Asia Partnership Conference of Pharmaceutical Associations (APAC)

Analysis Report

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

APAC Regulations and Approvals Expert Working Group

April 12, 2013
Tokyo, Japan

Member Associations	
HKAPI (Hong Kong)	The Hong Kong Association of the Pharmaceutical Industry
IPMG (Indonesia)	International Pharmaceutical Manufacturers Group
IRPMA (Taiwan)	International Research-based Pharmaceutical Manufacturers Association
JPMA (Japan)	Japan Pharmaceutical Manufacturers Association
KPMA (Korea)	Korea Pharmaceutical Manufacturers Association
KRPIA (Korea)	Korean Research-based Pharmaceutical Industry Association
OPPI (India)	Organization of Pharmaceutical Producers of India
PhAMA (Malaysia)	Pharmaceutical Association of Malaysia
PHAP (Philippines)	Pharmaceutical and Healthcare Association of the Philippines
PReMA (Thailand)	Pharmaceutical Research & Manufacturers Association
RDPAC (China)	China Association of Enterprise with Foreign Investment R&D-based Pharmaceutical Association Committee
SAPI (Singapore)	Singapore Association of Pharmaceutical Industries

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Contents

Abbreviation

Abbreviation	Description
ACTD	ASEAN Common Technical Document
ACTR	ASEAN Common Technical Requirements
ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
A.O.	Administrative Order (in Philippines)
ASEAN	Association of South-East Asian Nations
BP	British Pharmacopoeia
BSE	Bridging study evaluation
CDE	Center for Drug Evaluation
CDSCO	Central Drugs Standard Control Organization (in India)
cGMP	current Good Manufacturing Practice
CHP	Chinese Pharmacopoeia
CMC	Chemistry, Manufacturing and Control
CoA/COA	Certificate Of Analysis
CPP	Certificate of Pharmaceutical Product
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Clinical Trial
CTA	Clinical Trial Application
CTA	Clinical Trial Authorization
CTC	Clinical Trial Certificate
CTD	Common Technical Document
CTIL	Clinical Trial Import License(in Malaysia)
CTM	Clinical Trial Material
CTN	Clinical Trial Notification
CTP	Clinical trial permission
CTT	Clinical Trial Team
CTX	Clinical Trial Exemption
CV	Curriculum Vitae
DCGI	Drugs Controller General(in India)
DMF	Drug Master File
DOH	Department of Health
DP	Drug Product
DS	Drug Substance
EC	Ethical/Ethics Committee
EMA	European Medicines Agency
EP	European Pharmacopoeia
EPW	Empowered Procurement Wing (in India)
EU	European Union
FDA	Food and Drug Administration (in U.S.)
FDC	Fixed Dose Combination
FSC	Free Sale Certificate
FtoF or F2F or FTF	Face to Face
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GpvP	Good Pharmacovigilance Practice
GS-1	Global Standard One

Abbreviation	Description
GSB	Global Safety Board
GTIN	Global Trade Item Number
HA	Health Authorities
HAS	Health Sciences in Singapore
HKD	Hong Kong dollar
HSA	Health Sciences Authority (in Singapore)
IB	Investigator's Brochure
IC	Informed Consent
ICH	The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH E5	ICH E (Efficacy) 5 Guideline (Ethnic Factors in the Acceptability of Foreign Clinical Data)
IEC(EC)	Independent Ethics Committee
IND	Investigational New Drug
IP	Indian Pharmacopoeia
IP	International Pharmacopoeia
IRB	Institutional Review Board
JP	Japanese Pharmacopoeia
KGCP	Korean Good Clinical Practice
KP	Korean Pharmacopoeia
KRW	South Korean won
M2	module 2
MAV	Major Variation (in ASEAN)
MF	Master File
MFDS	Ministry of Food and Drug Safety
MHLW	Ministry of Health Labour and Welfare（in Japan）
MIDR	Million Indonesian rupiah
MIV	Minor Variation (in ASEAN)
MOH	Ministry of Health (in China)
MOHFW	Ministry of Health and Family Welfare (in India)
MOHW	Ministry of Health, Welfare (in Korea)
MOPH	Ministry of Public Health（in Thailand）
MRCT	Multi-Regional Clinical Trial
MREC	Medical Research Ethics/Ethical Committee
NADFC	National Agency of Drug and Food Control（in Indonesia）
NCE	New Chemical Entity
NDA	New Drug Application
NDAC	New Drug Advisory Committee
NF	National Formulary
NIBIO	National Institute of Biomedical Innovation
NiFDS	National Institute of Food and Drug Safety Evaluation
NLT	Not less than
NME	new molecular entity
NT$	New Taiwan dollar
OTC	Over-The-Counter（drug）
PD	Pharmacodynamics
PhP	Philippine peso
PI	Principal Investigator
PIC/S	The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

Abbreviation	Description
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency (JAPAN)
PMS	Post-Marketing Surveillance/Study
PP	Philippine Pharmacopoeia
PSUR	Periodic Safety Update Report
REMS	Risk Evaluation and Mitigation Strategy
RM	ringgit
RMB	renminbi = CNY (CHINESE YUAN)
RMP	Risk Management Plan
RRC	research review committee
Rs	Rupee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SFDA	State Food and Drug Administration (in China)
SKU	Stock Keeping Unit
SMF	Site Master File
SMP	Safety Monitoring Program (in Thailand)
SMPC	summary product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TFDA	Taiwan Food and Drug Administration
TOX	Toxicology
US	United States
USP	United States Pharmacopoeia
WHO	World Health Organization

Overall Summary

1. Introduction

In order to promote the access/availability of innovative medicines for the people in Asia, we will share information regarding the challenges faced in each economy and build a platform to transmit all necessary proposals of Asia Partnership Conference of Pharmaceutical Associations (APAC) as necessary. Furthermore, the pharmaceutical associations of each economy will propose solutions to their governments and the other stakeholders regarding the pharmaceutical-related challenges of each Asian economy.

As a result of discussion, two topics, (1) Offer recommendations to realize early submission and approval of NDAs for prescription drugs in Asia, and (2) Stable supply of quality drug at global standard, were selected for further discussion by Regulations and Approvals Expert Working Group (RA EWG).

2. Creation of "Analysis Report"

RA EWG agreed to take the first step to collect practical information about regulatory requirements from each association in order to identify differences. Information collected from several aspects throughout drug development from IND, if applicable, to post-marketing and the identified differences are summarized in the following pages.

3. Next step

RA EWG will create a strategic and concrete work plan to promote the access/availability innovative medicines for the people in Asia, using the report as basic information.

2. Analysis Results based on Individual Data Sheet
Points to Consider/Differences
in Regulatory Requirements between Asian Economies

Areas	Points to Consider/Differences
IND	● Differences in the approval period for clinical trial notification/IND application between countries Large gap : from less than 1 month up to one year or more ● Acceptance of the documentation written in English East Asian countries: Many requests for using their native languages. ● Differences in the requirements dossier between countries China, Korea, India, Philippines, Indonesia: Non-clinical, clinical, and CMC data are required. Others: Data is not required, or summary parts are only required.
NDA	● Acceptance of ICH-CTD format China : Not accepted Indonesia, Thailand and Malaysia : ACTD is accepted. Others : Accepted ● Differences in used language of application materials China : All application materials are requested in Chinese Japan, Korea : Requested in Japanese and Korean in the Module 2, respectively. Others : All application materials are accepted in English. ● Review time Most of countries/economies : About 12 months China : Officially it is said to be taken 6.7 months , but in practice it takes 22 months. ● Number of reviewers A huge difference between countries/economies : 100 to 1,400
Clinical Trial	● Acceptance of foreign clinical data (including Asian MRCT) for NDA Japan, Indonesia, Korea: Acceptable. The similarity in response needs to be shown in the data. China: No. It is only for reference. Others: Foreign clinical data are accepted without any requirements. ● Required number of local subjects for NDA in Asian MRCT China, India: Over 100 subjects in Phase Ⅲ Korea, Japan: Significant number needs to show similarity in response. ● Acceptance of foreign language in the necessary documents for initiation of clinical studies India, ASEAN countries: Accept documents written in English. East Asian countries: Request documents to be translated into their native language ● Usability of unapproved drug as the comparator China, India: Not acceptable. Others: Acceptable.

Manufacturing /Post Approval (GMP Evaluation System)	● Acceptance test for drugs (to be) imported China, Korea: Applied test methods will be changed based on the pharmacopoeia in the country. ● GMP system PIC/S members: Taiwan, Indonesia, Singapore, Malaysia Under application to PIC/S: Japan, Korea, Philippines, Thailand , Hong Kong Original GMP system: India ● Experience of on-site inspection to overseas manufacturing site Frequent: Japan, Korea, Taiwan, Indonesia Some : China Little (or none): Others ● Drug Master File (DMF) system Voluntary (optional): Japan, Taiwan Mandatory requirements: Korea (Annual reporting is also mandatory.) Under discussion: China DMF can be accepted in NDA: Singapore ● Packaging label requirements Partly harmonized (+ country specific requirements) : ASEAN Country specific requirements: Others ● Bar code requirements Guideline issued: Japan, China, Korea, Taiwan (draft) According to business requirements: Others ● Renewal system Introduced: China, Korea, Taiwan, Hong Kong, India, ASEAN Other system: Japan (Reexamination system) ● Risk management plan Required: Japan, Taiwan Planned: China, Korea Request of REMS/RMP in case submitted to US/EU: Hong Kong, Singapore, Thailand (some Biotech which submitted as ICH-CTD) ● Post-approval variation Harmonized variation guideline: ASEAN Country specific requirements: Others

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

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

Item	Contents	Detail or Example	China RDPAC	Hong Kong HKAPI	India OPPI	Indonesia IPMG	Japan JPMA	Korea KPMA/KRPIA	Malaysia PhAMA	Philippines PHAP	Singapore* SAPI	Taiwan IRPMA	Thailand PReMA
IND	Requirements of the applicant	CRO is possible?	Companies or regulatory agency (CRO)	Basically, CRO and doctors who can follow standards of GCP.	Sponsor companies, CROs and doctors who can follow standards of GCP.	CRO , Companies and doctors who can follow standards of GCP.	Basically, companies and doctors who can follow standards of GCP.	Company, CRO or doctor, who can follow standards of GCP, can be IND holder.	Investigator or sponsor or CRO should make the application.	Sponsor companies, CROs and doctors who can follow standards of GCP.	Sponsor company should make the application.	CRO can be an applicant (IND holder), just the company register in Taiwan with legal entity.	Drug manufacturing/import license holder or government (applicant can be sponsor or CRO)
	Clinical trial consultation system	System, Timing, Procedure	There are formal and informal consultations with CDE. 1) CDE started formal consultation system in 2011. 2) pre-IND, end of PhI, end of PhII or pre-NDA are applicable if the product accepted for special review procedure. Flow: application with questions and documents/data (-8Weeks), FtoF meeting, then, fixed minutes (4W) 3) If initiated by CDE, consultation meeting usually is held during IND or NDA review period.	No	Non-formal consultation is possible. Pre-screening of the application is done at DCGI office before accepting our application. 1. IND- For phase 1 trials of NCEs application is referred to IND committee scheduled to meet every quarter(for molecule discovered outside India FIM studies are not permitted. 2. Other IND application -The application is referred to New Drug Advisory Committee (NDAC) for review. Post review, the Sponsor/CRO is invited to a Face to Face meeting with NDAC where they need to present & defend the proposal	The consultation with Head of evaluator is very Tuesday and consultation with Assistant Director of registration every Wednesday or by appointment .	There are many kinds of charged consultation with PMDA. Ex. Pre-PhI/Pre-PhIIa/Pre-PhIIb/End ofPhII study, Pre-application, Quality, Safety, etc. Flow: Tentative application (-8Week), submit the questions and documents (-5W), Inquiries and the answers, PMDA' opinion(<-4day), FtoF meeting, Fixed minutes (30days)	Official pre IND consultation can be held 40 days before expected consultation meeting and it should be requested in written form. Meeting minutes will be issued 10 days after the meeting by MFDS(Ministry of Food and Drug Safety). Pre-review system covers IND preparations. F2F meeting 20 days, Final decision 30 days	No	For company-initiated local trial, the proposed clinical trial protocol is prepared by the medical department in consultation with a physician-specialist who becomes a co-author. The protocol is then submitted to the GSB and regional Safety Department & Regulatory Department for approval. The final approval comes from the FDA. For investigator-initiated trials, the proposed protocol is written by the authors subject to the approval of the medical dept of HI-Eisai. The protocol is then sent to the various departments similar to company-initiated trials. (see FDA Circular 2012-007)	No. But for first-in-human trials, HSA would prefer if company has a pre-submission consultation about 2 months before submission.	Regulation consultation service is available for all phases of product development. It is free of charge without legal binding. The way for the consultation can choice official letter response, face to face meeting etc. The procedure should be on-line submission first. Then the project manager of CDE will contact with the applicant for confirm the question which applicant raised and requesting more information.2 to 4 weeks after the submission can arrange the meeting. Also the project manager will arrange the appropriate time and attendee list for the consultation meeting. In general, 1 hour for FTF meeting, and meeting minutes may available 2 weeks after the meeting.	Can consult at FDA (Such as direct contact, telephone)
	Flow of clinical trial notification, IND application and IRB permission	Flowchart	Clinical trial can be initiated after IND approval and IRB permission. In China, clinical trial application is necessary. After getting clinical trial permission (CTP), sponsor should apply for IRB permission with CTP, protocol, IB etc. Even if IRB/IEC review is independent of CTP, all IRB/IEC require CTP as part of the application document.	Approval by DOH is required. IRB approval is also required.	Clinical trial on new drug shall be initiated after authorization by CDSCO (NOC:No Objection Certificate from DCGI) and approval of respective EC. In case of parallel applications, CDCSO will grant conditional approval and note that the trial should start after Ethics approval.	Flow Chart of Clinical Trial Notification see Attachment II a & II b , IIIa & IIIb , IV a & IV b , (See Annex 1)	In Japan, a clinical trial is conducted based on notification, not on application. Contracts with clinical sites should be signed after 30 days from the clinical trial notification (14 days from the second trial onwards).	There is no clinical trial notification system, and only IND approval is available. Clinical trial should be conducted within 2 years after IND approval. (See the flow chart at Annex 2)	Approval by National Medical Research Register is required. IRB approval is also required.	We now have a central ethical review board in the FDA. This board reviews the protocol. Once approved, the CT may proceed. Centers where the clinical trial is to be conducted is notified. Please see FDA Circular 2012-007 (p. 6 &8)	Approval by HSA and IRB approval are required respectively before start of clinical trial. Parallel submissions is possible to both the HSA and the respective IRB.	TFDA have clinical trial notification process and general IND application procedure. CTN process only review the administration documents by CDE without scientific review for protocol. IRB permission will depends on the site requirement and approval time also depends on IRB Most contract with clinical site needs to get IRB approval first then to signed the contract, the time for contract may takes around 2 months.	Apply for IRB or IEC Review and Approval - There are 8 accredited IRB/IEC by Thai FDA - For other study sites that IRB has not accredited, required to submit CT protocol to IRB of MOPH for approval. After IRB/IEC approval, submit the approval letter for IND application Flow chart: Refer to Guideline on Application for Drug Import permit into Thailand for Clinical Trial (2009)
	Time required for clinical trial notification, IND application and IRB permission obtainment	Official timeline: **working days Timeline based on actual experience	CTA review usually takes 12+/-2M months at least after application. After CTA approval, sponsor should conduct clinical trial within 3 years, otherwise, CTP shall be invalid.	3 months	IND review: 6-8 months EC review: 2-4 months	Timeline for evaluation is 14 working days for protocol & amendment of clinical trial after NADFC stated the protocol & amendment complete .	The rule of "after 30 days from the first clinical trial notification" for drugs containing new active ingredients, new ethical combination drugs and drugs with a new administrative route. The clinical trial can be started after 14 days from clinical trial notification for the second trial onwards (for the same product).	IND application official timeline: 30 working days Timeline based on actual experience: Given 1 time query by MFDS during their IND review period, it takes 2-3 months. According to sites, IRB review will be held every 2 weeks to every 2 months depending on the sites. Totally, for initial 3 months, we can get IND approval & IRB approval in parallel.	Not mentioned.	No specific timelines for trial notification. (Basically not more than 60 days from submission)	HSA review 4-6 weeks (30 days), CTT/IRB review 30-60 days.	The time for CTN will within 30 days. General IND application procedure will review protocol in detail by CDE and may request to revise protocol based on their review result. the approved time may takes around 30 to 45 working days. IRB permission time is depends. The approve time may takes around 3 to 4 months average.	IND notification : (to Thai FDA) - 20 days IND : (to Thai FDA) - 2 months IRB : (each study site or EC of MOPH) - 4-6 months
IND appli-cation materials	Application form	Requirements and language	Yes application form (in Chinese)	Application form for Certificate for Clinical Trial	Yes (Form 44, in English)	There is a checklist requirement .	Yes: Clinical trial notification form (in Japanese)	Yes: Clinical Plan Approval Request form (in Korean)	Application form for CTIL/CTX.	Yes, in English. Please see FDA Circular 2012-007	Application form for Clinical Trial Certificate (CTC) to HSA. IRB has no form.	Application form is needed and it can fulfill it in English. But the format is in Chinese.	Local form (in Thai)
	A statement regarding the reason why the sponsoring of the proposed clinical trial is scientifically justified	Requirements and language	Yes (in Chinese)	No	Yes (in English) and vernacular language	Yes	Yes	Yes	No	Please see FDA Circular 2012-007 (p.4)	No	Yes, the official letter to indicate the sponsoring of proposed clinical trial is needed.	Cover letter (have template in Thai)
	Protocol	Requirements and language	Yes (in Chinese）	Yes, in English	Yes (in English)	Yes	Yes (in Japanese in principle）	Yes (in Korean)	Yes, in English	Yes, in English	Yes, in English	Yes, Chinese or English version all can accept. But for global clinical trial, English version protocol is best choice.	See detail in guideline, can be in Thai or English

＊"IND" means Clinical Trial Application in Singapore.

