained above, GMP clearance is obtained either through desktop review (if PIC/S-GMP certified manufacturer), or through on-site inspection (for non-PIC/S) For locally manufactured company, GMP certificate is issued through actual inspection.	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 GUIDE-20 GMP Conformity Assessment of an Overseas Manufacturer (Last update Dec 2018) https://www.hsa.gov.sg/docs/default-source/hprg/therapeutic-products/guide-conformity-assessment/guide-mqa-020.pdf	The PMF checklist "new formats" has been implemented since Jan 1st, 2019. Please refer to TFDA website. (https://www.fda.gov.tw/TC/siteListContent.aspx?sid=301&id=417&chk=9e77d38c-4b40-4e38-839f-d035268b9653&param=pn%3d1%26sid%3d301) Updated dosage form classification in GMP was announced on 8-Aug-2018. https://www.fda.gov.tw/TC/lawContent.aspx?cid=68&scid=180&pn=3&id=2975	GMP accreditation was replaced by GMP clearance. The application require for all product application and sites presented in P3 On-site inspection will be required for non-PICs site.	GMP evaluation process 1.Authority announces decision to set up evaluation team at manufacturing site 2.Manufacturing establishment presents summary of organization, personnel and activities applying for GMP 3.Evaluation team conducts GMP assessment at the production facility. In cases where an establishment performs one or several stages of the production process, the evaluation content shall cover only the requirements corresponding to one or several production stages performed by the establishment; 4.Evaluation team meeting with manufacturing establishment to inform about any pending items 5.Evaluation team prepare and sign the evaluation form, to also be signed by manufacturing establishment 6.Complete the Evaluation Report: (Source: Article 7, Circular 35/2018/TT-BYT)
	GMP system Please describe frequency/number of on-site inspections to domestic/overseas manufacturers by the authorities.	Since Nov. 2019, CFDI newly established a column on its website to notice the list of drug registration applications received from CDE, to which CDE required research on-site inspections and manufacturing on-site inspections, till now 2 batches including 53 applications.	Since the manufacture license valid for only 1 year, inspection will be made at least on annual basis for the concerned manufacturers.	Annually. For overseas, CDSCO started inspection of Pharmaceutical firms for import registration of drugs.	BPOM do not disclose total amount of inspection in a year. Referring to the BPOM Regulation No. 7 year 2019 article 13: point 2 mentioned amounts of BPOM inspector at least 2 person and maximum 4 person each section Point 3. Mention that inspection conducted maximum 3 days for non steril products and 4 days for steril products. Point 4. Applicant's QA person shall accompany during inspection.	Number of on-site GMP inspections of overseas manufacturers in FY 2018 was 265.	In principle, 3 years of inspection frequency for domestic manufacturing sites, however this may be shortened due to RMP; and three years for sterile products and five years for non-sterile products of inspection frequency at overseas manufacturing sites. 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 2018, there are a total of 389 companies including 250(finished drugs), and 139(drug substances).	Number of GMP Inspections in 2018 was 440.	For local manufacturers, inspection is required prior to opening, with follow-up inspection within the validity of the issued license (three years). For foreign manufacturers, inspection is mandatory for non-PIC/S certified manufacturers. Follow-up inspection may be conducted but is not mandatory for renewal of GMP certificate. (Administrative Order No. 2013-0022 and FDA Circular No. 2014-016)	No data	Overseas inspection in 2019 for reference: 31 inspection cases. The on-site inspections already arranged for 2020 (as of Oct 31st 2019): 26 inspection cases. Reference: https://www.fda.gov.tw/TC/siteListContent.aspx?sid=301&id=418	- Domestic: Non-sterile drug: every 3 years Sterile drug: every 1-2 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 periodic inspection every 3 years, ad-hoc inspection based on risk-assessment (Source: Article 9, Circular 35/2018/TT-BYT)