Item	Contents	Detail or Example	China RDPAC	Hong Kong HKAPI	India OPPI	Indonesia IPMG	Japan JPMA	Korea KPMA/KRPIA	Malaysia PhAMA	Philippines PHAP	Singapore* SAPI	Taiwan IRPMA	Thailand PReMA
IND appli-cation materials	IB	Requirements and language	Yes (in Chinese) Usually synopsis or abstract of each report in Chinese is required, attached with source report.		Yes (in English)	Yes, (in Indonesian or English)	Yes (in Japanese in principle, English is acceptable in part)	Yes (English acceptable)		Yes, in English	Yes, in English	Yes, Chinese and English version IB all accept. But for global clinical trial, English version IB is best choice.	See detail in guideline (for unregistered drug in Thailand)
	CRF (sample)	Requirements and language	Yes (in Chinese)	Yes, in English	Yes (in English)	Yes, (in Indonesian or English)	Yes (in Japanese in principle, English is acceptable in part)	Yes (English acceptable)	Yes, in English	Yes, in English	Yes, in English	Yes, Chinese and English version CRF all accept. But for global cynical trial, English version CRF is best choice.	No requirement
	Informed consent	Requirements and language	Yes (in Chinese)	Yes, in English or Chinese	Yes (in a language that is non-technical and understandable by the study subject.)	Yes, (in Indonesian or English)	Yes (in Japanese)	Yes (in Korean)	Yes, in English	Yes, in English	Yes, in English	Yes (in Chinese)	No requirement
	Investigator's CV	Requirements and language	Yes	CV of PI	Yes (in English)	Yes, (in Indonesian or English)	No	No	GCP certificate for each investigator.	Yes, in English	CV of PI, in English	Yes, English and Chinese version is accept. But for global clinical trial, will request PI to provide English version CV.	No requirement
	Non-clinical summary	Requirements and language	Yes (in Chinese)	No	Yes (in English)	Yes, (in Indonesian or English)	No	Yes (in Korean)	Investigator's brochure.	Yes, in English	No	No.	including in IB
	Non-clinical report	Requirements and language	Yes (in Chinese) Usually synopsis or abstract of each report in Chinese is required, attached with source report.	No	Yes (in English)	Yes, (in Indonesian or English)	No	Yes (English acceptable)	Investigator's brochure.	Yes, in English	No	No.	including in IB
	Clinical summary	Requirements and language	Yes (in Chinese)	No	Yes (in English)	Yes, (in Indonesian or English)	No	Yes (in Korean)	No	Yes, in English	No	No.	including in IB
	Clinical report	Requirements and language	Yes (in Chinese) Usually synopsis or abstract of each report in Chinese is required, attached with source report.	No	Yes (in English)	Yes, (in Indonesian or English)	No	Yes (English acceptable)	Published clinical data.	Yes, in English	No (for HSA, every 6 monthly, status report of the trial to be submitted; for IRB usually annually)	No.	including in IB
	CMC summary	Requirements and language	Yes (in Chinese)	No	Yes (in English)	Yes, (in Indonesian or English)	No	Yes (in Korean)	No	Yes, in English	No	Yes, English version accept.	See detail in guideline (for NCE)
	CMC report	Requirements and language	Yes (in Chinese)	No	Yes (in English)	Yes, (in Indonesian or English)	No	Yes (English acceptable)	No	Yes, in English	No	No.	See detail in guideline (for NCE)
	GMP certificate of the investigational drug	Necessary or Unnecessary	GMP certificate is not required. But a statement that investigational products are formulated in accordance with GMP should be submitted.	Yes	YES.	Yes, (in Indonesian or English)	No	Necessary	Yes	Yes, in English	No (HSA application, to provide GMP certificate of the Drug Product site of Investigation drug, during CTC application)	Yes, provide CoA	unnecessary
	Sample of the investigational drug (for IND review)	Requirements and language	Yes for import product registration.	Yes, COA also.	Samples of reference standards and finished product (equivalent of 50 clinical doses or more, if requested by the Authority), with testing Protocol/s, full impurity profile and release specifications	No	No	No	No, COA only.	Yes (Laboratory testing may be requested)	No	No.	No requirement

＊"IND" means Clinical Trial Application in Singapore.

Item	Contents	Detail or Example	China RDPAC	Hong Kong HKAPI	India OPPI	Indonesia IPMG	Japan JPMA	Korea KPMA/KRPIA	Malaysia PhAMA	Philippines PHAP	Singapore SAPI	Taiwan IRPMA	Thailand PReMA
NDA	Acceptance of CTD format	CTD or ACTD or Others ?	CTD of CMC for chemical drug with registration category 3~6 can be acceptable. CTD of non-clinical, clinical documents are not acceptable at this moment. CTD of biologicals are still not acceptable.	Not specified. CTD can be accepted.	ICH-CTD is acceptable	ACTD format .	Application data for new drugs have to be handled by the CTD format.	CTD format is required for NCE	All applications are made in ASEAN CTD format.	Application data for new drugs have to be handled by the ASEAN CTD format. Besides, ICH-CTD can be accepted. There is only 1-2 FDA personnel dedicated in the review of ACTD submissions.	ACTD or CTD	Application for NCE have to be submitted in CTD format.	ACTD
	Category of NDA	ex. NCE, Generic, Supplemental,	1) New chemical entity never marketed in any country. i. Drug substance and its preparations made by synthesis or semi-synthesis. ii. Chemical monomer (including drug substance and preparation) extracted from natural sources or by fermentation. iii. Optical isomer (including drug substance and preparation) obtained by chiral separation or synthesis. iv. Drug with fewer components derived from marketed multi-component drug. v. New combination products. vi. A preparation already marketed in China but with a newly added indication not yet approved in any country. 2) Drug preparation with changed administration route and not marketed in any country 3) Drug marketed ex-China, including: i. Drug substance and its preparations, and / or with changed dose form, but no change of administration route. ii. Combination preparations, and / or with changed dose form, but no change of administration route. iii. Preparations with changed administration route and marketed ex-China. iv. A preparation already marketed in China but with a newly added indication approved ex-China. 4) Drug substance and its preparation with changed acid or alkaline radicals (or metallic elements), but without any pharmacological change, and the original drug entity already approved in China. 5) Drug preparation with changed dose form, but no change of administration route, and the original preparation already approved in China, 6) Drug substance or preparation following national standard. (Supplemental application is also described by regulations.)	Two categories: 1. New Chemical Entity (NCE); 2. Generic (i.e. drug substance already registered at Department of Health (DOH))	New Drug: 1) New Chemical Entity (NCE), 2) New indications, dosage, dosage form and route of administration 3) Fixed Dose Combination (FDC) (See 122E of the Drugs and Cosmetics Rule) Note: all vaccines and Recombinant DNA (r-DNA) derived drugs shall be new drugs unless certified otherwise by the Licensing Authority	A. New Registration , consist of : a. Category 1: New Drug and Biological Product registration including Similar Biological Product / Similar Biortherapeutic product . b. Category 2: copy drug / generic product. c. Category 3: Registration of other preparationt containing. B. Registration of drug variation, consist of : a. Category 4: Major variation registration (VaMa) b. Category 5 : Minor variation registration that needs an approval (VaMi-B) c Category 6.: Minor variation registration with notification (VaMa-A) C. Re-registration : a. Re-registration / renewal .	(1) Drugs containing new active ingredients (2) New ethical combination drugs (3) Druds with a new administration route (4) Drugs with a new indication (5) New dosage form drugs (6) New dosage drugs (7) Follow-on biologics (8) Drugs supplied in an additional dosage form (9) Similar ethical combination drugs (10) Other drugs (Minor changes in approved matters are handled by simply submitting notices.)	<Chemical> (1) Drug containing new active ingredient. 1) New chemical structure 2) Combination drug including novel ingredient (2) Data requering drug(Drug for data-based re-evaluation) 1) Drug with new salt or isomer 2) Drug with a new indication 3) New dosage drug - Increase/Decrease amount of API - New combination drug 4) Drug with a new adminstration route 5) Drug with a new dosage and administration 6) Yeast, Fungi derivated drug : New origines 7) Drug with a new formulation(same route) <Biologics> (3) Drug containing new molecular entities 1) DNA recombinant durg and Cell culture drug 2) Biologics -Vaccine, antitoxins -Blood products -Biologics other than above (therapeutic antigens, botilinium products, ect). (4) Data requiring drug(Drug for data-based re-evaluation) 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(recombinat DNA) 8) Others not separately classified	1) New Drug Product (New Chemical Entity): -Small molecule drugs with new chemical compound that has not been registered in Malaysia before, or - a new combination that has not been registered before, or - a registered compound with new indication for new population age (e.g. pediatric patients) - a registered compound with new dosage form for new indication 2) Biologics : - Any products that is produced using biotechnology, this includes vaccines, monoclonal antibodies, blood products, biosimilars etc. 3) Other Prescription Drugs: - A line extension (new dosage form, new strength) of a registered product (for the same indication) - Generic product registrations	(1) Drugs containing new active ingredients (2) New ethical combination drugs (3) Drugs with a new administration route (4) Drugs with a new indication (5) New dosage form drugs (6) New dosage drugs (7) Follow-on biologics (8) Drugs supplied in an additional dosage form (9) Similar ethical combination drugs (10) Other drugs Minor changes in approved matters are handled submitting notices and sometimes requires prior approval	NDA-1 for the first strength of NCE. NDA-2 for new combination, new dosage form, new route of administration or new indication of registered chemical entities. NDA-3 for subsequent strengths of a new drug product. GDA-1 for the first strength of a generic chemical product. GDA-2 for subsequent strenths of the generic chemical product.	New Drug I : (1) New chemical entity (2) New indication (3) New combination (4) New administration route New Drug 2 (1) New dosage form (2) New usage dose (3) New unit dose	1) Chemical drugs 1.1) New Drugs (NCE, NI, NCO, ND, NR, NDOS, NS) 1.2) New Generic (NG) 1.3) Generic (G) 2) Biological Products *NCE = New Chemical Entity, NI = New Indication, NCO = New Combination, ND = New Delivery system, NR = New Route of administration, NDOS = New Dosage form of Approved New Drug, NS = New Strength of Approved New Drug
	Requirement of CPP	Timing of submission. ex. at NDA, before approval Number of required CPP. Source country. ex. Manufacturing/exporting country, Marketing country (FSC)	Import drug require CPP at NDA. Both CPP granted by manufacturing country or marketing country are acceptable.	To be submitted at the time of application No. of CPP required: NCE: 2 ICH countries Generic: 1 (source country only)	CPP or Free sale certificate (FSC) issued by country of origin is required at NDA	Copy CPP is submitted during pre-registration. The original CPP should be present during registration. CPP only required for imported product. The product with one CPP will evaluated with 300 working days . The product with three CPP (one CPP from manufacturing country , two CPP from harmonized country evaluation{ EU} or country which well known good evaluation system { US, TGA, UK } will evaluated with 150 working days.	Not required	Required for Import Drugs Timing : When CPP is not be submitted at NDA, MFDS(Ministry of Food and Drug Safety) requests it as one of supplementary queries. So it should be submitted as supplementary data. Number : One original document Source : Manufacturing country/Marketing country (It could be submitted separately.)	Category 1 & 2: CPP required at time of application Category 3: CPP required at time of application but not required for locally produced generics+N25s	Timing of submission is at NDA or before approval. Number of required CPP is 1 from Source country e.g. ex. Manufacturing/exporting country, Marketing country (CPP or FSC/GMP)	Submission of CPP is not compulsory and depends on type of submission. In case of NDA with CPP, basically required at NDA.	NDA can be submitted without CPP but it needs clinical trial(Ph1+Ph3 or Ph2+ Ph3) conducted in Taiwan (Clinical development in Taiwan in earlier) then can be waived. NDA can be submitted with one CPP in one of 10 advanced countries but also need one clinical development in Taiwan (Ph1 or Ph2 or Ph3) within limited Taiwan subjects enrolled into the study. Product have to be launched in source country or 10 advanced countries.	at NDA submission 1 original CPP Manufacturing country

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NDA	Approval can be obtained by utilizing foreign clinical trial data.	Requirement of bridging data/report and global clinical trial data/report. Necessity of PK study in local population.	Global / MRCT clinical data for chemical drugs are acceptable, but Chinese P3 and PK data is indispensable. For biologicals, global / MRCT clinical data is unacceptable at this moment.	The overseas clinical trial data is acceptable. Bridging data are not required.	Clinical data in Indian population is required except few life saving therapeutic categories which is at the discretion of the regulatory agency.	Overseas clinical trial data is acceptable, as long as it is aligned with ICH and/or WHO guideline. Local regulatory trials is required for new pyschotropics and drug for family planning program /	The overseas clinical trial data is accepted in accordance with ICH E5. The drugs approved by using a bridging strategy or global clinical trial data have increased. But Japanese PK data is indispensable.	Only for New Drugs, bridging data is needed additionally. (See figures at Annex 3)	Overseas clinical trial data is acceptable, as long as it is aligned with ICH and/or WHO guidance, and accepted by the major reference countries. Local regulatory trials is not required.	The overseas clinical trial data is accepted.	Overseas clinical trial data is acceptable	The overseas clinical trial data are accepted in accordance with ICH E5. BSE is mandatory for NCE NDA. Complete clinical data package relevant to the Asian population is required to BSE. Bridging study is generally required when there is ethnic difference. A bridging study is to provide clinical data of pharmacokinetic / pharmacodynamic or clinical data on efficacy, safety, dosage and dose regimen in Taiwan that will allow extrapolation of the foreign clinical data to different populations. Taiwanese PK may be waived through BSE submission. Some time may needs Taiwan PK or PD or dose-response data, it depends on the product. The product with ethical difference may needs Taiwan local PK or PD data to support NDA approval.	Not required
	Application fees	Fees necessary for applying for approval as for NME drug with full data (Category (1))	Application fees of drugs includes: - registration fee: IND: 45,300 RMB (import drug); 3,500 RMB (local drug) NDA: 45,300 RMB (import drug); 20,000 RMB (local drug) - drug quality test: around 50,000 RMB, based on test items - GCP inspection: free charge - GMP inspection: free charge	Application fee: HKD 1100 License fee: HKD 1370 Renewal fee (every 5 years): HKD 575	Application fees: NDA: INR 50000 (include MAA fee) Import License: Rs 1000 Registration Certificate (for import drug): USD 2500 Manufacturing License: Rs 6000 (+1500 for inspection fee)	Application fee : **Pre-Registration** : 1 Million IDR (MIDL) **Registration fee for** : **Category 1** : new product & Biological Product : 30 MIDR, new indication : 20 MIDR **Category 2**: copy product 7.5 MIDR, copy product with BA/BE data: 12.5 MIDR **Category 3** : other product: 7.5 MIDR **Category 4**: VaMa : 2 MIDR for each dosage form/packaging **Category 5**: VaMa-B : 2 MIDR for each dosage form/packaging. **Category 6**: VaMi-A : 1 MIDR for each dosage form/packaging. **Category 7**: renewal : 5 MIDR **For pre-inspection GMP document**: 7.5 MIDR. **For GMP site inspection**: three inspector three day = 90 MIDR	Application fees of drugs containing new active ingredients To Government : 533,800 yen To PMDA for review : 23,788,100 yen for paper-based compliance inspection : 6,559,600 yen for GCP inspection : domestic 2,723,200 yen, overseas 3,011,900 yen +Travel expense for GMP inspection : domestic 739,800 yen, overseas 933,500 yen +Travel expense	Application fee (1) Chemical : NCE for review : 3,726,000 KRW (STM review + S&E review + GMP review) (2) Biologics : NME for review : 3,726,000 KRW (STM review + S&E review + GMP review) (3) Biosimilar for review : 1,134,000 KRW (STM review + S&E review + GMP review) 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. cf. Generics: KRW 720,000(BE, CMC, GMP review included)	For NCE and NBEs: - Single ingredient: RM4000 -2 or more active ingredients: RM5000 For Prescription products (generic/line extensions): - Single ingredient: RM2200 - 2 or more active ingredients: RM3000	Pre-NDA evaluation: 125 USD NDA submission: 500 USD (1USD= 40 PhP) * above rates are current; however these may change pending implementation of proposed new revised fees: PHASIN- IN FEES - Jun 2013 (30%); Dec2013 (60%); Jun2014 (100%)	Screening Fees: Abridged/verification $500 Full dossier: $2,750 Evaluation Fees: NDA-1 & NDA-2 (abridged): $11,000, NDA-3 (abridged): $5,500 NDA-1 & NDA-2 (verification): $16,500 NDA-3 (verification): $5,500 NDA full dossier: $82,500 GDA-1 (abridged): $3,850 GDA-2 (abridged): $2,200 GDA-1 (verification): $10,000 GDA-2 (verification): $5,000	Application fee of new chemical entity to TFDA : NT$ 600,000. Application fee of new combination, new indication and new route of administration: NT$ 50000. Application fee of new dosage form, new used dose, new unit dose, or controlled release: NT$ 35000. GCP inspection: domestic only NT$ 15,000. GMP inspection: Domestic NT$60,000 per site. Dosage form addition NT$20,000 per dosage form. Overseas: NT$ 560,000 per site. Dosage from addition NT$ 35000-105000 per dosage form. different building, different air system or water system, the application fee will vary.	Not required 2,000 baht (pay after approval)
	Other requirements				Application for Import License is required after marketing approval and Registration Certificate	Specific country requirement on product labeling on product package, example: generic name, retail price, symbol of prescription drug, imported by .				Brand name & Trademark evaluation/approval. Reference Standard Sample (at least 300 mg) Please refer to MR list for the complete list of requirements.	For GDA, the reference product must be the registered product with Singapore HSA		
NDA application materials (NME)	CMC summary	Requirements and language	Yes (Chinese)	for NCE only (document in English)	Yes, in English	Yes (in Indonesian or English as in part II Quality)	Yes (in Japanese as M2 in CTD)	Yes (M2 in CTD, Korean)	Yes (M2 in CTD) - in English	Yes, in English	Yes (in English) Singapore Quality Overall Summary(SQOS) is required.	Yes (In English as M2 in CTD)	Requirement, see ACTR/Eng (Aneex 4)
	CMC report/body of data	Requirements and language	Yes (Chinese)	for NCE only (document in English)	Yes (English is acceptable as M3 in CTD)	Yes (in Indonesian or English as in part II Quality)	Yes (English is acceptable as M3 in CTD)	Yes (M3 in CTD, English is acceptable, but spec.and test methods should be prepared in Korean)	Yes - in full (M3 in CTD) - in English	Yes, in English	Yes (in English)	Yes (In English as M3 in CTD)	Requirement, see ACTR/Eng (Annex 4)
	Non-clinical summary	Requirements and language	Yes (Chinese)	for NCE only (document in English)	Yes, in English	Yes (in Indonesian or English as in part II Quality)	Yes (in Japanese as M2 in CTD)	Yes (M2 in CTD, Korean)	Yes (M2 in CTD) - in English	Yes, in English	Only for full dossier, in English	Yes (In English as M2 in CTD)	Requirement, see ACTR/Eng (Annex 5)

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NDA application materials （NME）	Non-clinical report	Requirements and language	Yes (Chinese) Usually synopsis or abstract of each report in Chinese is required, attached with source report.	for NCE only (document in English)	Yes (English is acceptable as M4 in CTD)	Yes (in Indonesian or English as in part III Non Clinical Data)	Yes (English is acceptable as M4 in CTD)	Yes (M4 in CTD, English is acceptable)	Not a standard requirement. Need to provide when required	Yes, in English	Only for full dossier, in English	Yes. (In English as M4 in CTD)	Requirement, see ACTR/Eng (Annex 5)
	Clinical summary	Requirements and language	Yes (Chinese)	for NCE only (document in English)	Yes, in English	Yes (in Indonesian or English as in part IV Clinical Data))	Yes (in Japanese as M2 in CTD)	Yes (M2 in CTD, Korean)	Yes (M2 in CTD) - in English	Yes, in English	Yes (in English)	Yes. (In English as M2 in CTD)	Requirement, see ACTR/Eng (Annex 6)
	Clinical report	Requirements and language	Yes (Chinese) Usually synopsis or abstract of each report in Chinese is required, attached with source report.	for NCE only (document in English)	Yes (English is acceptable as M5 in CTD)	Yes (in Indonesian or English as in part IV Clinical Data). Indonesia required full clinical study report	Yes (English is acceptable as M5 in CTD)	Yes (M5 in CTD, English is acceptable)	Yes - but only the synopsis of study reports, overall clinical overview, - in English.	Yes, in English	Yes (in English)	Yes. (In English as M5 in CTD)	Requirement, see ACTR/Eng (Annex 6)
	Other required documents	Requirements and language	application form summary part of application dossiers: (1) Name of the drug (2) Certified Documents, including CPP etc. (3) Objectives and basis for development (4) Summary of CMC, Non-clinical and clinical (5) packaging insert and its reasons, and latest references (6) artwork and labeling	Needs to be in English. General requirement for product registration: 1. Authorization letter from manufacturer – to authorize HKOP register, import and market the product 2. Manufacturer license – original 3. CPP- original 4. Information on the manufacturing facilities and practices of the manufacturer & GMP Certificate - original 5. Registration sample – color photos/scanned image to show the product and sales pack/container appearance. 6. Proposed sales pack – color prototype 7. Proposed pack insert - prototype 8. Master formula (Batch formula not accepted) - Non-proprietary names of ingredients, colour Index number or E-number for all colourants used should be provided 9. Finished product specifications 10. Method of analysis 11. COA of a representative batch 12. Stability data 13. Bioequivalence data for anti-epileptic drugs 14. Safety documents for ingredients with animal origins Additional requirements for NCE registration 1. 2 ICH country approvals 2. expert evaluation reports on the safety, efficacy and quality of the product. CV of experts who draft the report. 3. EU-RMP and/or US-REMS, if applicable. Information on whether any risk management plan activities and mitigation strategies will be implemented in HK. 4. clinical and scientific documentation substantiating the safety and efficacy of the product.	AS described in Schedule Y of the Drugs and Cosmetics Rules 1945 1.1 Comprehensive table of contents (Modules 1 to 5) 1.2 Administrative information 1.2.1 Application in Form 44 and Treasury Challan (fee) 1.2.2 Legal and statutory documents 1.2.3 Coordinates related to the application 1.2.4 General information on drug product 1.2.5 Summary protocol of batch production and control 1.2.6 List of countries where MA or import permission for the said drug product is pending and the date of pendency. 1.2.7 List of countries where the drug product has been licensed and summary of approval conditions. 1.2.8 List of countries where the drug product is patented 1.2.9 Domestic price of the drug followed in the countries of origin in INR 1.2.10 A brief profile of the manufacturer's research activity 1.2.11 A brief profile of the manufacturer's business activity in domestic as well as global market. 1.2.12 Information about the expert(s)/ Information regarding involvement of experts, if any 1.2.13 Environmental risk assessment 1.2.14 Samples of drug product	ACTD Section I : Administrative Doc.& Drug Information (SMPC & Patient Information Leaflet) Sub Section A: All Table of Content Sub Section B: Administrative Documents ▯ Registration Form ▯ Statement of Applicant ▯ Certificate and other Administrative Documents ▯ Result of Pre-registration ▯ Invoice/ Receipt of payment & other documents Sub Section C: Product Information and Labeling Section II: Quality Documents Sub section A: Summary of Quality Document Sub section B: Quality Documents S. Active Substance P. Finished Drug Section III : Non clinical Study Section A: Review of Nonclinical Study Section B: Summary and PreClinical Study Matrix Section C: Non Clinical Study Report x Section D: References Section If the manufactured not yet registered, it should provide SMF.	CTD Part I (Module 1) 1.1 Table of Contents 1.2 Approval application (copy) 1.3 Various certificates 1.4 Information on patent matters 1.5 Data concerning the origin or background of development 1.6 Information on the use of the drug in foreign countries 1.7 List of similar products from the same therapeutic category with the same efficacy 1.8 Package insert 1.9 Documents pertaining to the non-proprietary name of the drug 1.10 Summary of data pertaining to the designation as a poisonous drug, etc 1.11 Master plan for post-marketing surveillance 1.12 List of attached data 1.13 Other data	Module 1 1.1 Table of contents 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 the use of the applied drug in Korea 1.7 Various documents related to Enforcement regulation of Pharmaceutical Affairs Act Article 24-1) 1.7.1 CPP 1.7.2 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: ACTD Part I :ADMINISTRATIVE DATA AND PRODUCT INFORMATION - Table of Content SECTION A: PRODUCT PARTICULARS -Product Description -Pharmacodynamics & Pharmacokinetics (for full evaluation only) . -Indication/Usage -Dose/Use Instruction ▯ Recommended Dose & Route of administration (for full evaluation only) ▯ Contraindication ▯ Warnings and Precautions . ▯ Drug Interactions ▯ Side Effects /Adverse Reactions ▯ Pregnancy and Lactation (for full evaluation only) . ▯ Signs and Symptoms of Overdose and Treatment ▯ Storage Conditions ▯ Shelf Life ▯ Therapeutic Code (If any) SECTION B: PRODUCT FORMULA ▯ Batch Manufacturing Formula ▯ Manufacturing process (for abridged evaluation procedure only) ▯ Attachment of In Process Quality Control (for abridged evaluation procedure only) ▯ Attachment of Finished Product Quality Specification (for abridged evaluation procedure only) ▯ Attachment of Stability Data (for abridged evaluation procedure only) 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 CERT	ASEAN CTD Part I and Attachments 1.1 Table of Contents 1.2 Approval application 1.3 Various certificates 1.4 Information on patent matters/batch numbering system 1.5 Data concerning the origin or background of development 1.6 Information on the use of the drug in foreign countries 1.7 Reference Standards and MSDS 1.8 Package insert 1.9 Data on assay and test results 1.10 Representative Samples 1.11 Master plan for post-marketing surveillance 1.12 List of attached data 1.13 Other data Please see MR list of requirements	Module 1 (or ACTD Part Ⅰ) documents e.g, Letter of authorizations Declarization Artwork of packaging material GMP certificate Patent declaration Reference country/product approval and approved package insert, if applicable	CTD Module 1 (Taiwan Specific) 1 Administrative Information and Prescribing Information 1.1 Table of Contents of the Submission Including Module 1 1.2 Application Fee Receipt 1.3 Official Letter and Document 1.4 Application Form (original copy and duplicate copy) 1.5 Affidavit 1.6 Form for Sticking Label and Package Insert 1.7 Certificate/License 1.8 Letter of Authorization 1.9 CPP of Source Country 1.10 Formulation Basis 1.11 Certificate of PIC/S GMP/cGMP 1.12 CPP 1.13 Bridging Study Evaluation 1.14 Status of Clinical Study Taiwan involved 1.15 Status of Bioavailability (BA)/ Bioequivalence (BE) Study Taiwan involved 1.16 Contract Manufacturing 1.17 Applications of Contract Analysis 1.18 Radiation Dosage Study Report 1.19 Risk Evaluation and Mitigation Strategy (REMS) 1.20 Other Documents or Reports	ACTD Part I documents (administrative and product information)

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Approval review	Review organization	Review organization, Decision organization, Advice committee	Review CDE (Center for Drug Evaluation) Decision SFDA (State Food & Drug Administration) Inspection Regional Drug Administration	Review: Drug Office, DOH Approval: Pharmacy and Poisons Board	CDCSO/DCGI (Drug Control General of India) Twelve New Drug Advisory Committees (NDAC) were newly constituted to examine the applications for permissions for clinical trials and approvals for new drugs.	1. Committee of Safety-Efficacy Evaluation with the task of evaluating the safety and efficacy aspect to be discussed in the periodic meeting of National Committee/ KOMNAS. 2. National Committee on Drug Evaluation with the task of discussing , formulating, giving consideration and decision of the results of drug evaluation through a periodic forum meeting. 3. Committee of Quality Evaluation with the task of evaluating the quality aspect. 4. Committee of Product Information Labeling Evaluation with the task of evaluating in the aspects of Product Information and Labeling.	Review PMDA (Pharmaceutical and Medical Device Agency) Decision MHLW (Ministry of Health, Labour and Welfare) Advice CDFS (Council on Drug and Food Sanitation)	MFDS and NiFDS(National Institute of Food and Drug Safety Evaluation) Advice : National Pharmaceutical affairs Committee	National Pharmaceutical Control Bureau (NPCB): Receive and review the new drug applications, and propose it to the Drug Control Authority (DCA) for approval/rejection. Drug Control Authority (DCA): A committee that meets once a month to decide on new product registrations & licenses.	Philippines FDA	HSA (Panel of internal and external reviewers.)	-	Thai FDA
		Number of reviewers ex. Clinical, Non-clinical, CMC, Chemical/Biological	All staffs : 104 Traditional Chinese drug : 17 CMC : 27 Biologics : 8 Non-clinical : 13 Clinical : 20 Biostatistics : 3 Clerical work : 14 (As of April, 2012)	Undisclosed	CDSCO total manpower 327 (as of 2009). No detailed information.		All staffs : 672 Pharmacology : 384 Medical doctors and Dentists : 42 Engineering : 44 Veterinarian and Toxicity : 25 Biostatistics : 13 Science and agriculture, etc. : 63 Clerical work : 101 (As of April 1, 2012)	MFDS Chemical Administration(Drug policy): 54 GMP: 19 Clinical Trial Management: 19 Narcotics: 29 Bio Administration(Bio policy): 19 Bio GMP: 13 Traditional medicine: 13 NiFDS Circulating System: 15 Oncology: 16 Digestive System: 12 Bioequivalent: 24 Biologics: 20 Recombinant Protein: 16 Cell & Gene Therapy: 12 Herbal: 11 Total staffs : 1,760 (As of April, 2013)	Total staff: ~ 220 Centre for Drug Evaluation: 59	All staffs : 400 FDA employees	No info	TFDA all staffs: around 140 (CDE around 60) No detail information	See Attached sheet-Number of reviewers (Annex 10)
	Review process	Append the flow of the review of applications for new drug with the attached paper.	SFDA accepts the NDA application documents and transfer these documents to CDE in 30 work days, then CDE reviews and evaluates it in 150days ,finally,SFDA approves it in 30 work days. CDE review process for IND/NDA is attached for reference.	Undisclosed	DCGI accept the application in Form 44 and then it is forwarded to NDAC for expert review.	Pre-registration review document until complete documents --> Payment of pre-registration fees -->submit pre-registration --> Evaluation--> Approval Pre-Registration Registration review document --> Payment of registration fees --> Submit registration documents --> Clock start of registration review Note : * Only NCE/Biological Product Non-Clinical & Clinical were evaluated through Committee of Safety-Efficacy evaluation and National Committee then continue with Committee of Quality Evaluation , and Committee of Product Information. *Others (Generic & variation) were evaluated with Committee of Quality Evaluation , and Committee of Product Information. .	See Annex 8	See figures at Annex 9	Dossier Submission via online--> Screening & Acceptance of dossier via online--> Payment of registration fees--> clock start of registration review--> Sending for external expert review on clinical section for NCE/Biologics-->	Please see Flowchart_PSD_ revised_Aug 2007	Screening/evaluation/queries, input requests/regulatory decision	See Annex 7	Annex 11 - the timeframe for approval

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Approval review	Review time	The standard period of time from acceptance of applications to the approval of new drugs.	Official timeline of CTA / NDA of import drug from submission to approval: 145 working days But, actual timeline is much longer. The recommendation timeline for 2012 by RDPAC: CTA or NDA of import drug is 22 months; MRCT of category 1 drug is 10 months while MRCT of category 3 drug is 13 months. (MRCT:Muti-Regional Clinical Trial)	NCE: 8-15 months Generic: 6-9 months	About 12-15 months for marketing approval and registration certificate. About 3 months for Import License.	Timeline of pre-registration 40 working days after completed documents for category 1,2,3,4,5.Timeline of registration 100 working days after completed documents for : a. New Drug & Biological Product that are indicated for the treatment of serious life-threatening human disease , or classify as Orphan drug, or classify for public health program, or new drug which development by Pharmaceutical industry / research institution in Indonesia b. New registration of generic essential copy drug. c. New registration of copy drug with standard electronically information (Stinel). d.Major variation . Timeline of registration 150 working days after completed documents for a New Drug , Biological Product , major variation with : 3 (three) CPP from countries with known good evaluation, system or approved in the country that has applied harmonized evaluation system (EU , EPAR, EMEA). b. New Registration of Copy Product without Stinel. Time line of registration of 300 working days after completed documents:1 CPP from original country.	Review time of FY 2011(Median) Priority review products : 6.5 months Standard review products : 11.5 months	10 ~15 months	NCE/NBE: 245 Working days Priority review : 6-9 months Other pharmaceutical products (line extensions or generics): 210 working days	Review time of FY 2012 (Median) Priority review products : 9 months Standard review products : 15 months	Screening: 25 working days Evaluation: Full dossier: 270 working days Abridged: 180 working days Verification: 60 working days	Review time Priority review products: 12 months standard review products: 18 months	Annex 11 - the timeframe for approval
	Priority review system	Presence of priority review system, Content of system, Subject drug for priority review ex. unmet medical needs, for serious life-threatening disease	Special review procedure exists, which is appropriate for following applications of new drugs: 1) Active ingredients extracted from plants, animals or minerals, etc. and their preparations not yet marketed in China, and newly discovered Chinese crude drugs and their preparations; 2) Chemical drug substance and their preparations and biological products not yet approved for marketing in China or abroad; 3) New drugs for the treatment of diseases such as AIDS, malignant tumors and rare diseases, etc. with significant clinical advantages; and 4) New drugs for the treatment of diseases, for which effective therapeutic method is not available. For those drugs specified in items 1) & 2), the applicant of drug registration (hereinafter "the Applicant") may apply for the special examination and approval when submitting the application for clinical trials of the new drugs. For those drugs specified in items 3) & 4), the Applicant may apply for the special examination and approval only when submitting the production applications.	usually no; except official request from Hospital Authority upon urgent situation	There is no formal priority review system. Depends on therapeutic area and unmet requirement.	There is no priority system. The review following the timeline of registration (100 or 150 or 300 working days)	The priority review system exists. Orphan drugs receive priority review automatically. New drugs not designated as orphan drugs which target other serious diseases and which are apparently expected to contribute to the improvement of quality of healthcare may be designated as "non-orphan priority review products" based on overall evaluation of the seriousness of the target disease and medical usefulness of the drugs. Designation is made based on the opinions of external experts if an application is submitted with an application for marketing approval.	The priority review system exists 1) Drugs which target for life-threatening diseases such as AIDS, cancer etc. 2) Drugs which can use for replacement of current therapeutic method/drugs which become a tolerance for patients 3) Other drugs such as anti-cancer agents, orphan drug, DNA chip and so on : recognized by MFDS minister 4) Herbal medicines for cancer or AIDS	There isn't a formal priority review system in place. Priority review status will be provided on case to case basis, based on the applicants' justification. Usually priority review status is granted for the following group of products: - life-saving products, e.g. viral infection/oncology drugs - fulfill unmet medical needs - treatment for rare diseases where currently there isn't a treatment option available.	The priority review system exists. For serious diseases and life-threatening conditions and which are apparently expected to contribute to the improvement of quality of healthcare based on overall evaluation of the seriousness of the target disease and medical usefulness of the drugs. Consideration is made based on the opinions of external experts if an application is submitted with an application for marketing approval.	No separate priority review system or pathway. Only if product is submitted via Abridged Evaluation (with 1 reference country approval); and meets the pre-defined criteria in the guide (unmet medical need, etc). Grant of priority review is on case-by-case basis, at discretion of the Agency during Screening. Applicant will be notified at the point of acceptance of application, if request is granted.	The priority review system exists Unmet medical needs and drug for serious life threatening disease and is major medical advance can apply to priority review system. It should be apply for priority review first, after recognition by TFDA as priority review case then can be reviewed by priority review process.	There will be the fast track for life-threatening desease e.g. HIV drug, anti-cancer drug.