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Manu -facturing	DMF system Please describe DMF system (or plan for introduction). Is DMF mandatory or optional?	Mandatory for NDA. According to NMPA Announcement on Relevant Issues of Further Improving the Bundling Review and Approval and Supervision Work (No.56 2019) and CFDA Announcement on Adjusting the Review and Approval Matters of the API, Excipients and Packaging Materials (No.146, 2017), CDE established a registration platform for API/excipients/packaging materials to support bundling review and approval with DP. The platform registration is mandatorily implemented before DP application submitted, besides special reasons. In these cases, DP applicant may provide research dossier of APIs/excipients/packaging materials when submitting the DP registration application, instead of the platform registration.	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 Master File (MF) is optional. Drug substance, Intermediate, New excipient, Packaging material etc. are components of the 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.) - orphan drugs, DNA recombinant products, cell culture products, biologics, cell therapies, gene therapies, radiopharmaceuticals, export-only drugs, pharmacologically inactive ingredients (excipients, additives, etc.) are excluded. crude drugs whose pharmacological active ingredient, etc. is not identified Only drug substance (API) is subject of DMF. API for newly registered sterile injection should be submitted DMF since 2017. - Ingredients that fall under the drug shortage prevention drugs classification, and drug substances aimed at providing nutrients (e.g. glucose, amino acids, fatty acids, vitamins, minerals, etc.) are excluded.	A DMF is required for API registration, and may be replaced by a CEP or full details of Part II S ACTD.	With the adoption of the ASEAN CTD, maintenance of DMF is mandatory but not required for submission.	DMF is optional, 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' (GUIDELINE ON DRUG MASTER FILE (DMF)) describes the DMF process and documentary requirements for DMF submission (Last update 15 Jan 2019) https://www.hsa.gov.sg/docs/default-source/hprg-tpb/drug-master-file/appendix-11_guideline-on-drug-master-file.pdf	Drug substance DMF is mandatory for NDA approval. DMF dossier can be reviewed during NDA review process or applied as a separated application. DMF is required for replacing or alternative sites of drug substance.	Only SMF is required for GMP clearance.	N/A
	DMF system Annual or periodical update reporting required?	Yes Annual report should be submitted through CDE Applicant's Window within the first quarter of each year. Variation issues should be included in the annual report.	Not specified.	N/A	N/A	No annual updated system. Partial change application or notification is required for changes. ICH Q12 is under consideration.	Yes Annual report should be submitted by Jan. 31 every year if the relevant changes are applicable for the subject of annual report	No (Changes are to be submitted as post-approval variation applications.) 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.	Only when required.	Yes DMF holders and 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 (see Chapter F Post-Approval Process). Appendix 11: GUIDELINE ON DRUG MASTER FILE (DMF)	There is no annual update reporting in Taiwan. However, DMF approval is valid for 5 years and combined with NDA drug license. Once the change including major or minor change, it should be filed to TFDA, the detail post-approval major/ minor change classification, please refer to appendix 12 of "Drug Review and Registration Guidance."	No Not required	No 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	The required contents are described in CFDA order 24, Regulation on Drug Insert Sheet and Label. The contents should be written in Chinese	English or English and Chinese, requirements described in Guidelines on the Labeling 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.	Annex X and XI , Drug Registration Guideline No. 24 year 2019 on minimum information that must be stated in the product information and packaging materials.	The required contents are described in Article 50 of the PMD Act. The contents should be in Japanese language.	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.	Details given in the DRGD. The labeling for pharmaceutical products are in English or Bahasa Malaysia. Some labelling statements are mandatory in Bahasa Malaysia.	The required contents are described in Guidelines on the Labelling of Pharmaceutical Products. The contents should be written in English and/or Filipino. (Administrative Order No. 2016-0008)	Refer to: GUIDANCE ON THERAPEUTIC 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 requirement is described in Article 20 of "Regulations for Registration of Medicinal Products." The contents of outer box should be both 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. 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; 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 of imported drugs); l) Origin of the drug. 2. The outer packaging label of a drug raw material (including medicinal materials, traditional medicinal 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". 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; 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. 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	According revised China DAL (Article 12), the State establishes and improves upon a drug traceability system.	Not required for product registration.	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.	New Regulation 2D Barcode Perka BPOM 33/2018 which published on Dec 7, 2018. There are grace period 5 years for identification and grace period 7 years for authentication. The grace period for both primary and secondary packaging. The regulation for drug, food, herbal medicine, cosmetic & health supplement.	Yes Bar Code display including information such as expiration date, serial number or serial number and product code.	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.	No Bar code is optional.	Following FDA Circular No. 2016-011, the requirement for barcode is voluntary	No No regulatory requirement on bar code. It is an internal company logistics requirement.	The implementation temporarily suspended for prescribed drugs OTC products should be printed QR code in the outer box by Dec 31st 2019.	No No regulatory requirement for Bar code But some hospitals require barcode	Yes The label of the drug's, the drug's raw material outer packaging must be printed with a bar code or a QR (quick response) code or a Data Matrix Code (DMC):
Post approval	Renewal system of approved license	Renewal is required every 5 years, and should be submitted by MAH within 6 months before expiration date of approval license.	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 required every 5 years	Not renewal, but a 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.」 c. If reporting history pursuant to the above paragraphs a, b is not available, SOP data shall be submitted. 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" s tated 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 required every 5 years. Renewal needs to be submitted 6 months prior to registration expiry.	Renewal required every 5 years.	Reference to "RETENTION OF THERAPEUTIC PRODUCT ON THE PRODUCT REGISTER TPB-GN-002-001". 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 required for approved license every 5 years. On-line renewal procedure (e-submission) is mandatory from 1st Jul 2020.	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 new Thai Drug Act 2019, the certificate of drug formula registration shall be valid for seven years from the date it was issued. The certificate of drug formula registration holder who wishes to apply for renewal of the certificate of drug formula registration shall submit an application to the licensing authority before the expiry date of the certificate of drug formula registration. The drug classified as narcotics and psychotropics shall subject to renewal every 5 years. Product license will be automatically withdrawn if no production/importation every 2 consecutive years.	MA validity is from 3-5 years (3 years: NCE 1st time registered in VN; 5 years: generics and extensions).