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Approval review	Orphan drug system	Presence of orphan drug system, Criteria for designation, Incentive, etc.	No orphan drug designation system.	No	The orphan drug system does not exists.	The orphan drug will evaluate will evaluated within 100 working days. No regulation establishing for Orphan drug.	The orphan drug system exists. Designation criteria <u>Number of patients</u> Less than 50,000 in Japan <u>Medical need</u> There are no appropriate alternative drugs or treatment methods. The efficacy and safety are expected to be outstandingly greater than those of existing drugs. <u>Possibility of development</u> There is a theoretical ground for using the drug for the target desease and the development plan is acceptable. Incentives (1) Subsidy payment(The total budget for financial year 2010 was 650 million yen.) (2) Guidance and consultation on research and development activities (HMLW, 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. <u>Designation criteria</u> - Less than 20,000 in Korea - Standard treatment has not been established without any substitution product or drug product which is superior to already approved product in safety and efficacy - Pharmaceutical product whose annual sum of importation does not exceed 1.5 million USD or annual sum of GDP does not exceed 1.5 billion KRW(On condition that less than 500 pateints in Korea, pharmaceutical product whose annual sum of importation does not exceed 5 million USD or annual sum of GDP does not exceed 5 billion KRW) - 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. Incentives 1) PMS : 6years 2) Exemption of following data 1) CMC(specification and test method) : No review, but in-house spec. should be submitted 2) GMP 3) DMF 4) following data for S&E review - bridging data - Some Toxicity data : only single dose toxicity and 1 to 3 months repeat dose toxicity data are needed - Pharmacology data will be replaced by pharmacodynamic data or clinical trial data - Phase 2 study will be included in phase 3 study 5) Korean labeling 3) Priority review	The MoH is in the process of establishing the orphan drug system. Meanwhile, the registration of orphan drugs will have to follow the standard/priority review registration track.	The orphan drug system does not exists but we have a DOH A.O. 4 s. 1992 for Compassionate Special Permit for life-saving drugs. This is the closest that we can get in as far guidelines for orphan drugs are concerned.	Available in Regulations but implemented as Named-Patient Basis pathway.	The orphan drug system exists. Designation criteria: <u>Number of patients:</u> the standard for rare diseases is if it's prevalent in less than 1/10,000. It is different with US (U.S. it is considered a rare disease if it affects less than 200,000 people/ prevalent in less than 7.5/10,000) and Japan (the number of patients total less than 50,000 /prevalent in less than 5/10,000) <u>Definition of Rare Disease:</u> The rare diseases specified in this Act refer to diseases with prevalence lower than that formulated and publicly announced by the central competent authority, and recognized by the Committee specified in Article 4 of this Act; or diseases designated and publicly announced by the central competent authority under special circumstances. Reward: To encourage the R&D and manufacturing of orphan drugs, TFDA announced and implemented the "Rewarding Standards for the Manufacturing and R&D of Orphan Drugs. But it focus on Domestic manufacturer.	Available, the requirement for orphan drug registration is only Admin part and some of Quality part.
	approval matters	You may append the approval matters with the attached paper.	・Approval number ・Marketing License Holder and its address ・Manufacturer and its address ・Non-proprietary Name ・Brand name in Chinese if applicable ・Active ingredents and Contents or Nature ・Dosage form ・Dosage strength ・Packaging size ・Shelf life ・Specification & test methods ・labeling and artwork ・packaging insert		・Generic Name ・Brand name ・Manufacturing Method ・Dosage and Administration ・Indications ・Storage Methods and Expiration Date ・Specifications and Test Method ・Name of the Manufacturing Site used to Manufacture the Product	Besides Marketing Authorization , it attached with : * Registration Form * Approved Labelling * Approved Package Insert * Approved Patient Information Leaflet	・Non-proprietary Name ・Brand name ・Ingredents and Contents or Nature ・Manufacturing Method ・Dosage and Administration ・Indications ・Storage Methods and Expiration Date ・Specifications and Test Method ・Name of the Manufacturing Site used to Manufacture the Product, Address, License/Accredetation Category, etc.	・Non-proprietary Name ・Brand name ・Ingredents and Contents or Nature ・Appearance ・Manufacturing Method ・Dosage and Administration ・Indications , Precautions for use ・Storage Conditions and Expiration Date ・Specifications and Test Method ・Name of the Manufacturing Site used to Manufacture the Product, Address, License/Accredetation Category, etc.					

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Approval review	Other information concerning approval review			N/A		NCE should provide API Drug Master File or Internal Monograph as required in Part II Quality . Approval of SMF should also be considered to get approval of registration number.			Information on API - the product monograph & complete Drug substance data. Please refer to the API guidelines as Annex 12.				
Pre-approval inspection	GCP inspection		GCP on-site inspection is executed by provincial FDA for lcoal manufacturing drug at principal investigator's site. GCP on-site inspection for import drug is not mandatory yet.	Not required	DCGI may conduct GCP on-site inspection. DCGI will issue instructions to the CDSCO officers/Inspectors to conduct the inspection identifying the clinical trial site/ facilities to be inspected. CDSCO issued 'GUIDANCE ON CLINICAL TRIAL INSPECTION' in Nov. 2010.	GCP inspection for local clinical study in Indonesia . GCP inspection for import product is not required.	The GCP on-site inspection is executed by PMDA to 2 or 4 medical institutions and applicants.	GCP on-site inspection to sites, company and CROs according to MFDS's yearly plan. Self-inspection by sites was adopted and is being implemented from 2012.	Not applicable, as registration trials are not required in Malaysia	The GCP on-site inspection is executed by FDA to medical institutions and applicants. Frequency not clear.		The GCP on-site inspection is executed by TFDA around 4-6 weeks after CSR submitted to TFDA in selected medical institutions (depends on the number of involved site)	
	GMP inspection	ex. On-site inspection, Document inspection, CPP/GMP certificate from source country accepted	For local drug, GMP on-site inspection should be done before manufacturing license approval. For import drug, SFDA started GMP on-site inspection at the end of 2011. Only few import drugs were selected at that time. Moreover, GMP on-site inspection was done after IDL approval at this moment, which is different from for local drug. It is sure that SFDA expects GMP on-site inspection prior to IDL approval once experience acuumulated. (IDL:Import Drug License)	Document inspection only, CPP/GMP certificate from source country accepted	GMP inspection of Indian mfg. units will be arranged before granting the manufacturing license and periodic review of the mfg. unit The Licensing authority or by any other persons to whom powers have been delegated in this behalf by the licensing authority of India may inspect the manufacturing premises of mfg. units outside India on need basis	For imported product : Based on evaluation of Site Master File , if necessary GMP inspection site will be request by NAFDC .	Since the amendment of the Pharmaceutical Law (PAL) in April 2005, GMP compliance inspections have become a requirement that must be met for marketing approval. Application for GMP compliance inspections for all manufacturing sites listed in the applicaitions for marketing approval must be submitted to the GMP compliance inspection authority (PMDA or prefectures) by each manufacturing site.	GMP inspection can be done for manufacturing sites of drug product and drug substance. Basically MFDS conduct on-site inspection (from 2009). Before conducting site inspection, they request "Minimum requirements" documents. Document inspection; inspected site within 1yr/aseptic product, 2yr/ sterile product, 3yr/ non-sterile product	For Imported products: From Jun 2012, there will not be an on site inspection. All registration of imported products need to provide a GMP cert issued/inspected by member countries of PIC/S or ICH. For locally manufactured products: There is site inspection before issuance of GMP by the Health Authority.	Since 1989, GMP compliance inspections have become a requirement that must be met for marketing approval. Furthermore, Site Master File, CPP and GMP certificate is being required.	GMP conformity assessment is required usually in document review. GMP certificates must be issued by PIC/S member, US FDA and/or Japan MHLW. If not, onsite inspection by HSA Audit Branch required, before product approval is granted.	GMP inspection is request and the approval should be got then NDA can be approved accordingly. Otherwise NDA Approval will be hold till GMP inspection approval. The GMP compliance inspection should be done by TFDA for each manufacturing site, even toll manufacture site or packaging site.	GMP certificate (PIC/S) New foreign manufacturer may be inspected on site if needed.
	Other inspections	ex. GLP requirement and evaluation	For local drug, source data on-site inspection including GLP and CMC is mandatory after IND/CTA or NDA submission.	Not required	N/A	In the GMP inspection site , the Laboratory is inspected by NAFDC . The Laboratory inspected following GLP requirements.	"Paper-based compliance inspections" is executed by PMDA to confirm whether data attached to NDA applications accurately reflect the results of clinical trials and other studies, and whether those are made in accordance with GCP, GLP and reliability standards.	n/a	Subject to companies internal audit & ethics committees of the research institutions requirements.	Paper-based compliance inspections is executed by FDA to confirm whether good distribution practice is being implemented.		Current Taiwan had not perform GpvP inspection. But the regulation for GLP site inspection already exists and some study will be performed GLP site inspection. As to the regulation related to GpvP inspection is under discussion.	

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Clinical trials	Necessary procedures to start clinical trials	The actual procedures to start clinical trials, for example, IND/CTA => import of investigational drugs => IRB etc.,	IND/CTA => CTP => IRB => clinical trial clinical trial should be started within 3 years after obtaining CTP.	a. IRB approval b. if study medication is required to be imported, then Application of clinical trial certificate (CTC) at Drug Office, Department of Health is required	Clinical trial on new drug shall be initiated after authorization by CDSCO and approval of respective EC. In case of parallel applications, CDCSO will grant conditional approval and note that the trial should start after Ethics approval. Trials should also be registered with CTRI (Indian Registry) before screening patients	1. After having Clinical Trial Approval Letter from NAFDC, the Clinical Study can be start . Implementation of Clinical Trial.	Notice of claimed investigational new drug exemption to MHLW. Clinical trial can be started after 30 days if there is any comment from Authority	Get IND Approval and IRB approval in apparel. After that, it will be implemented CTA. Normally, it will take about 3 months.	Application to The Research Review Committee (RRC) & The Medical Research Ethics Committee (MREC) required. Also, application to the National Pharmaceutical Control Bureau (NPCB) for clinical trial import license is (CTIL) necessary. Parallel submission is possible.	Clinical Trial Protocol approval is required. Please see FDA Circular 2012-007 (flowchart).	Approval by both HSA (to obtain CTC) and IRB approval are required respectively before start of clinical trial.	IND approval by TFDA＋Import permit of IMP→ IND approval by IRB →CTA approval by medical insitiuation→Payment pay to medical institution completely→Site initiated visit.	EC approval -> FDA for import permit -> start
	Necessary data/ documents/ brochures to start clinical trials	Necessary Tox data for initiation of clinical trials (specify local requirement other than ICH-M3 or S6)	Protocol & IB. Usually TOX data aren't be required for initiation of clinical trial because all data have been reviewed by authorities. So site/IRB follows CTP always.	Please refer to the guidelines (file name: CT-guid)	List of necessary Tox data is shown in APPENDIX III of Schedule Y, the Drug and Cosmetics Rules 1945.	Clinical Trial Documents consist of : UK-1 Form, Protocol, Investigator's Brochure, Informed Consent, Documents of trial drugs, Summary Protocol of Batch Production (for Vaccine and biological products).	Generally we will follow ICH requirement. Sometimes add reproductive toxicity testings before clinical trials.	Mostly according to ICH requirements but regarding repeat dose toxicity in rodents, administration period is longer(6 months) than ICH guidelines(3 months). Sometimes add reproductive toxicity testings before clinical trials.	Submission of Investigator Brochure is required.	Generally follow ASEAN requirement. Please see FDA Circular 2012-007	1. Clinical trial protocol 2. Patient information sheet and ICF form. 3. Subject recruitment procedures and advertisements (if applicable) 4. Listing of overseas trial centres (if applicable) 5. Principal investigator(s) CV, GCP cert 6. GMP certificate or certificate of accreditation 7. CoA (if appicable) 8. Letter of approval issued by IRB 9. Other relevant supporting documents, if applicable 10. IB	It depends on the product characteristic and study phase. Some time Tox data may needed for initiation of clinical trials. General requirement also follow ICH guidance.	ICH E6
		Are there any necessary documents/brochures outside IND/CTA dossier	CRF & ICF signed by patients. Contract with site IRB approval Some sites require insurance certificate for the trial	Please refer to the guidelines (file name: CT-guid)	As per Schedule Y Registration of clinical trial is mandatory in the ICMR Clinical Trial Registry prior to initiation of the trial.	Informed Consent to the patient	Documents needed to get patients' consent	CRF(Case Report Form), GMP warranty letter or certificate, documents to get patients' consent	refer to CTIL guideline	Documents needed to get patients' consent. Please see FDA Circular 2012-007.	Original declaration document of the principal investigator and sponsor has to be submitted	No extra documents requirement outside IND/CTA dossier. Only for biosample needs to send out to oversea, the statement from central lab is needed.	Material Transfer Agreement
		Document Language (acceptability of English document)	In Chinese.	preferably English and patients consent form in English and Chinese/Chinese only	English	Indonesian or English	Usually Japanese documents are requested	Protocol, ICF should be translated into Korean. However English IB is acceptable to MFDS.	English	English	English	Usually English version are requested.	Thai and/or English
	Requirement of domestic clinical data for NDA application, if there is foreign data	Necessary or Not-necessary -Necessity in PK / healthy sbj. -Necessity in patient data	Usually Chinese patient's data including DB study and PK study are needed, which indicates similarity in drug response (i.e. efficacy and safety) with foreign data.	Not necessary	Necessary	Generally, Indonesian patient's data requested which indicates similarity in drug response (i.e. Efficacy and safety) with foreign data for new psychotropic drug, drug for family planning programme and other drugs based on request from Authorized body , for example public health programme for TB , etc.	Usually Japanese patient's data requested, which indicates similarity in drug response (i.e. efficacy and safety) with foreign data.	Foreign data is acceptable. But bridging data in Korean should be generated.	Not necessary	Local clinical trial is optional; PSUR submission will be required in lieu of Post-Marketing Surveillance.	Not necessary	If there is foreign data available, it doesn't need domestic PK data for IND application. But some situation may needs domestic PK data for supporting NDA approval even there is foreign data approval, that is the product with ethical difference between Asis population and Caucasians.	Not-necessary
	Acceptance of foreign clinical data for NDA	Is there any conditional requirements, for example similarity in PK/PD?	No, just for reference. (Even if the similarity in PK/PD is indicated we can't rely only on foreign data to China NDA)	Yes (for NCE products) Not required for generic products	Foreign Clinical data can be a supportive document, however Indian data (PhaseIII) is must.	Acceptable if the clinical data following GCP and the result based on evaluation of safety and efficacy is good.	Acceptable if the similarity in PK/PD is indicated.	Acceptable; in case of similarity on S&E or PK/PD.	Yes	Acceptable if the similarity in PK/PD is indicated.	Yes	Acceptable if the similarity in PK/PD is proofed.	Yes
	Required number (or rate) of local subjects in pivotal clinical studies for NDA approval	Please explain for both local and multinational clinical trials, if necessary. *ex.* totally around 100 *ex.* 1/5 of all subjects in multi-national studies	At least 20-30 for Ph-1, 100 for Ph-2, 300 for Ph-3 in treatment group for local trial (for category 1). For registration purpose, 100 pairs of Chinese patients in pivotal studies is requested whatever local studies or MRCT. Meanwhile, it is requested to show similarity in drug response and safety profile between Chinese and foreign patients in MRCT.	Not specified	P-I: 1-2 centers. At least 2 patients. P-II: 3-4 centers. At least 10-12 patients. 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)	Local clinical trial is needed for new psychotropic drugs .drugs for family planning programme, certain drug based on request from Authorized body.	It is requested to show the consistency in drug response between Japanese and foreign patients in multi-regional clinical trials. For this purpose, at least 15-20% of all subjects is hopefully to be Japanese.	No definite requirement. For both local and multinational clinical trials, statistically meaningful number of subject is needed.	N/A	There is no required number of local subjects in clinical trials for NDA approval. For PMS studies, it is suggested (but not required) that there should be 3,000 subjects. PSUR system shall take over the PMS upon finalization by our FDA on January 2013.	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 and 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: Sample size ≧200-Taiwan No.≧30 or 5%, : Sample size ＜200-Taiwan No.≧10.	Not-necessary

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Clinical trials	Practicable number of clinical centers or sites in the country	# of sites with facility of clinical trials Is there any license system for clinical study site?	Involved clinical center or site should get a license of SFDA. More than 300 sites/hospitals are qualified.	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.	Not specified.	It around 50 clinical centre .	Clinical trial can be initiated in many study sites. No license system for clinical study sites.	Certified sites by MFDS: 156 sites(Sep. 2012)	CRC(Clinical Research Centre) controls 17 clinical centers, 50 hospitals and 100 clinics.	Clinical trial can be initiated in many study sites. No license system for clinical study sites but the protocol should be evaluated by IRB/EC.	There are 13 public hospitals and 16 private hospitals which can conduct clinical trials.	Total 99 sites can perform clinical trials through JIRB review scheme that includes 17 medical centers and teaching hospital and area hospital. 38 clinical sites get confirmation by TFDA for IRB certification and allow these 38 IRBs can do review and approve without TFDA approval. IRBs are qualified by TFDA and updated every 2 years. Once the IRB not in this TFDA list, the IRB approval result needs to be reconfirmed by TFDA again then can execute study after TFDA approval. There is no license system for evaluate clinical study sites.	8 officially recognized sites (EC site) No (Beware of USFDA blacklist)
	IRB system for clinical trials	Installation of IRB/EC in sites Is there National IRB?	IEC at each site	Yes. An IRB for each cluster of hospitals	Independent Ethical Committee (IEC) & Institutional Ethics Committee	There are National IRB system .	Institutional IRB.	Institutional IRB	institutional and national IRB (MREC) available depending on sites	Institutional IRB/Ethic Committee. The general guidelines on CT may be referenced from the "National ethical Guidelines for Health Research 2011 edition. Another reference is FDA Circular 2012-007 that recognize ERB/ERC for purposes of conducting CT of Investigational Medicinal Products and it also validates the agreement between the FDA and PNHRS or Philippine National Health Research System which includes the establishment of a clinical trial registry.	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	There is JIRB which cover 99 clinical sites. Almost medical center has own IRB. There is different requirement between different IRB.	available Yes, National IRB or Central IRB.
	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 observed in all clinical sites. Same as Japan.	GCP is observed in all clinical studies	Yes, GCP is observed in all clinical sites. ICH Guidelines, GCP E6	GCP is observed in all clinical studies	GCP is observed in all medical center and teaching hospital.	a must
	Investigators	ex. about 50 physicians have been trained in US/EC	uncountable number of physicians	Yes	Large pool of trained Investigators in diverse therapy areas	Investigator must have GCP training before the trial and understand the protocol comprehensively in order to conduct the trial in accordance to GCP. No requirement investigator have been trained in US/EC.	uncountable number of physicians in Japan	uncountable	Information not available	Uncountable number of physicians. In addition to CVs, IRBs require that investigators undergo GCP training and this should be renewed or refreshed every 2 years.	No info	TFDA regulated necessary training hours needed for GCP and ethical then qualified to conduct clinical trial. No actual number of investigator to get GCP training.	no information (Beware of USFDA blacklist)
	Investigational drug	Condition of customs procedure	Tax and custom clearance. If imported investigational drugs to be used, CTP is necessary for Customs procedures and clearance.	Application of Import License based on the approved CTC	Permission to import of investigational product shall be obtained by applying for a test license. The application should be made in Form 12.	Sponsor request to import unregistered product was to NAFDC. Approval letter for Importation from NAFDC is used for release product in the customs . .		After the IND approval. Import permit should be gotten from Korea Pharmaceutical Traders Association in advance.	clinical trial import license and proper clearance required	yes	Application for Import License of CTM required. Online application is possible. Can import less than the amount approved in the CTM, but not more. The approved CTM form needs to be submitted to the Trade Net office for custom clearance.	It needs to get import permit that issue from TFDA, then Customs will allow investigational product import into Taiwan within the quantity on the import permit.	Condition of customs procedure - import license, CoA, Airway bill, invoice
		Investigational drug labeling (requirements and language)	Chinese label is needed.	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 (As per Rule 96 and Schedule DII)	In Indonesia language for clinical trial in Indonesia.	Japanese label is needed	Korean label is needed Requirements : 1) Investigational use only statement 2) Code name or generic name 3) Lot/batch number, expire/retest date 4) Storage condition and type of container 5) IND holder's name and address 6) "It can not be used for other purposes except clinical trial" statement	refer to CTIL guideline. English acceptable	yes, in English	1. Designation or other identification mark on each item of such material. 2. Name/address of manufacturer. 3. Batch number. 4. Name or other identification mark of the subject. 5. Manufactured date and expiry date. 6. Storage condition. 7. 'The product should only be used under strict medical surveillance' ; and/or "for Clinical Trial Use only" 8. Must comply with GCP labeling requirements.	Chinese label is needed	Wording 'for clinical trial use only'; Thai language

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Clinical trials	Investigational drug	Usability of an unapproved drug as a comparator	No (almost impossible).	Yes	No	Unapproved drug should provide data as below: Quality Data, Investigator's Brochure, and Summary Report of Non - Clinical & Clinical data, Summary of Batch Production Report (for Vaccines and Biological Product)	It is possible to use an unapproved drug as a comparator if the unapproved drug is the international standard drug. It is recommended to gather relevant safety information of the unapproved drug in Japanese.	Possible if the unapproved drug is the international standard drug. It is recommended to discuss with MFDS in advance.	depend on protocol design and supporting documents provided. E.g. drug approved in another country and not MYS, should be acceptable as long as required supporting documents (e.g. safety data) provided	It is possible to use an unapproved drug as a comparator if the unapproved drug is the international standard drug. It is recommended to gather relevant safety information of the unapproved drug.	As long as protocol and CTC approved, can be used	It is possible to use an unapproved drug as a comparator if the unapproved drug is the international standard drug. It is recommended to gather relevant safety and efficacy information of the unapproved drug in English.	Possible subject to EC approval
	Export shipment of bio-samples from subjects	*ex.* possible, can be measured at Central Labs.	There is specific regulation for export of human samples. Samples can be exported after approval.	Possible	Possible	There are Regulation no 657/MenKes/Per/VIII/2009 for export shipment of bio-samples from subject. The request for export of bio-samples to Ministry of Health.	Samples can be exported	Samples can be exported	samples can be exported. Export permit required	Possible, can be measured at central laboratory	Can, as long as meet the importing countries necessary requirements. It is the applicant's responsibility to comply with importing country's requirements	Possible, can be measured at Central labs. But it needs statement from Central lab, also the information for the Central lab needs clarified in the statement in detail, ex address, contact window. For Biogene sample, it needs to indicate the test gene information in advance then can allow to export.	Possible (MTA required by most IRB)
	Availability of multi-national CRO	*ex* . ** has local branch, many local CROs	Multi-national CRO is available in China, such as Quintiles, ICON, Covance, ICN, PPD, PRA, RPS etc	Yes (domestic and multi-national companies)	Multi-national CROs like Quintiles, Parexel, PPD, ICON etc are available	Multi-national CRO is available in Indonesian.	multi-national CRO is available in Japan	There are many multi-national CROs branch. Many local CROs.	available	Multi-national CRO is available in Philippines	Available	Multi-national CRO is available in Taiwan	Approximately 10 CROs available
	Adverse reaction reporting during clinical trial	*ex* . SAE: report to Authority within 7 days etc.,	SAE: it is requested to report to the authority in 24 hours after knowing the event.	Serious and unexpected adverse events - Fatal/life threatening: no later than 7 calendar days; submit report in 8 additional calendar days - Others: 15 calendar days NSAE and serious expected adverse events: - Brief summary at the end of trial	As per Sch Y,Unexpected SAEs have to be reported to CDSCO within 14 calendar days. Draft guidance on 'REPORTING SERIOUS ADVERSE EVENTS OCCURING IN CLINICAL TRIALS' was issued by CDSCO in 2011. In July 2012 an excel sheet shared by CDSCO to furnish information on death cases.	Investigator should report all serious unexpected adverse event to sponsor /CRO as soon as possible after known it, if there are some next adverse event, report a.s.a.p. until end of event. Sponsor should report all serious adverse event in Clinical Trial include death to Head of NAFDC and Ethics Committee within 15 days start from known the event , if there is next event, report it a.s.a.p until end of event.		Report SUSAR to MFDS within 7 days : Death, life-threatening within 15days : other SUSARs	refer to CTIL guideline	SAE: report to Authority within 3-7 days. Please see FDA Circular 2012-007 (p.9-10)	Fatal or life-threatening unexpected ADRs: within 7 calendar days. All other serious unexpected ADRs: within 15 calendar days. (See MEDICINES CLINICAL TRIALS REGULATIONS 2000 REVISED EDITION RG 3). Follow CIOMMS reporting	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.	SAE within 7 days (death/life threatening); 15 days (other SAE), 15 days after end of study (Non-SAE)
	GCP site inspection										Will be conducted by the HSA Clinical Trial Branch, on locally conducted clinical trials.		

Item	Contents	Detail or Example	China	Hong Kong	India	Indonesia	Japan	Korea	Malaysia	Philippines	Singapore	Taiwan	Thailand
			RDPAC	HKAPI	OPPI	IPMG	JPMA	KPMA/KRPIA	PhAMA	PHAP	SAPI	IRPMA	PReMA
Manu -facturing	Acceptance test for Import drug	How the specifications & test methods for acceptance test of import drugs are set in your country?	Specifications and test methods are to be set according to quality verification test done by authority and ChP.	Based on the approved particulars.	Specifications and test methods are to be set according to registered specifications. Official in pharmacopoeia or in-house specifications with validation data are available.	Specification and test methods are following Indonesian Pharmacopoeia, USP, BP, or other Pharmacopoeia.	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.	The specifications can be set by company, as long as it is aligned with the international reference & approved by the reference countries.	Specifications and test methods are to be set according to registered specifications.	To be tested according to approved specifications & test methods	Specification and test methods are to be set according to international pharmacopoeia, like JP, EP, USP/NF. For innovative product, it is allow to use Company Own specification and test methods with validation data and scientific justification.	Both compendial and non-compendial method are acceptable
	Pharmacopeia	What is standard pharmacopeia ? What is other accepted pharmacopeia? ex. USP/NF, JP, EP	CHP (Chinese Pharmacopoeia)	BP, USP, EP and JP. In-house specification for NCE would be accepted by DOH.	If a DP/DS is official in the Indian Pharmacopoeia(IP) than must conform to IP if not official in IP than BP/USP/EU Pharmacopoeia standards are to be followed	Standard Pharmacopoeia : Indonesian Pharmacopeia Other accepted Pharmacopoeia : USP/NF, BP, EP, JP.	JP (Japanese Pharmacopeia)	Standard : KP Accepted : JP, Ph. Eur(EP), USP(NF), BP, Deutshces Arzneibuch, Pharmaacipee Francaise	USP/NF, JP & EP	JP, USP/NF, EP, BP, PP (Philippine Pharmacopoeia)	BP, EP, USP/NF	Accepted pharmacopoeia are JP, EP, USP/NF.	USP 27, BP 2004, IP 2008, Thai-pharmacopoeia, EP (under public hearing)
	GMP system	What is current GMP requirements? ex. PIC/S	Chinese GMP 2010 version(MOH order 79)	PIC/S has been adopted for local manufacturer licensing PIC/S would be adopted for overseas manufacturer within a few years.	Indian GMP as outlined in Schedule M of DRUGS AND COSMETICS RULES, 1945	PIC/S GMP requirements	Japan applied for membership in the PIC/S GMP (March 2012)	KGMP Korea applied for membership in the PIC/S GMP(May 2012)	mainly PIC/S, alternatively ICH standard	Philippine applied for membership in the PICS (June 2010)	PIC/S GMP requirements	Taiwan is PIC/S member since Jan 2013.	Under application for PIC/S membership.
		Please describe GMP evaluation process by the authorities. ex. GMP clearance/ accreditation required before NDA ex. On-site or document inspection ex. Acceptability of GMP certificate from original country	1)For local drug, GMP compliance is pre-requisite for obtaining a Product Marketing Approval in China (see "NDA" - GMP inspection). GMP inspection to licensed manufacturer is carried out every five years by on-site inspection. And the application for GMP renewal should be submitted 6 months before GMP expiration. 2)For import drug, GMP on-site inspection was just started. so only few import drugs were selected for GMP inspection and it were done after license approval.	For overseas manufacturer, inspection is usually not required. For local manufacturer, an inspection by pharmacist inspector will be conducted at the company's premises within 2 weeks from the submission of a new application. The application will be considered by the committee. If approved, a license valid for 1 year will be granted.	GMP inspection will be arranged before granting the manufacturing license and periodically The Licensing authority or by any other persons to whom powers have been delegated in this behalf by the licensing authority of India may inspect the manufacturing premises of mfg units outside India on need basis.	The manufacturer which is first time register export product to Indonesia should provide SITE MASTER FILE (SMF) for GMP evaluation. After evaluation of SMF, the NADFC will approve to continue registration process of NDA or request site inspection. Before inspection, the manufacturer should provide Pre-inspection document for preparation of the site inspection . After inspection, the NADFC will issue approved or reject to continue registration NDA. The inspection report from other Authorized Health Authority is needed to support evaluation of SMF.	GMP compliance is pre-requisite for obtaining a Product Marketing Approval in Japan (see Pre-approval inspection, GMP). GMP inspection to licensed manufacturer is carried out every five years either by on-site or document inspection.	Pre-approval GMP review: 1) documents (Minimum requirements) -based 2) Site inspection. In case MFDS visits the same site within 3 years for another products which used the same manufacturing method, on-site inspection could be waived. (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.	For Imported products: The GMP needs to be issued by members of PIC/S , or ICH. For locally manufactured products: Site inspection is required before issuance of GMP cert	GMP compliance is pre-requisite for obtaining a Product Marketing Approval in Philippines. GMP inspection of licensed manufacturer is conducted by local FDA every 2 years, either by on-site or document 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 Guidance Notes on GMP Conformity Assessment of an Overseas Manufacturer (Dec, 2008)	GMP compliance on-site inspection is pre-requisite for NDA approval for new manufacturing site. The already registered manufacturing site should be get routine GMP renewal (follow up management) through onsite inspection or document inspection every 2 to 4 years depends on the first approved expiry date.	GMP accreditation required for submission of import-permission of sample drug before NDA submission Document inspection (or on site if needed) Accept GMP PIC/S from original country
		Please describe frequency/number of on-site inspections to domestic/overseas manufacturers by the authorities. ex. number of inspections conducted in last year	At the end of 2011, 7 GMP on-site inspections to overseas manufacturers were conducted. The situation of 2012 is unclear. GMP on-site inspection to domestic manufacturers were 126 in 2011, and it were 141 as of 30th Nov. 2012.	Since the manufacture license valids for only 1 year, inspection will be made at least on annual basis for local manufacturers	Annually. For overseas, CDSCO started inspection of Pharmaceutical firms for import registration of drugs. Six on-site inspections in 2011 for DS manufacturing site in China, and four China drug manufacturing sites in 2012.	Every month there are on site inspection to domestic and overseas manufacturers by the Authorities. Almost Asia countries are inspected.	Number of on-site GMP inspection to overseas manufacturer in 2011 was 61. About 70% are in Asia. On-site inspection to Japanese domestic manufacturer by PMDA in 2011 was 185.	Number of on-site inspection to overseas manufacturers in 2011 was 90. Domestic manufactures in 2011 : 232 by MFDS (90 by other authorities, e.g. FDA, EMA)	No on-site inspection overseas based on the recent policy change. Domestic manufacturers are inspected at least once a year for annual manufacturing license.	No details as of this moment.		TFDA: domestic: about 180, overseas: about 30 (in 2012).	- Domestic: Non- sterile drug: every 3 years Sterile drug: every 1.5 year - Overseas: if needed
	DMF system	Please describe DMF system (or plan for introduction). Is DMF mandatory or optional?	DMF system is investigated but not yet implement.	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.)	No DMF system, but it is optional to use DMF in application submission.	The submission of MF (Master File) is optional. Drug substance, Intermediate, New excipients, Packaging materials etc. are subjects of MF.	NCE should be submitted DMF since 2002. But all APIs should be registered by 2015. (Every year, MFDS announced the list of APIs which should be registered.) Only drug substance(API) is subject of DMF.	If a CEP is not available, a DMF is required for NCE registrations starting Jan 2012. There is plan to introduce this requirement for scheduled poisons and non scheduled poisons but the timing is to be determined. Note – poison = pharmaceuticals. Biologics are exempted.	No DMF system.	Yes. It is optional to use DMF in application submission.	Current only DMF regulation for drug substance available. But now it is no mandatory request for all API. TFDA will announce the product list for DMF compliance in next year. It may effective since year 2016 for all API.	No DMF system