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Post approval	Post marketing surveillance or safety monitoring program	Yes 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. In addition, safety annual report is requested by NMPA.	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 clinical trial imposed.	Indonesia PV Guideline 2011 article 3 & annex 1 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 need to be submitted every 6 months for the initial 2 years, and every years for 3 years later	Yes According to the ICH E2C(R2) guidelines, PSUR has been changed to PBRER. PBRER submission is mandatory every 6 months in the first two years and annually after two years. Use-result survey data should be included in the submission.	< Expedited reporting of safety information> A. Those who received item licensure, when a foreign government adopted measures equivalent to marketing suspension or recall, or significant information subject to reporting directed by the Minister of the MFDS became available, shall report to the Minister of the MFDS within 15 days from the day they became aware of these developments. B. They shall report to the head of the Korea Institute of Drug Safety and Risk Management (KDSRM) within 15 days from the day they became aware of the serious adverse drug reactions (occasions where they became aware of the serious adverse drug reactions occurred overseas are also included). C. Expedited reporting of safety information pursuant to B above shall be done through the home page of the KDSRM or by post with relevant electronic data attached. D. Safety information other than the expedited reporting made pursuant to above A and B, shall be reported within 1 month following the end of every quarter through the home page of the KDSRM, or by post with relevant electronic data attached. However, if reporting cannot be made in time for unavoidable reasons, scheduled reporting dates and detailed reasons for delay shall be submitted to the head of the KDSRM. <Regular updated reporting of safety information> A. Those who received item licensure for drugs with risk management plans (RMP) prepared, signal analyses, etc. for collected safety information, or benefit/risk assessment results shall be reported regularly to the Minister of the MFDS. B. Every six months for two years following drug approval, and every year for three years after that, and for the duration assigned by the Minister of the MFDS in line with item properties, safety evaluation shall be carried out, and evaluation results shall be reported within two months after the duration concerned is over.	Yes PSUR/PBRER is mandatory for NME: every 6 months in the first 2 years, and annually for the subsequent 3 years. Other safety monitoring programs may be requested if deemed necessary.	There is a requirement to conduct local Phase IV Clinical trials, in lieu of submitting PSURs. The protocol for the Phase IV trial is submitted together with the NDA Dossier. (FDA Circular No. 2018-012 and FDA Circular No. 2013-004) This is still subject to discussion with the submitted industry position.	Yes 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.	Yes 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/PBRER submission period can be adjusted based on global international birthday (IBD) and its data lock point (DLP) within 3 months of drug license collection.	Yes Active pharmacovigilance for early approval drugs for example clinical phase II registration, SMP will be classified by risk level of drugs. Monitoring period depends on risk level (as FDA announcement on 28 Apr 2017).	Yes Requirements regarding the safety [and] efficacy surveillance and evaluation reports 1. Pharmaceutical business establishments, medical service establishments shall monitor, supervise, collect, synthetize, evaluate information and send reports to the competent authority of cases of post vaccination adverse reactions, drug adverse reactions. 2. The drug registrant shall report on the safety [and] efficacy evaluation of drugs: a) To DI&ADR National Centre every 6 months throughout the marketing registration's validity period for synthetizing, evaluation and reporting to Drug Administration; b) To Drug Administration upon submission of application dossiers for extension of marketing registration certificate;

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Post approval	Risk Management Plan (RMP)	-Adopt to ICH E2E for the NDA submitted after Feb. 12th 2020 and the NDA approved after May. 12th 2020. -For the initial NDA or BLA of oncology drug in China, RMP should be submitted to CDE together with NDA/BLA. When NDA/BLA approved, MAH should strictly implement the pharmacovigilance plan and risk minimization measures specified in the RMP. -RMP is required the dynamic review and update, which initial review will be 2 years after drug launching. When 5-year renewal of license, MAH also needs to report the implementation status of RMP.	One of the mandatory requirements for NCE registration.	N/A at present	Draft RMP under preparation	RMP document is mandated for NDA as CTD 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. New drugs, stem cell therapeutics, orphan drugs and drugs for which the Minister of the MFDS deems it necessary to submit risk management plans due to occurrence of serious side effects following marketing (e.g. valproic acid, isotretinoin, alitretinoin-contained drugs, etc.), drugs requiring re-evaluation as they are different from the already-approved drugs (for new composition of effective ingredient, only change on contents, new administration route and new indication), and drugs for which applicants deem it necessary to submit RMP RMP shall be prepared with the following items included: 1. Safety-focused review items A. Summary of safety data from non-clinical studies B. Summary of safety data from clinical studies 1) Limitations of safety data on humans 2) Patient population for which safety was not reviewed at the time of application for item licensure 3) Adverse reactions and adverse events that occurred after use of relevant drugs A) Defined risk requiring follow-up assessment B) Potential risk requiring follow-up assessment 4) Defined interactions and potential interactions related to relevant drugs 5) Epidemiological analysis results for indications and adverse events of relevant drugs 6) Common actions of similar effective groups with the same pharmacological mechanism C. Summary of important safety review items requiring follow-up assessment 2. Efficacy-focused review items 3. Pharmaceutical surveillance plans A. General drug surveillance activities B. Measures to address important safety/efficacy review items requiring follow-up assessment C. Important audit schedule and summary of measures to be completed D. Post-marketing surveillance plans, including Items B and C (drug use surveillance results, therapeutic use clinical trials, etc.) 4. Risk mitigation measures A. Manuals for patients B. Elements to ensure safe use 1) Education for patients who use relevant drugs 2) Education for doctors who diagnose and prescribe relevant drugs and pharmacists who dispense and provide medications and instructions 3) Secure control systems to make safe use relevant drugs C. Instructions for experts such as doctors, pharmacists, etc. D. Packaging inserts (drafts) C. Instructions for experts such as doctors, pharmacists, etc. D. Packaging inserts (drafts) 5. Drug surveillance methods	RMP document may be required for New Drug Products/ Biologics, as noted in DRGD.	RMP is required for submission of NDAs. There's no local format of RMP, but FDA recommends compliance to EU format.	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 20 Apr 2018, the Thai FDA announce a guideline on RMP for biological product list announced by FDA for NDA.	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