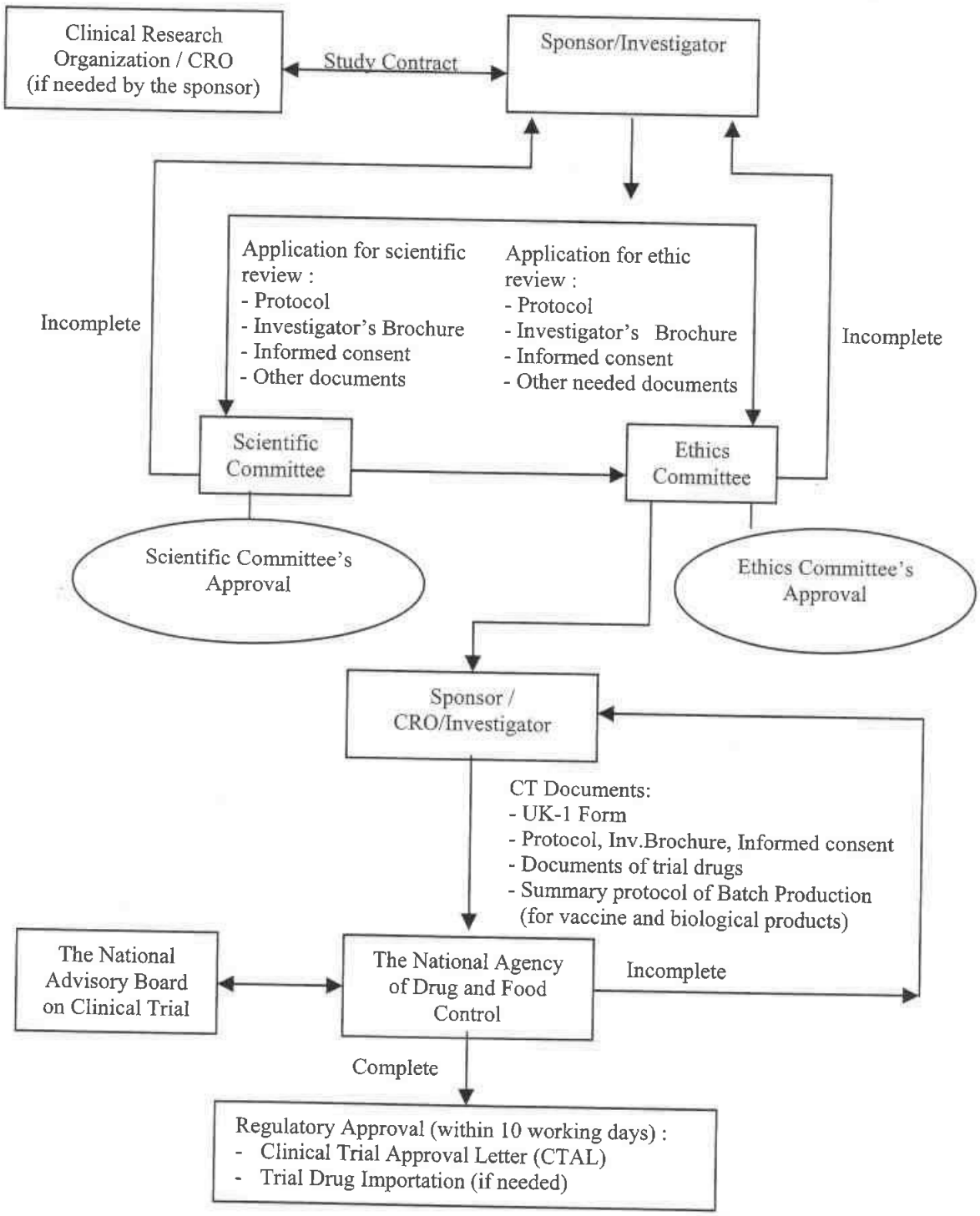
Item	Contents	Detail or Example	China RDPAC	Hong Kong HKAPI	India OPPI	Indonesia IPMG	Japan JPMA	Korea KPMA/KRPIA	Malaysia PhAMA	Philippines PHAP	Singapore SAPI	Taiwan IRPMA	Thailand PReMA
Manu -facturing	DMF system	Annual or periodical update reporting required?	not yet implement.	Not specified	N/A	N/A	No annual updated system. Partial change application or notification is required for changes.	Annual report should be submitted by Jan. 31 every year if there is any change.	Manufacturers of finished products should establish a mechanism by which manufacturers/suppliers of an API shall provide information on any changes (i.e. variations) in manufacture and control that may have impact on the safety, purity and quality of the API. It is the MAH's responsibility to provide the Agency with the appropriate documentation (referring to relevant parts of the dossier) to prove that any intended or implemented variation will not have an impact on the safety, purity and quality of the API that has been previously approved.	N/A	Applicants are responsible to maintain and update the DMF. Applicants must file variations when any changes to the DMF that will result in a post-approval variation.	No annual updated system. Partial change application or notification is required for changes.	Not required
	Contents of packaging label and language	Please describe required contents of packaging label and language to be used. ex. refer to guidance document	The required contents are described in SFDA order 24. The contents Should be written in Chinese.	English or English and Chinese, requirements decribed in Guidelines on the Labelling of Pharmaceutical Products	The required contents are described in rule 96 & Schedule D2 of the Drug and Cosmetic Rules 1945. PI and packaging labels should be written in English.	New guideline 2011 for labeling prescription drug : request to provide Package insert (English or Indonesia), Patient Information Leaflet (Indonesian), outerbox should following packaging requirement (name of the product, active substance, volume, indication, contraindication, dosage and administration, storage condition, manufacturing name & address , imported by,) also retail price, Registration number, Harus dengan resep dokter, Logo of prescription drug. In the label, after product name should follow active substance names, Label also following regulation on registration. Guideline for OTC : inner box and all product information should be in Indonesian language.	The required contents are described in Article 50 of the Pharmaceutical Affairs Act. The contents Should be written in Japanese.	Language : Korean Requirement : Follow Article 56 of the Pharmaceutical Affairs Act and in Article 75 of the Enforcement regulation of Pharmaceutical Affairs Act.	The labeling content is stated in Drug Regulatory Guidance Document. The labeling for pharmaceutical products are in English.	The required contents are described in Generic Labeling Law. The contents Should be written in English. (see A.O. 55, series 1988)	Refer to: GUIDANCE ON MEDICINAL PRODUCT REGISTRATION IN SINGAPORE APPENDIX 6 POINTS TO CONSIDER FOR SINGAPORE LABELLING	The required contents are described in Article 20 of "drug review and registration guideline". The contents should be written in English and Chinese.	Follow ASEAN labeling requirements Thai language required for - category of drug - expiration date - special warning
	Bar code on packaging materials	Please describe requirements of Bar Code on packaging materials and concerned regulations.	Bar code on packaging material for national essential drugs should be completed by Feb. 2012, while the deadline for whole drugs is by Dec. 2015.	For product registration, no concern. For supply to government hospital: GTIN barcode as issued by GS-1	For product registration, no concern. For supply to government hospital: GTIN barcode is required Barcode requirements using GS1 identification standards has been implemented. (reference: The Office Memorandum No: Z-16025/02/08-EPW dated 6th May 2011 by MoHFW)	No regulatory requirement on bar code. It is an internal company logistics requirement.	The contents Should be written in Japanese.	Requirement : Article 75 of the Pharmaceutical Affairs Act. & Means of Usage and Management of Bar Code and RFID tag for medicinal Product(MOHW Notification) GS1-128 barcode system (Product code + manufacturing date + expiry date + Batch no… and so on) should be used.	No regulatory requirement on bar code. It is a internal company logistics requirement.	Barcode is required per SKU. It is not a regulatory requirement but more of a marketing requirement.	No regulatory requirement on bar code. It is a internal company logistics requirement.	Current barcode labeling of product code is required to manufacturers/distributors depending on package unit (carton) or outer box. Barcode regulation on product unit (per tablet for blister, per bottle, per vial for injection) is draft and under discussion. The requirement for the barcode will be GTIN(GS1) data matrix.	No regulatory requirement for Bar code But some hospitals require barcode.

Item	Contents	Detail or Example	China RDPAC	Hong Kong HKAPI	India OPPI	Indonesia IPMG	Japan JPMA	Korea KPMA/KRPIA	Malaysia PhAMA	Philippines PHAP	Singapore SAPI	Taiwan IRPMA	Thailand PReMA
Post approval	Renewal system of approved license	Please describe renewal system of marketing authorization or manufacturing license. ex. renewal required every 5 years ex. re-evaluation system	Manufacturing license system is adopted for drug administration. So, renewal system is based on manufacturing license. Renewal is required every 5 years, and should be submitted within 6 months before expiration date of license.	Renewal required every 5 year.	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.	Marketing Authorization: Required every 5 years. Renewal application needs to be submitted 6 months prior to registration expiry. If needed, the NADFC will do re-evaluation system. Manufacturing License: Required every 5 years of every GMP facility and dosage form. Sometimes the NADFC will inspect the GMP facility before giving the renewal of Manufacturing license.	Not renewal but re-examination system is adopted. Drug monitoring is required for 8 years for NCE drug, 4 years for new indication/ administration route and 10 years for orphan drug.	Renewal system of approved licenses will be implemented from drugs which would be approved in 2013 (applicable for existing drugs as of Jan. 1, 2018). Documents should be submitted : 1) Summary reports on Safety and Efficacy of the drug product including the last 5-year 2) Usage in foreign countries, Any action related to safety in foreign countries 3) Data on Product Quality 4) Safety update report 5) In case anything would be changed from approval, its evidential data 6) Document on Drug Display (Label in carton, PI and so on) 7) Manufacturing or Importing records during the last five-year 8) Product Permission letter issued by MFDS	Renewal is required in every 5 years of every product registration. Renewal needs to be submitted 6 months prior to registration expiry.	Renewal system is being implemented. Drug renewal is 3 years for NCE, 5 years for new indication/ administration route or other type of applications.	Product licenses should be renewed every 12 months. Auto renewal system is implemented since 2009.	Renewal system of approved license is existed. The approved license needs to be renewed every 5 years.	There are 3 kinds of license in Thailand which are Manufacturing license, Import license and Sale license, all of which require annual renewal. Based on current Thai Drug Act, the product license is life-long, no requirement of renewal.
	Post marketing surveillance or safety monitoring program	PSUR submission required? Other post-approval safety requirements? ex. Safety monitoring program/monitored release	PSUR submission is mandatory annually until the first renewal date and every 5 years after the first renewal date. Special monitoring over drugs within the new drug observation period as well as drugs imported for the first time within 5 years is mandatory performed. The monitoring results shall be summarized, analyzed, evaluated and reported as required.	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. In August 2012 CDSCO issued a letter to industry enforcing the implementation of a 30 day cut off period and Indian data for PSUR submissions. This requirement has been in Sch Y from the beginning.	PSUR submission is required only for NCE and certain product if it is required by HA. There is an obligation to report all Adverse Events (unexpected/expected , serious/ non serious in Indonesia or foreign countries) to NADFC .	PSUR submission is mandatory every 6 month in first two years and annually after two years. Use-result survey data should be submitted together.	PSUR submission is mandatory every 6 month in first two years and annually after two years. Use-result survey data should be submitted together.	PSUR is mandatory for NCE: 6 months once in the first 2 years, and 12 months once in the subsequent 3 years.	PSUR submission will be mandatory instead of Post marketing surveillance: FDA requires MAH to submit PSURs on the International Birthdates (date of MA) - monitored release (every 6 months for the first 3 years); initial registration (yearly for first 3 years); regular registration (every 2 years). NOTE: regulation is expected to be finalized by Jan2013	When requested by HSA, PSUR should be submitted 6 months for the first 2 years, and 12 months for the subsequent 3 years. Ad-hoc submission requests can be raised if required.	PSUR submission is mandatory every 6 months in first two years and annually after two years. For NCE product, it necessary to submit PSUR in first 5 years. Other post approval safety requirement like RMP/REMs will be initiated by TFDA or Pharmaceutical company, it depends. For non-CPP NDA submission case, it is mandatory requirement to submit RMP/REMs together with NDA submission. For one-CPP NDA submission case, it may request by TFDA after their evaluation.	Yes, T-FDA requires PSUR for unconditional approval of New drug. SMP (Safety Monitoring Program) for NCE is required under conditional approval for 2 years.
	Risk Management Plan (RMP)	Please describe requirements of RMP/REMS. ex. Mandatory at NDA, submit up on request from the authorities	Not yet officially implemented. For the product which is accepted for special review procedure, Risk Management and Implementation Plan should be submitted at NDA.	One of the mandatory requirements for NCE registration	N/A at present	Not required yet. RMP regulation will establish later on.	From Apr 2013, RMP should be prepared and submitted at NDA.	MFDS has a plan to adopt REMS within several years.	Not a mandatory requirement. May be required on request by the authorities, in particular for biosimilar products.	N/A at present. RMP should be prepared as future requirement.	When available, RMP/REMS submitted to EMA/US-FDA may be requested at NDA, The need to implement a risk management plan in Singapore would be assessed on a case-by-case basis during the review process.	Mandatory at NDA for non-CPP product, submit up on request from TFDA.	Require for some specific group. Ex. Thalidomide .
	Adverse drug reaction reporting after marketing	Please describe reporting requirements of ADR for marketed products.	Reporting is mandated for ADR observed in post-marketing products including PMS. Reporting period of Serious ADR and expected ADR are within 15 days (30 days for non-Serious ADR for drugs within the new drug observation period or imported drugs within 5 years from the date of initial import permission).	For generic products, reporting is by means of voluntary basis. For NCE, SUSARs have to be reported within 15 calendar days from date of first receipt.	Serious ADR: Within 15 days of initial receipt of the information by the applicant. Other to be reported in PSUR.	Reporting is mandated for ADR observed in post-marketing products. 1. AE Spontaneous serious unexpected in Indonesia , as soon as possible, not more than 15 calendar days. 2. AE spontaneous non-serious unexpected in Indonesia, report every 6 months. 3. AE Spontaneous serious expected in Indonesia, as soon as possible, not more than 15 calendar days. 4. AE spontaneous serious unexpected in froiegn countries, as soon as possible, not more than 15 calendar days.	Reporting is mandated for ADR observed in post-marketing products including PMS. Reporting period of Serious ADR is within 15 days (or 30 days for expected ADR).	Reporting is mandated for ADR observed in post-marketing products including PMS. SAE : within 15 days from reported day NSAE : within next year Feb from reported day	Reporting is mandated for ADR observed in post-marketing products including PMS. Non serious ADR / Serious but non-life threatening ADR: 15 days from date learned; Serious ADR(fatal and life threatening is within 7days.	Reporting is mandated for ADR observed in post-marketing products including PMS. Reporting period of Serious ADR is within 3-7 days (or 30 days for expected ADR).	Fatal/life-threatening ARs: NLT 7 calendar days. Serious ARs: NLT 15 calendar days. Product withdrawal/product recall/product defect: Within 24 hrs Significant safety issues: Within 7 calendar days See The Guidance for Industry – Safety Reporting Requirements for Registered Medicinal Products, April 2011	Reporting is mandated for ADR observed in post-marketing products including PMS. Reporting period of Serious ADR is within 7 days for death and life threatening, within 15 days for other Serious ADR.	Follow Guidance for Industry Post-marketing Safety Reporting Requirements for Human Drug and Biological Products Including Vaccines (Annex 13)

Item	Contents	Detail or Example	China	Hong Kong	India	Indonesia	Japan	Korea	Malaysia	Philippines	Singapore	Taiwan	Thailand
			RDPAC	HKAPI	OPPI	IPMG	JPMA	KPMA/KRPIA	PhAMA	PHAP	SAPI	IRPMA	PReMA
Post approval	Variation guideline	Is there any guideline document for post-approval changes? If yes please show the title.	The variations to be approved or filed are listed in Drug Registration Regulation order 28. Meanwhile, Guideline for Variations of Post-market Chemical Drug Products has been implemented.	Please refer to the guidelines for Change of particulars (file name: copGuide).	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)	There is regulation number Hk.o3.1.23.12.11.10690 .2011 regarding Implementation of Pharmacovigilance for Pharmaceutical Industry . Variation guideline are included in the Criteria and Procedure of Drug Registration no HK 03/23.10.11.08481. year 2011 /	Partial change application should be submitted for approval of changes. For minor changes, notification system can be applied. Scope and handling of these changes are stipulated in the Pharmaceutical Affairs Law and several notices.	Changes in post-license should be applyed to MFDS according to the level of the changes. Pharmaceutical Affairs Act, Several notices and Guidelines exist.	Malaysian variation guidelines is in the Drug Regulatory Guidance Document. Malaysia target to implement the ASEAN Variation Guidelines by Jul 2013.	Partial change application should be submitted for approval of changes. For minor changes, notification system can be applied. (Pending implementation) See attached files MaV and MiV	There are two sub-categories for each Major and Minor variation. Guidelines are found in Chapter H and Appendix 15 for MIV and Chapter G for MAV.	"drug review and registration guideline" was specify the document needed for post approval change.	Yes, "Asean variation guideline" which will be implemented in Jul 2013. ASEAN Variation Guideline

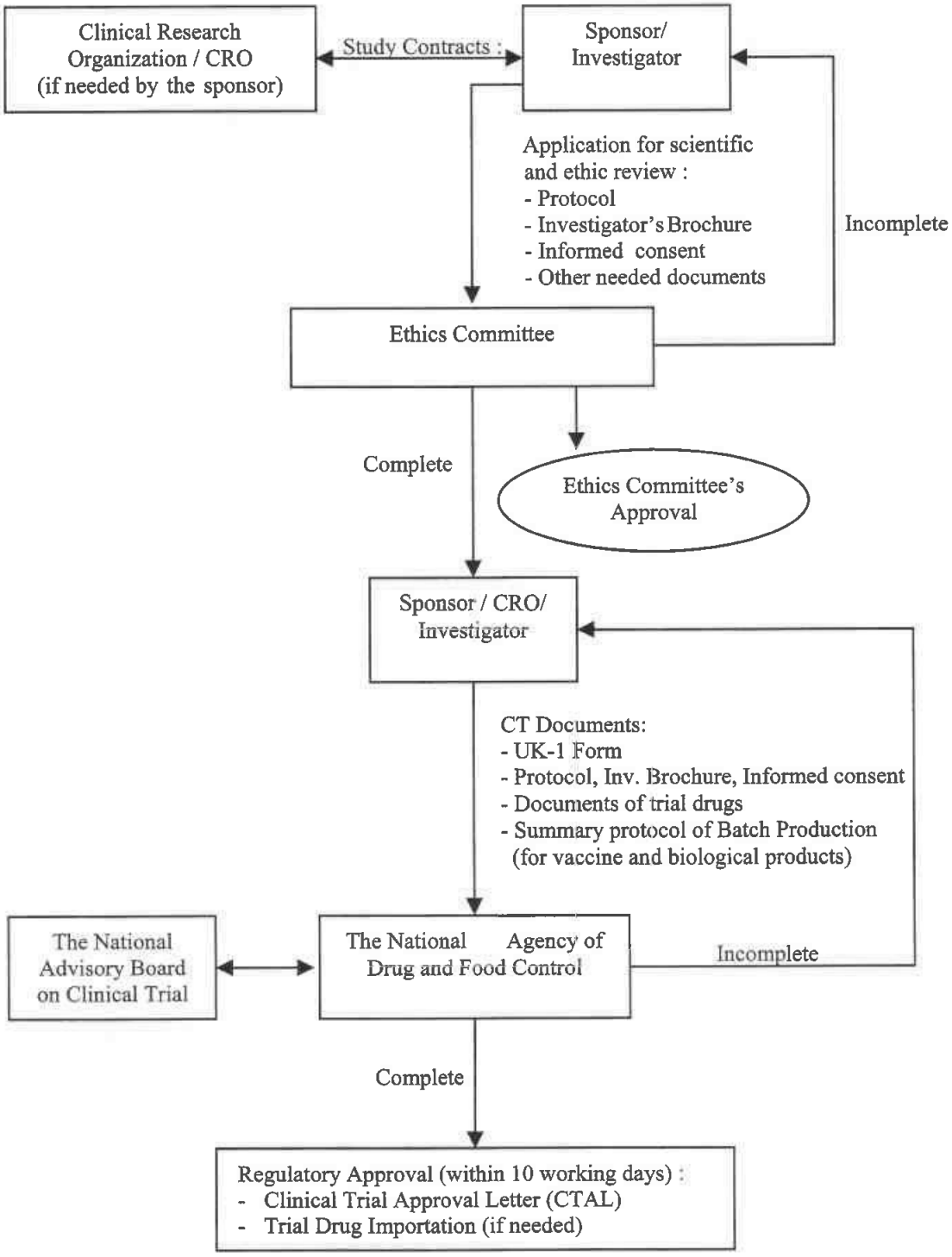
ATTACHMENT IIa
DECREE OF THE HEAD OF THE NATIONAL AGENCY OF DRUG AND FOOD CONTROL
REPUBLIC OF INDONESIA
NO 02002/SK/KBPOM
REGARDING CLINICAL TRIAL PROCEDURE

Flow Chart
Pre-Marketing Trial



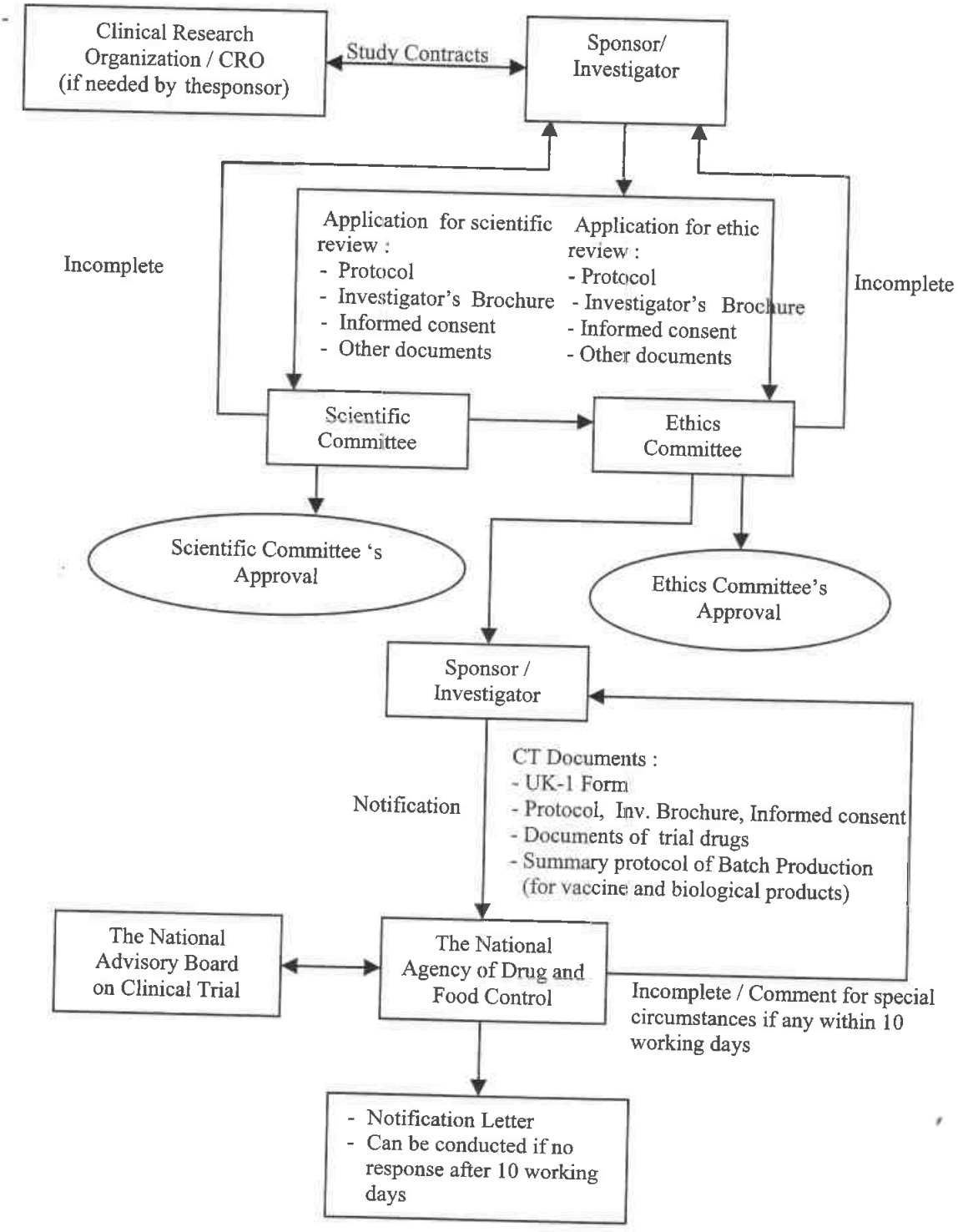
ATTACHMENT IIb
DECREE OF THE HEAD OF THE NATIONAL AGENCY OF DRUG AND FOOD CONTROL
REPUBLIC OF INDONESIA
NO 02002/SK/KBPOM
REGARDING CLINICAL TRIAL PROCEDURE

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



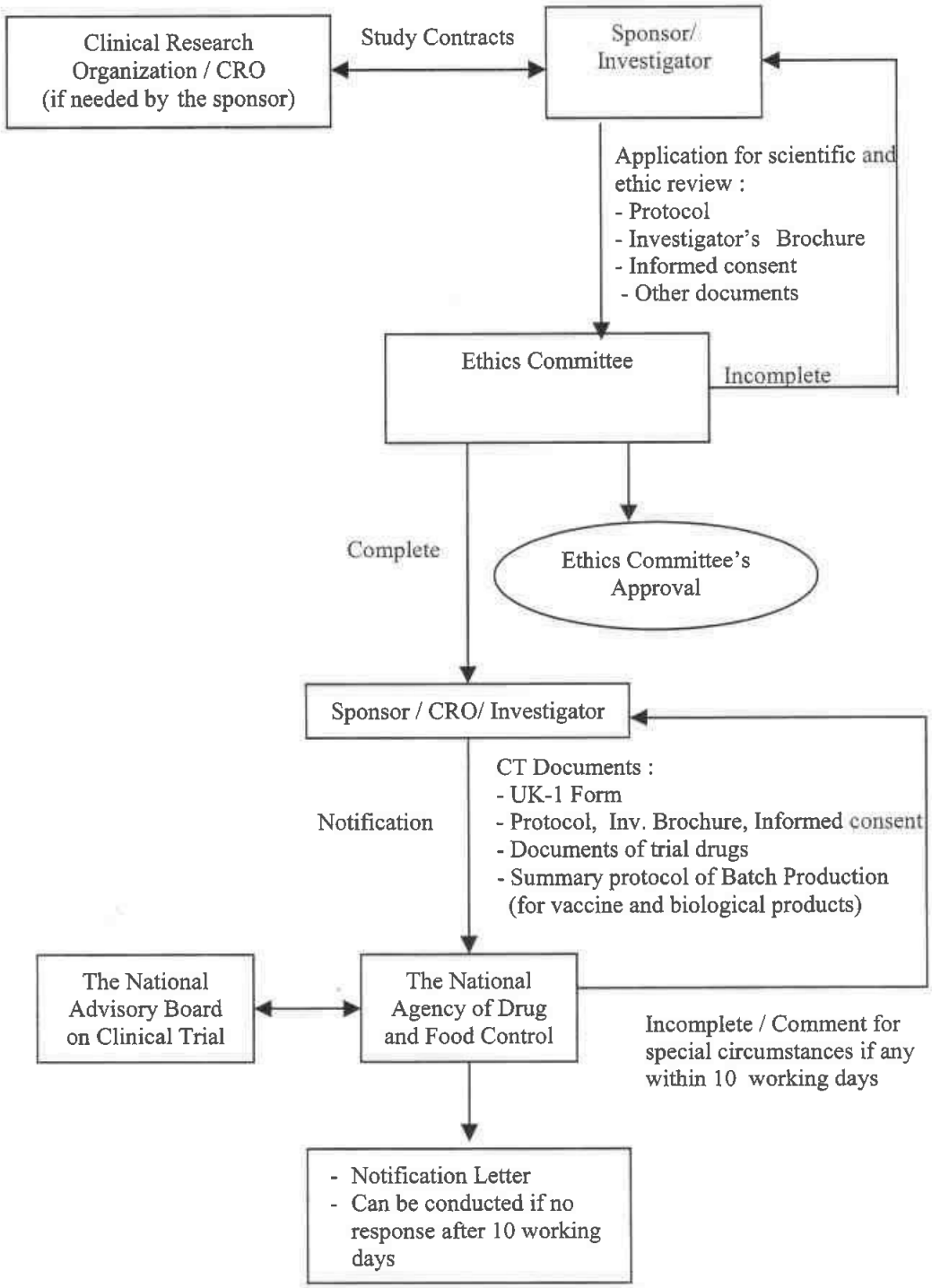
ATTACHMENT IIIa
DECREE OF THE HEAD OF THE NATIONAL AGENCY OF DRUG AND FOOD CONTROL
REPUBLIC OF INDONESIA
NO 02002/SK/KBPOM
REGARDING CLINICAL TRIAL PROCEDURE

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



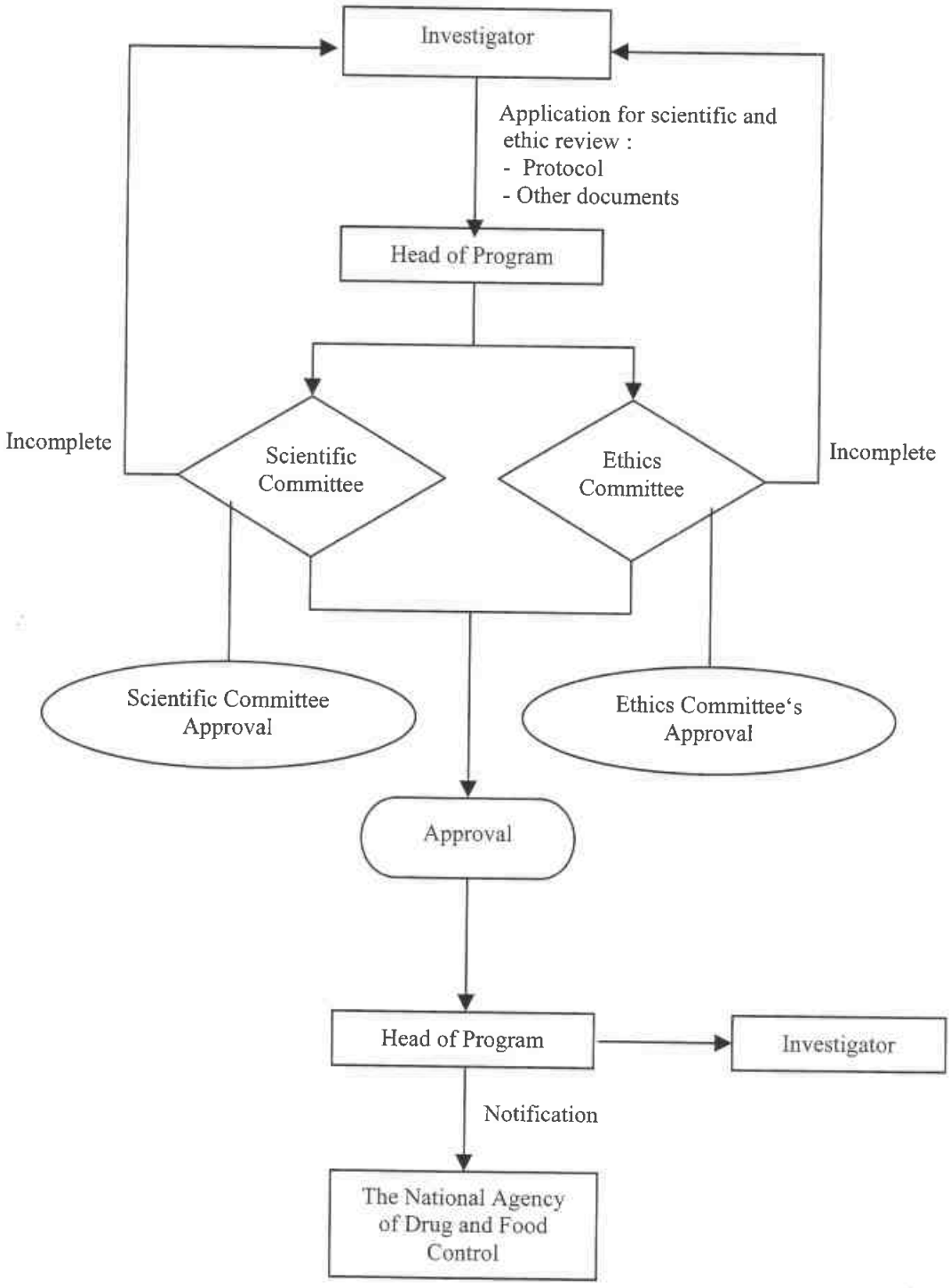
ATTACHMENT IIIb
DECREE OF THE HEAD OF THE NATIONAL AGENCY OF DRUG AND FOOD CONTROL
REPUBLIC OF INDONESIA
NO 02002/SK/KBPOM
REGARDING CLINICAL TRIAL PROCEDURE

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



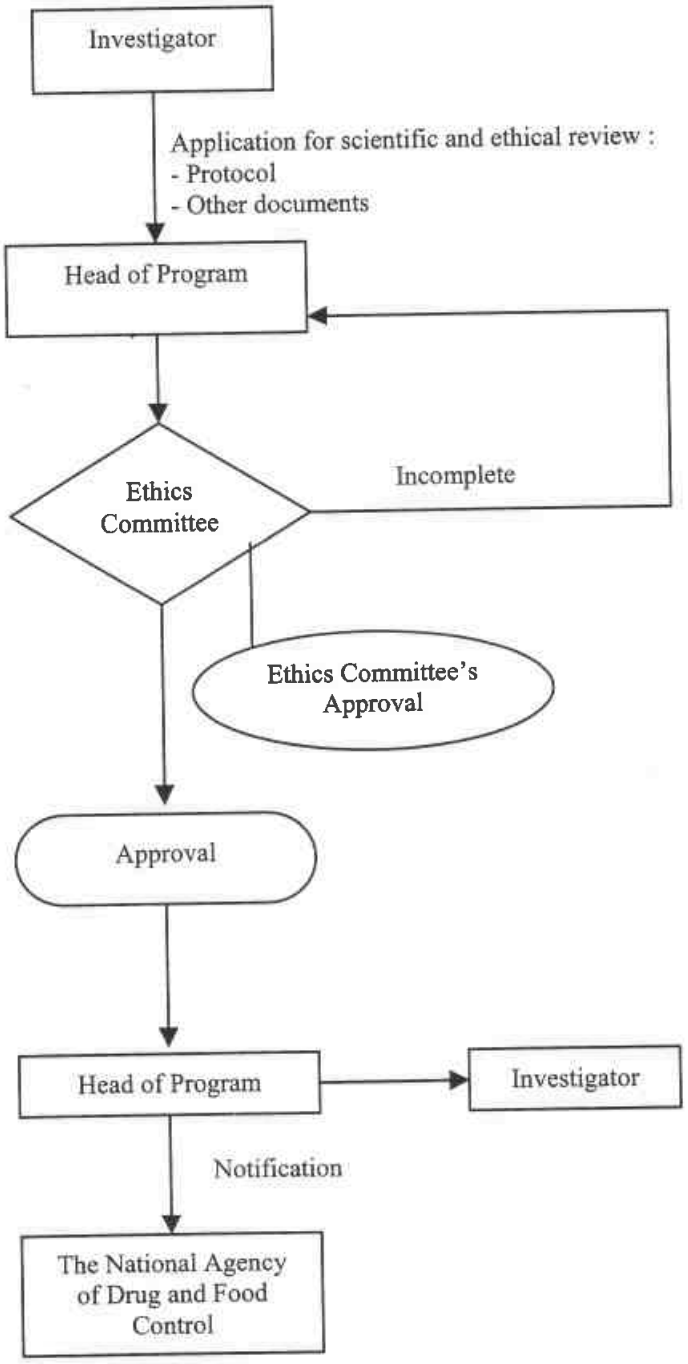
ATTACHMENT IVa
DECREE OF THE HEAD OF THE NATIONAL AGENCY OF DRUG AND FOOD CONTROL
REPUBLIC OF INDONESIA
NO 02002/SK/KBPOM
REGARDING CLINICAL TRIAL PROCEDURE

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



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

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



UK-1 FORM

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

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

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

I. GENERAL INFORMATION

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

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

Yes ☐ No ☐

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

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

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

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

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

II. INSTITUTIONS

Multi-center Clinical Trial

Yes ☐ No ☐

Local Center :

Overseas Center :

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

III. STUDY DRUG

Study medication : Imported ☐

Local ☐

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

IV. COMPARATOR DRUG

Study medication	: Imported	☐
	Local	☐

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

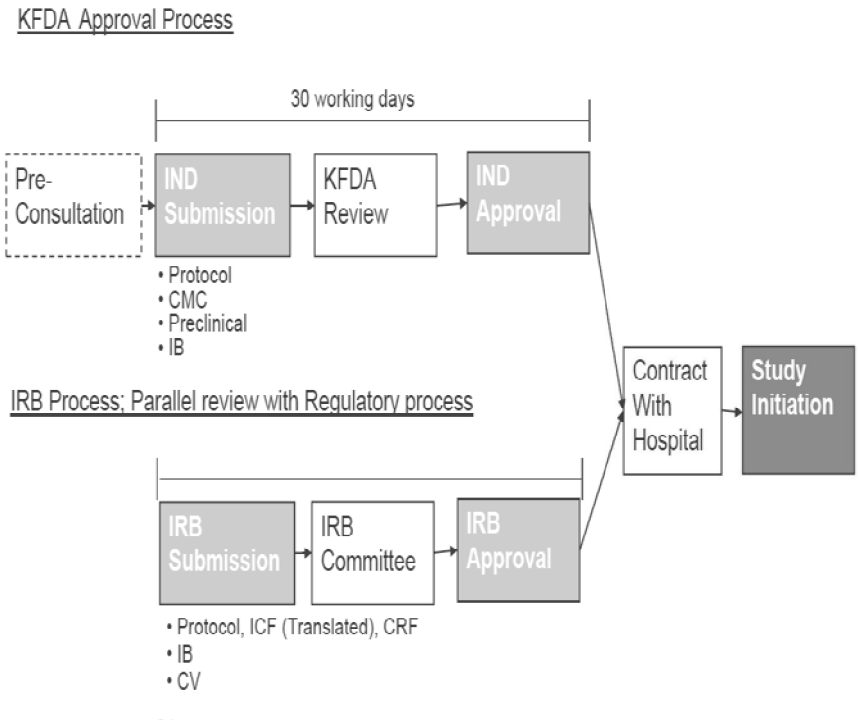
V. SPONSOR

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

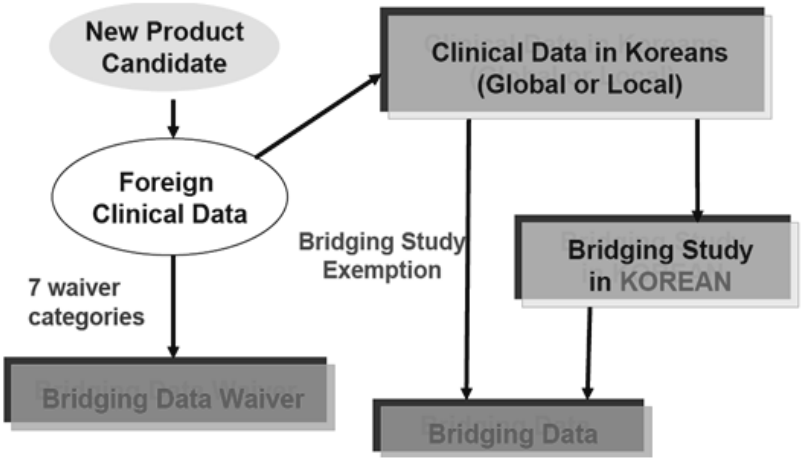
VI. SCIENTIFIC COMMITTEE AND ETHIC COMMITTEE' S APPROVAL