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Post approva	Adverse drug reaction (ADR) reporting after marketing	MAHs are required in this Announcement to submit the annual summary report of adverse drug reaction monitoring of the last year prior to March 31 each year. The writing requirements for the annual report will be published on the website of the National Center for ADR Monitoring of China.	Serious adverse drug reactions have to be reported as soon as possible and not later than 15 calendar days from date of first receipt	Serious unexpected adverse reactions: must be reported to the licensing authority (DCGI) within 15 calendar days of initial receipt of the information by the applicant. Serious and Non-serious adverse reactions need to be report to PvPI (Pharmacovigilance program of India) within 15 days and 30 calendar days respectively. Other: to be reported in PSUR	Indonesia PV Guideline year 2011, article 3 and annex 1 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 foreign countries, as soon as possible, not more than 15 calendar days	Reporting is mandated for ADR observed in the 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	Reporting is mandated for ADR observed for marketed products. PRHs are required to monitor and report any product safety issues that arise locally or internationally to the NPRA. 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.	Reporting is mandated for ADR observed in the post-marketing products. For medical care institutions and pharmacies: 1. Severe ADR cases cause death or life-threatening, the timeline of reporting and forwarding to license holders is 7 days. The required documents should be submitted within 15 days. 2. other SADRs except of death and life-threatening, the timeline is 15 days For license holders, the report in accordance with regulations shall be submitted within 15 days once knowing the SADRs.	Follow Guidance for Industry Post-marketing Safety Reporting Requirements for Human Drug and Biological Products Including Vaccines	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 - Anamnesis - Reporter's details Name, profession, place of practice, contact no., email address

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Post approval	Variation guideline	Yes NMPA (Former CFDA) issued Technical Guideline for Post-approval Changes to Manufacturing Process on Chemical Drugs on Aug. 29th, 2017. (No.140 of 2017) NMPA issued 3 draft Technical Guidelines, including Post-approval Changes to CMC on both chemical drug products and biological products, and Post-approval Changes to Clinical Trial of Drugs on Nov. 8th 2019 for public comments.	Please refer to the Guidance Notes on Change of Registered Particulars of a Registered Pharmaceutical Product/Substance, issued by the 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 XVI): Criteria and Procedure of Drug Registration, 1.Major Variation 2.Minor Variation 3.Minor Notification Do and Tell	Yes Partial change application should be submitted for approval of changes. For minor changes, the notification system can be applied. Scope and handling of these changes are stipulated in the PMD Act and several notices.	Pharmaceutical Affairs Act, Several notices and Guidelines exist. One of the several Guidelines is "Regulation on Pharmaceuticals Approval, Notification and Review".	Yes Malaysian Variation Guideline for Pharmaceutical Products; Malaysian Variation Guideline for Biologics	Three guidelines exist for post-approval changes: 1.FDA Circular No. 2014-008 2.FDA Circular No. 2014-008-A 3.FDA Circular No. 2016-017 Requirements and process is similar to ASEAN Variation Guidelines, with additional country-specific changes and requirements. Note that the "Revised Guidelines for Minor Variations and Notifications for Pharmaceutical Products" is drafted in Jun 2019.	Yes Reference to "GUIDANCE ON THERAPEUTIC PRODUCT REGISTRATION IN SINGAPORE TPB-GN-005-005"; Chapter F Post-Approval Process.	Yes In Pharmaceutical Affairs Act and "Regulations for Registration of Medicinal Products", there are some regulation taken as guideline. For the e-submission system (EXPRESS) online application for "drug product registration process, license renewal, withdrawal and the post-market administration variation are mandatory to submit by the system from 1st Jul 2020 and related detail announced by TFDA is on the following website: https://www.fda.gov.tw/TC/siteContent.aspx?sid=9922	Yes As per ASEAN Variation Guideline (AVG).	Yes. As ASEAN harmonization. But some Vietnam-specific items are modified or added.
	Post marketing clinical trial as approval requirement	Yes In the case of "conditional-approval", post-marketing clinical trials may be requested.	Not required.	It shall be based on the condition mentioned in New drug approved. Generally, all drugs approved for first time in India are requested to conduct post-marketing surveillance/trial.	No conditional approval in Indonesia. We need to submit completed report for NDA submission	Yes The Authority may request post-marketing clinical trials as an approval requirement if further assessment of efficacy and/or safety is deemed appropriate by the Authority. These requested trial plans are included as a part of the Risk Management Plan (RMP).	No MFDS request post-marketing surveillance data as an approval requirement. If products such as orphan drugs, etc. have been conditionally approved, a phase 3 clinical trial is required as an approval requirement.	No Post marketing clinical trial is not a standard approval requirement currently.	There is a requirement to conduct local Phase IV Clinical trials, in lieu of submitting PSURs. The protocol for the Phase IV trial is submitted together with the NDA Dossier. (FDA Circular No. 2018-012 and FDA Circular No. 2013-004) The FDA may also request for any other additional studies before approval.	No requirement	Yes	Yes Active pharmacovigilance for early approval drugs for example clinical phase II registration, SMP will be classified by risk level of drugs. Monitoring period will be between 1-2 years depends on risk level	No. But Phase 4 can be requested by Advisory Council on issuance of marketing registration certificate for Drugs that have been licensed for marketing but still require further safety [and] efficacy assessment

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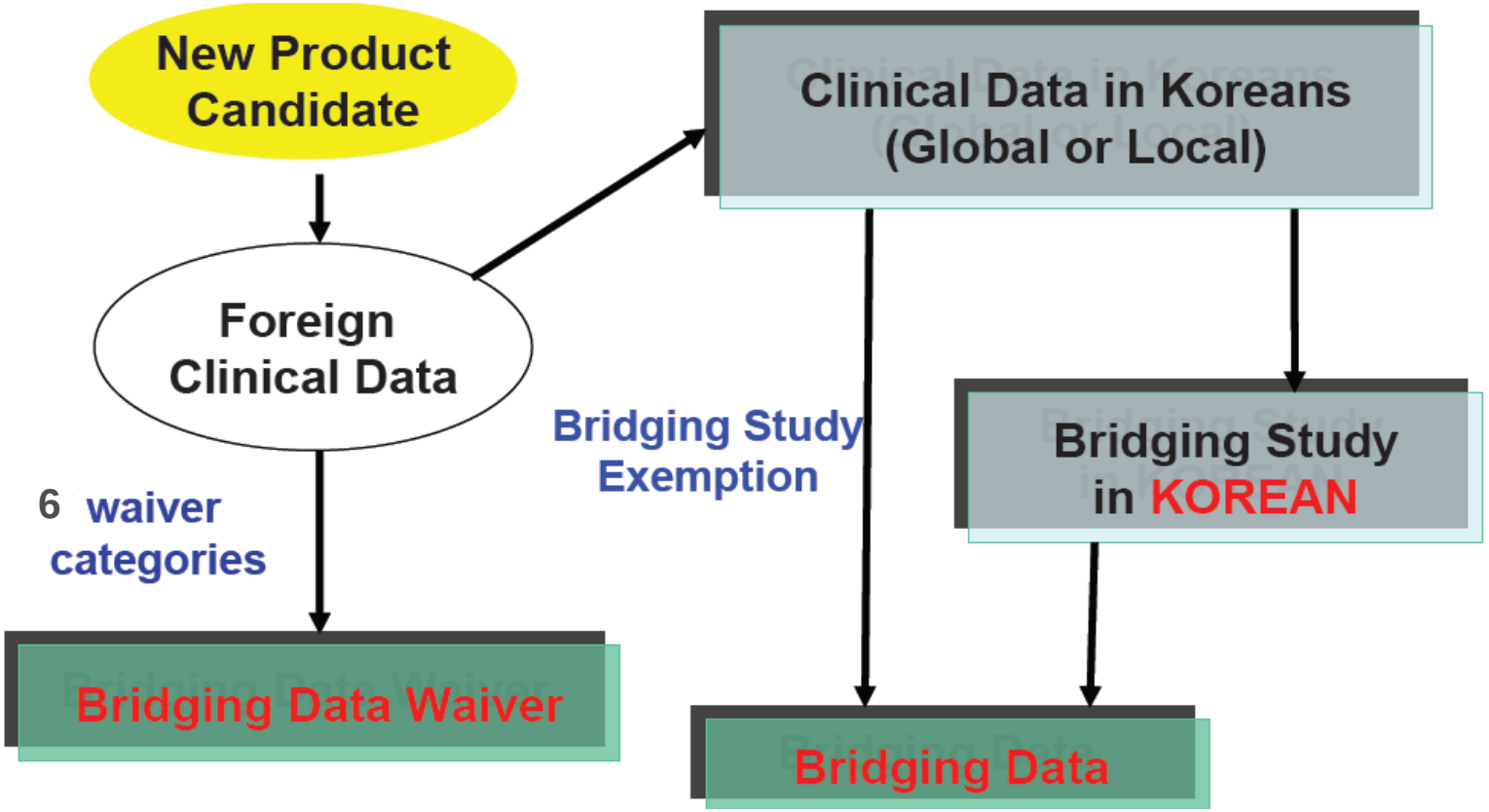
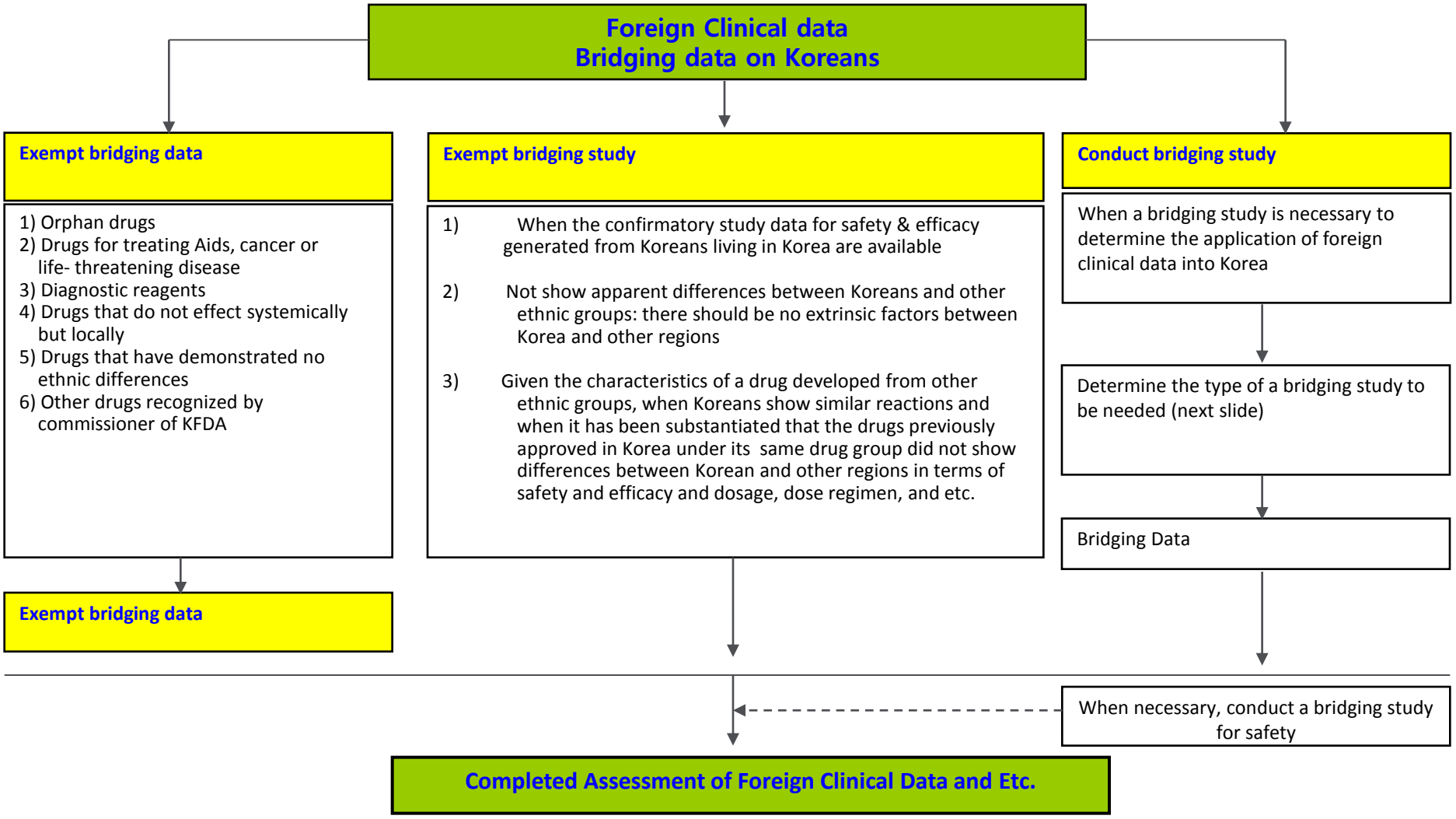

New Product Candidate
Foreign Clinical Data
6 waiver categories
Bridging Data Waiver
Clinical Data in Koreans (Global or Local)
Bridging Study Exemption
Bridging Study in KOREAN
Bridging Data


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.

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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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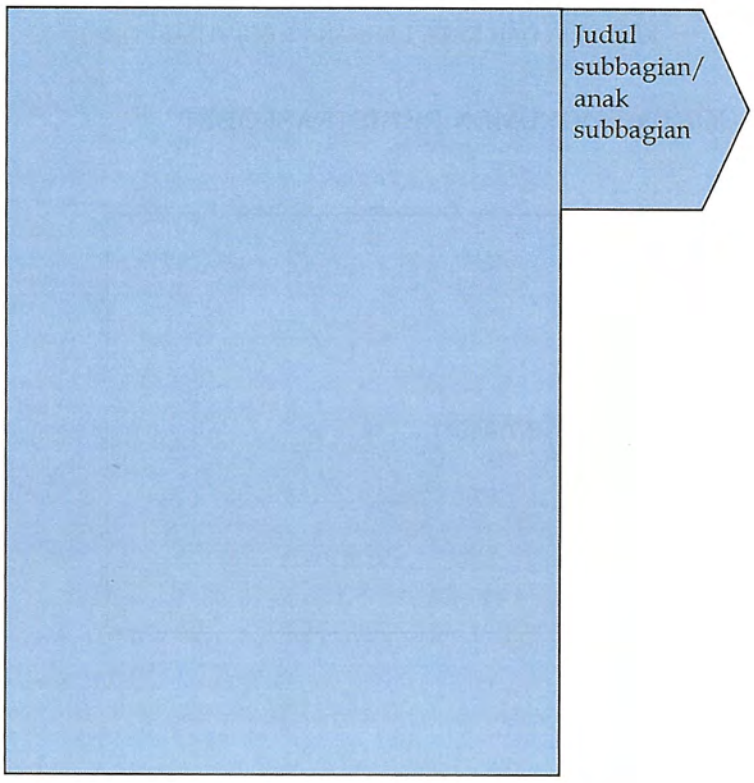
CONTOH DOKUMEN REGISTRASI OBAT

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°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

	Lokasi dalam CTD :	Volume. No studi.	Obat uji : *(1)* Halaman		
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		
	AUC	t ½	Kadar	T/P [1)]	Kadar	T/P [1)]	waktu

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				
No. *Batch*	Kemurnian (%)	Obat Aktif Kemurnian tertentu *(1)*	Nomor Studi	Obat Uji *(1)* 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 :

Lama pemberian Obat: J:

No. Studi

Spesies/Strain:

Hari Kawin: *(8)* B:

Umur awal studi:

Hari Bagian-C:

Tanggal pemberian dosis pertama:

Cara pemberian:

Ciri-ciri khusus:

Pembawa/Formulasi:

NOAEL:

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.

Species/Strain :
Umur awal studi:
Tanggal pemberian dosis pertama:
Ciri-ciri khusus :

Hari Bagian-C:
Cara pemberian:
Pembawa/Formulasi:

Hal.

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
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

(5)

\- 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 Paparan Obat pada subjek studi berdasarkan dosis harian rata-rata dan durasi pemaparan.

Tabel 4.2 Profil demografi subjek pada studi berpembanding.

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
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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
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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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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

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LAMPIRAN XIII
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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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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)	v g)		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

KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA,

ttd.

PENNY K. LUKITO

LAMPIRAN XV
PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA
NOMOR 24 TAHUN 2017
TENTANG
KRITERIA DAN TATA LAKSANA REGISTRASI OBAT

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	-

KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA,

ttd.

PENNY K. LUKITO

LAMPIRAN XVI
PERATURAN KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA
NOMOR 24 TAHUN 2017
TENTANG
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

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG HARUS DISERAHKAN
			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

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG HARUS DISERAHKAN
		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.

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG HARUS DISERAHKAN
	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

No	JENIS PERUBAHAN	PERSYARATAN	DOKUMEN YANG HARUS DISERAHKAN
		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 reprodusibilitas 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.

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			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.

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		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

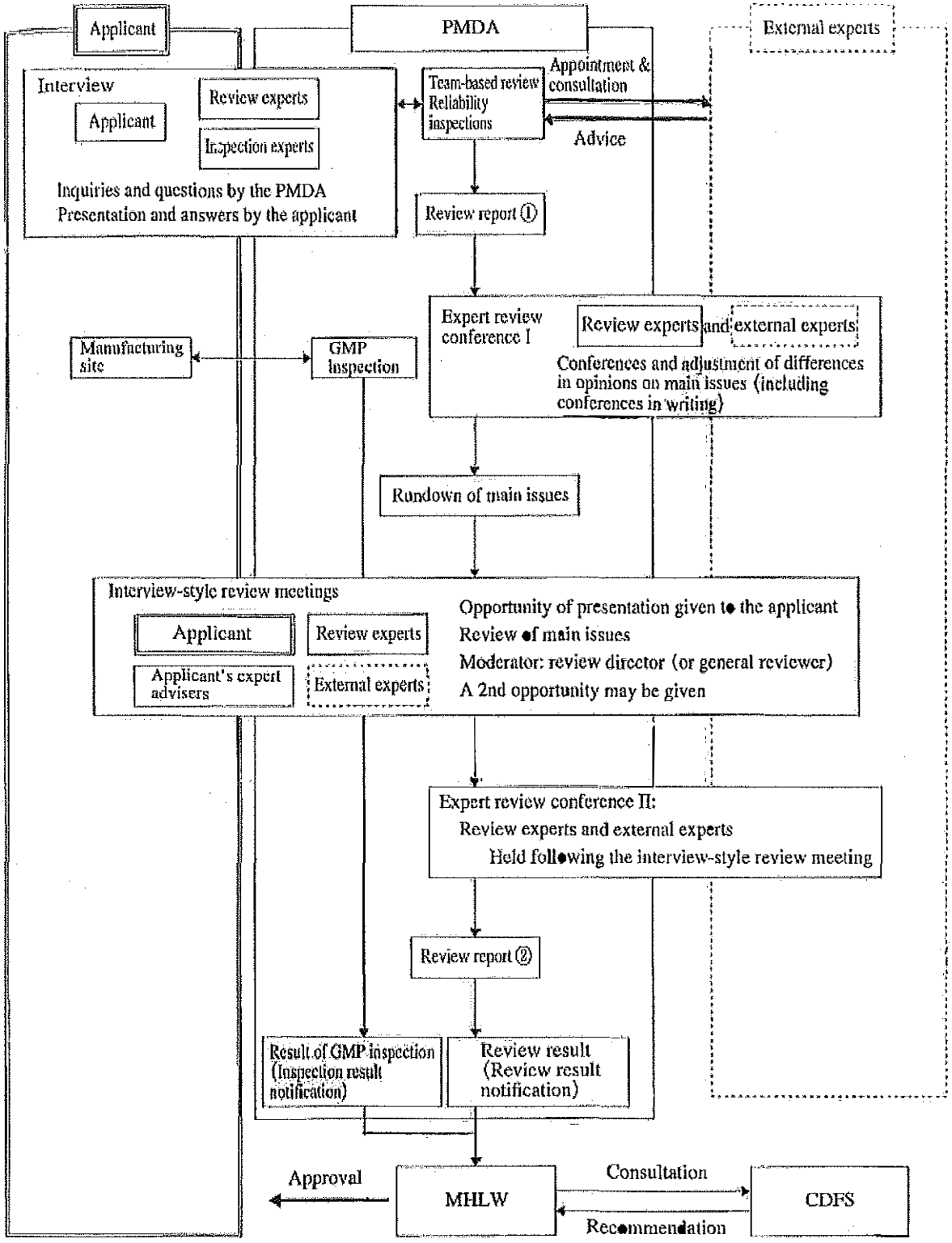
Number of reviewers	New Drugs							New Generic (NG)	Generic (G)	Biologics		
	NCE	NI	NCO	ND	NR	NDOS	NS			NB	BF	B
CMC	2	-	2	2	2	2	2	2	2	2	2	2
Clinical	2	2	2	2	2	2	2	2(BA/BE)	-	2	1	
Non-clinical	2	2*	1*	1*	1*	-	1*			2	1	1(labelling,efficacy&safety)

1(labelling,efficacy&safety)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

Application Review Process



(Source: Jiho. Drug Approval Licensing Procedures in Japan 2010. Tokyo. Jiho, Inc, 2011; P. 489.)

CHAPTER B REGISTRATION PROCESS

A company seeking to market a therapeutic product in Singapore must obtain marketing approval from HSA through making an application for product registration. The registration process involves a series of steps, as shown in Figure 1.

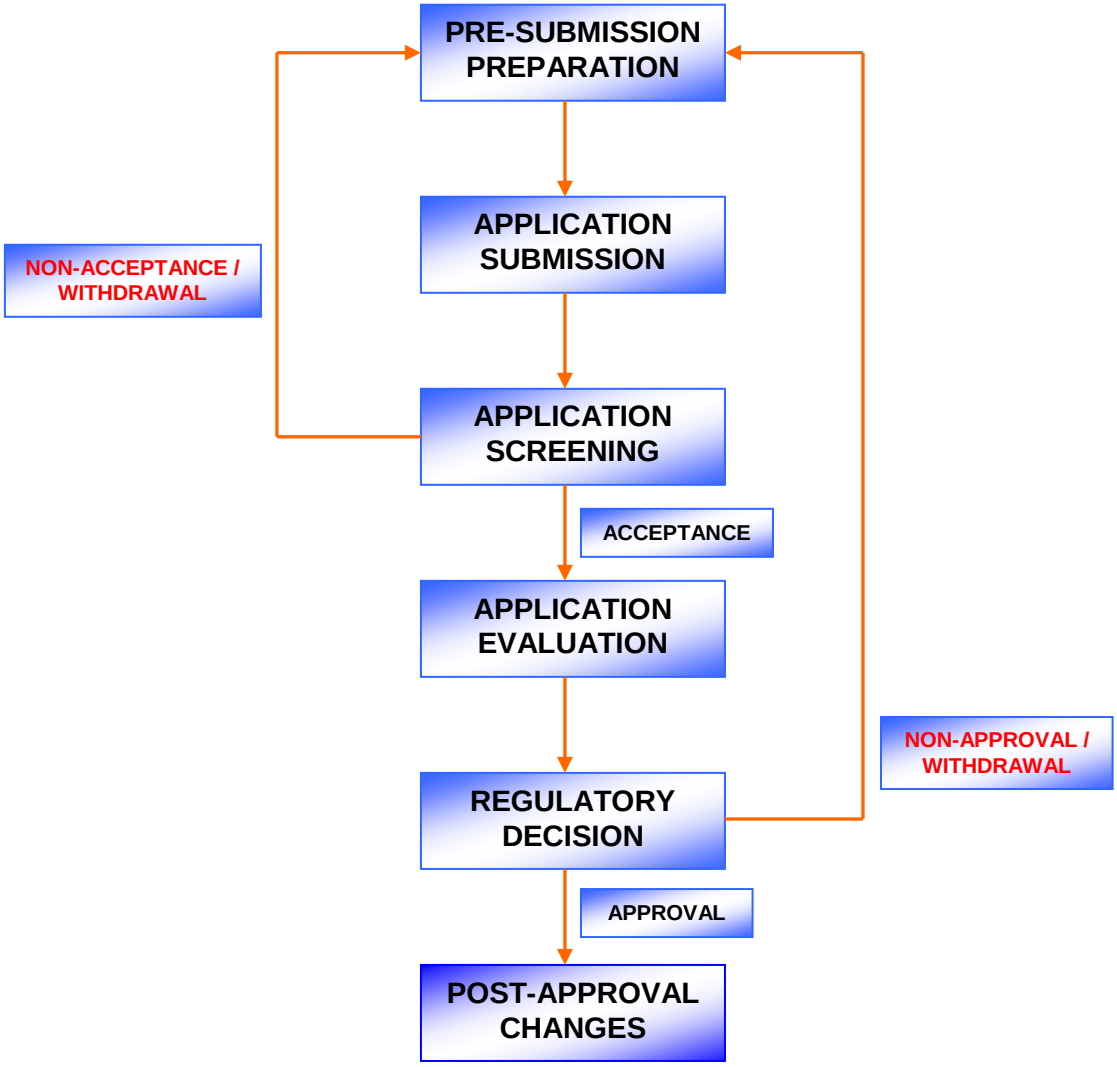


Figure 1 Registration Process for a Therapeutic Product

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

Annex 7 India

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)

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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