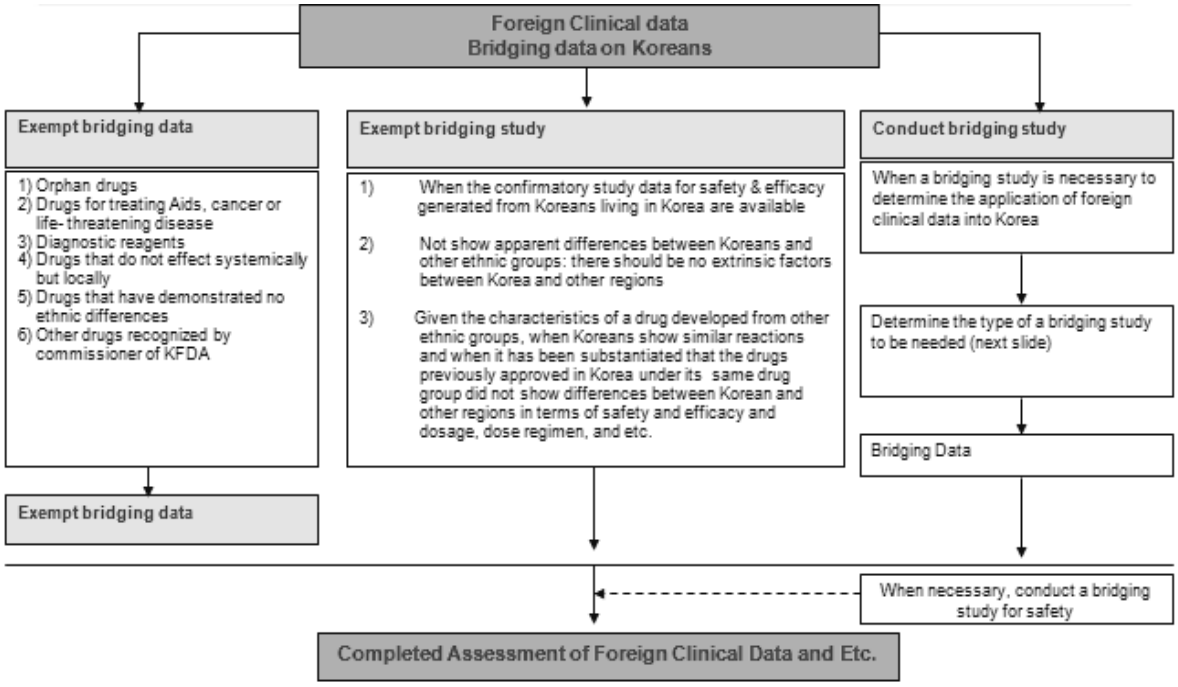
Conclusion of scientific review (attached)
Conclusion of ethical review (attached)
Scientific Committee's approval (attached) - Number and date : - Name and address of Institution :
Ethics Committee' s approval (attached) - Number and date : - Name and address of Institution :

Annex 2



Annex 3





II
GUIDELINES/REFERENCE FOR ACTR QUALITY

No	PARAMETERS	GUIDELINE/REFERENCE	
		NCE/BIOTECH	G
S	DRUG SUBSTANCE		
S1	General Information	Q6A ;Q6B	Nat. Pharmacopoeia; USP; BP
	1.1 Nomenclature		
	1.2.Structure		
	1.3. General Properties		
S2	Manufacture		
	2.1. Manufacturer(s)		
	2.2. Description of Manufacturing Process and Process Controls	Q5A; Q5B; Q6B	
	2.3. Control of Materials	Q5A; Q5B; Q5C; Q5D; Q6A; Q6B	
	2.4. Controls of Critical Steps and Intermediates	Q6A; Q6B; Q5C	
	2.5. Process Validation and/or Evaluation	Q5A; Q5D; Q6B	
	2.6. Manufacturing Process Development	Q3A; Q6B	
S3	Characterisation		
	3.1. Elucidation of Structure and other characteristics	Q6A; Q6B	Nat. Pharmacopoeia; USP; BP
	3.2. Impurities	Q3A; Q3C; Q5C; Q6A; Q6B	Nat. Pharmacopoeia; USP; BP
S4	Control of Drug Substance		
	4.1. Specification	Q6A; Q6B	Nat. Pharmacopoeia; USP; BP
	4.2. Analytical Procedures	Q2A; Q6B	Nat. Pharmacopoeia; USP; BP
	4.3. Validation of Analytical Procedures	Q2A; Q2B; Q6B	
	4.4. Batch Analyses	Q3A; Q3C; Q6A; Q6B	
	4.5. Justification of Specification	Q6A; Q6B	
S5	Reference Standards or Materials	Q6A; Q6B	Nat. Pharmacopoeia; USP; BP
S6	Container Closure System	-	-
S7	Stability	Q1A; Q1B; Q5C; Q2A, Q2B	Nat. Pharmacopoeia; USP; BP
P	DRUG PRODUCT		
P1	Description and Composition	Q6A; Q6B	
P2	Pharmaceutical Development		
	2.1. Information on Development Studies	Q6A; Q6B	
	2.2. Components of the Drug Product		
	2.3. Finished Product		
	2.4. Manufacturing Process Development		
	2.5. Container Closure System		
	2.6. Microbiological Attributes		
	2.7. Compatibility		

No	PARAMETERS	GUIDELINE/REFERENCE	
		NCE/BIOTECH	G
P3	Manufacture		
	3.1. Batch Formula	Q6B	
	3.2. Manufacturing Process and Process Control		
	3.3. Control of Critical Steps and Intermediates	Q2A; Q2B; Q6A; Q6B	
	3.4. Process Validation and/or Evaluation	Q6B	
P4	Control of excipients		
	4.1. Specifications	Q6A; Q6B	Nat. Pharmacopoeia; USP; BP
	4.2. Analytical Procedures	Q2A; Q6B	Nat. Pharmacopoeia; USP; BP
	4.3. Validation of Analytical Procedures	Q2A; Q2B; Q6B	ASEAN Guideline
	4.4. Justification of Specifications	Q3C; Q6B	
	4.5. Excipient of Human or Animal Origin	Q5A; Q5D; Q6B	Nat. Pharmacopoeia; USP; BP
	4.6. Novel Excipients		
P5	Control of Finished Product		
	5.1. Specification	Q6A; Q6B	
	5.2. Analytical Procedures	Q2A; Q6B	
	5.3. Validation of Analytical Procedures	Q2A; Q2B; Q6B	ASEAN Guideline
	5.4. Batch Analyses	Q3A; Q3C; Q6A; Q6B	
	5.5. Characterisation of Impurities	Q3B; Q6A; Q6B	Nat. Pharmacopoeia; USP; BP
	5.6. Justification of Specification(s)	Q3B; Q6A; Q6B	
P6	Reference Standards or Materials	Q6A; Q6B	
P7	Container Closure System		
P8	Stability	Q1A; Q1B; Q2A; Q2B; Q5C (modified)	ASEAN Guideline
P9	Product Interchangeability		ASEAN Guideline

ASEAN Common Technical Requirement for Pharmaceutical Registration : Quality (ASEAN CTR : Quality)

No	PARAMETERS	COMPONENTS	REQUIREMENTS					Max. Pages
			NCE	BIOTECH	MaV	MiV	G	
S	**DRUG SUBSTANCE**							Issue open for discussion
S1	**General Information**							
	1.1 Nomenclature	- Information from the S1	✓	✓	✓	✓	✓	
	1.2.Structure	- Structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass.	✓				✓	
	1.3. General Properties	- Physico chemical characteristics and other relevant properties including biological activity for biotech.	✓	✓	✓	✓	✓	
		- Schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass as appropriate.		✓				
S2	**Manufacture**							
	2.1. Manufacturer(s)	Name and address of the manufacturer (s).	✓	✓			✓	
	2.2. Description of Manufacturing Process and Process Controls	- The description of the drug substance manufacturing process and process control that represents the applicant's commitment for the manufacture of the drug substances.	✓	✓				
		- Information on the manufacturing process, which typically starts with a vial(s) of the cell bank, and includes cell culture, harvest(s), purification and modification reaction, filling, storage and shipping conditions.		✓				
	2.3. Control of Materials	- Starting materials, solvents, reagents, catalysts, and any other materials used in the manufacture of the drugs subtance indicating where each material is used in the process. Tests and acceptance criteria of these materials.	✓	✓				
		- Control of source and starting materials of biological origin.		✓				
		- Source, history and generation of the cell substrate .		✓				
		- Cell banking system, characterisation and testing.		✓				
		- Viral safety evaluation.		✓				
	2.4. Controls of Critical Steps and Intermediates	- Critical steps : Tests and acceptance criteria, with justification including experimental data, performed at critical steps of the manufacturing process to ensure that the process is controlled.	✓	✓				
		- Intermediates : Specifications and analytical procedure, if any, for intermediates isolated during the process.	✓	✓				

No	PARAMETERS	COMPONENTS	REQUIREMENTS					Max. Pages
			NCE	BIOTECH	MaV	MiV	G	
		- Stability data supporting storage conditions.		✓				
	2.5. Process Validation and/or Evaluation	- Process validation and/or evaluation studies for aseptic processing and sterilization.	✓	✓				
	2.6. Manufacturing Process Development	- Description and discussion of significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing non-clinical, clinical, scale-up, pilot and if available, production scale batches.	✓					
		- The development history of the manufacturing process as described in S 2.2.		✓				
S3	**Characterisation**							
	3.1. Elucidation of Structure and other characteristics	- Confirmation of structure based on e.g. synthetic route and spectral analyses.	✓					
		Compendial requirements or appropriate information from the manufacturer					✓	
		- Details on primary, secondary and higher-order structure and information on biological activity, purity and immunochemical properties (when relevant).		✓				
	3.2. Impurities	- Summary of impurities monitored or tested for during and after manufacture of drug substance	✓	✓				
		Compendial requirements or appropriate information from the manufacturer					✓	
S4	**Control of Drug Substance**							
	4.1. Specification	- Detailed specification, tests and acceptance criteria.	✓	✓				
		Compendial specification or appropriate information from the manufacturer					✓	
		- Specify source, including as appropriate species of animal, type of microorganism etc.		✓				
	4.2. Analytical Procedures	- The analytical procedures used for testing of drug substance.	✓	✓				
		Compendial methods or appropriate information from the manufacturer			✓	✓	✓	
	4.3. Validation of Analytical Procedures	- Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance	✓	✓				
		Non-compendial methods					✓	

No	PARAMETERS	COMPONENTS	REQUIREMENTS					Max. Pages
			NCE	BIOTECH	MaV	MiV	G	
	4.4. Batch Analyses	- Description of batches and results of the analysis to establish the specification.	✓	✓				
	4.5. Justification of Specification	- Justification for drug substance specification.	✓	✓				
S5	**Reference Standards or Materials**	- Information on the reference standards or reference materials used for testing of the drug substance .	✓	✓				
		Compendial reference standard.			✓	✓	✓	
S6	**Container Closure System**	Descriptions of the container closure systems.	✓	✓				
S7	**Stability**	- Stability report.	✓	✓				
		- Literature data .			✓	✓	✓	
P	**DRUG PRODUCT**							
P1	**Description and Composition**	Description - Dosage form and characteristics. - Accompanying reconstitution diluent (s) if any. - Type of container and closure used for the dosage form and reconstitution diluent (s), if applicable.	✓	✓	✓	✓	✓	
		Composition Name, quantity stated in metric weight or measures, function and quality standard reference.	✓	✓	✓	✓	✓	
P2	**Pharmaceutical Development**							
	2.1. Information on Development Studies	- Data on the development studies conducted to establish that the dosage form, formulation, manufacturing process, container closure system, microbiological attributes and usage instruction are appropriate for the purpose specified in the application.	✓	✓				
	2.2. Components of the Drug Product	- Active ingredient -Justification of the compatibility of the active ingredient with excipients listed in P1	✓	✓				
		-In case of combination products, justification of the compatibility of active ingredients with each other.						
		-Literature data.			✓	✓	✓	
		- Excipients Justification of the choice of excipients listed in P1, which may influence the drug product performance.	✓	✓				
	2.3. Finished Product	- Formulation Development A brief summary describing the development of the finished product, (taking into consideration the proposed route of administration and usage for NCE and Biotech).	✓	✓			✓	

No	PARAMETERS	COMPONENTS	REQUIREMENTS					Max. Pages
			NCE	BIOTECH	MaV	MiV	G	
		- Overages Justification of any overage in the formulation(s) described in P1 .	✓	✓			✓	
		- Physicochemical and Biological Properties Parameters relevant to the performance of the finished product e.g pH, dissolution.	✓	✓			✓	
	2.4. Manufacturing Process Development	- Selection and optimisation of the manufacturing process	✓	✓	✓	✓	✓	
		- Differences between the manufacturing process (es) used to produce pivotal clinical batches and the process described in P.3.2, if applicable	✓	✓				
	2.5. Container Closure System	Suitability of the container closure system used for the storage, transportation (shipping) and use of the finished product.	✓	✓	✓	✓	✓	
	2.6. Microbiological Attributes	Microbiological attributes of the dosage form, where appropriate	✓	✓	✓	✓	✓	
	2.7. Compatibility	Compatibility of the finished product with reconstitution diluent(s) or dosage devices.	✓	✓	✓	✓		
		Literature data					✓	
P3	**Manufacture**							
	3.1. Batch Formula	Name and quantities of all ingredients	✓	✓	✓	✓	✓	
	3.2. Manufacturing Process and Process Control	~~Detail~~ Description of manufacturing process and process control	✓	✓	✓	✓	✓	
	3.3. Control of Critical Steps and Intermediates	Tests and acceptance criteria	✓	✓			✓	
	3.4. Process Validation and/or Evaluation	Description, documentation, and results of the validation and/or evaluation studies for critical steps or critical assays used in the manufacturing process.	✓	✓			✓	
P4	**Control of excipients**							
	4.1. Specifications	- Specifications for excipients	✓	✓				
		Compendial requirements or appropriate information from the manufacturer			✓	✓	✓	
	4.2. Analytical Procedures	- Analytical procedures used for testing excipients where appropriate.	✓	✓				
		Compendial requirements or appropriate information from the manufacturer			✓	✓	✓	
	4.3. Validation of Analytical Procedures	- Analytical validation information where appropriate	✓	✓				

No	PARAMETERS		COMPONENTS	REQUIREMENTS					Max. Pages
				NCE	BIOTECH	MaV	MiV	G	
			Non-compendial method.			✓	✓	✓	
	4.4. Justification of Specifications		Justification for the proposed excipient specifications where appropriate	✓	✓				
	4.5. Excipient of Human or Animal Origin	-	Information regarding sources and or adventitious agents.	✓	✓				
			Compendial requirements or appropriate information from the manufacturer			✓	✓	✓	
	4.6. Novel Excipients		For excipient(s) used for the first time in a finished product or by a new route of administration, full details of manufacture, charcterization and controls, with cross reference to supporting safety data (non-clinical or clinical)	✓	✓				
P5	**Control of Finished Product**								
	5.1. Specification		The specification(s) for the finished product.	✓	✓	✓	✓	✓	
	5.2. Analytical Procedures		Analytical procedures used for testing the finished product	✓	✓	✓	✓	✓	
	5.3. Validation of Analytical Procedures	-	Information including experimental data, for the analytical procedure used for testing the finished product	✓	✓				
			Non-compendial method	✓	✓	✓	✓	✓	
			Verification of compendial method applicability - precision & accuracy			✓	✓	✓	
	5.4. Batch Analyses		Description and test results of all relevant batches.	✓	✓	✓	✓	✓	
	5.5. Characterisation of Impurities	-	Information on the characterisation of impurities	✓	✓				
			Compendial requirements or appropriate information from the manufacturer			✓	✓	✓	
	5.6. Justification of Specification(s)	-	Justification of the proposed finished product specification(s).	✓	✓				
			Compendial requirements or appropriate information from the manufacturer			✓	✓	✓	
P6	**Reference Standards or Materials**		Information on the reference standards or reference materials used for testing of the finished product.	✓	✓				

No	PARAMETERS	COMPONENTS	REQUIREMENTS					Max. Pages
			NCE	BIOTECH	MaV	MiV	G	
		Compendial requirements or appropriate information from the manufacturer			✓	✓	✓	
P7	**Container Closure System**	Specification and control of primary and secondary packaging material, type of packaging and the package size, details of packaging inclusion (e.g. desiccant, etc)	✓	✓	✓	✓	✓	
P8	**Stability**	Stability report : data demonstrating that product is stable through its proposed shelf life. Commitment on post approval stability monitoring	✓	✓	✓	✓	✓	
P9	**Product Interchangeability** **Equivalence evidence**							
		- In Vitro Comparative dissolution study as required			✓		✓	
		- In Vivo Bioequivalence study as required			✓		✓	
		Reference : WHO, Regulatory Support Series No 5 ,"Bioequivalence Studies in Humans."						

GUIDELINES TO ACTR ON NONCLINICAL DATA:

	PARAMETERS	Guideline / Reference
1.0	**PHARMACOLOGY**	
	M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals	ICH-M3 62 FR 62922
	Safety Pharmacology Studies for Human Pharmaceuticals	ICH-S7A
2.0	**PHARMACOKINETICS**	
	Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies	ICH-S3B
	Toxicokinetics: Guidance on The Assessment of Systemic Exposure in Toxicity Studies	ICH-S3A
3.0	**TOXICOLOGY**	
3.1 / 3.2	▪ **Single and Repeat Dose Toxicity**	
	Single Dose Acute Toxicity Testing for Pharmaceuticals	ICH-S4 61 FR 43934
	Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals	ICH-M3 62 FR 62922
	Duration of Chronic Toxicity Testing in Animals (Rodent and Nonrodent)	ICH-S4A
3.3	▪ **Genotoxicity**	
	Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals	ICH-S2A
	A Standard Battery for Genotoxicity Testing of Pharmaceuticals	ICH-S2B
3.4	▪ **Carcinogenicity**	
	Guidelines on the Need for Carcinogenicity Studies of Pharmaceuticals	ICH-S1A
	Testing for Carcinogenicity of Pharmaceuticals	ICH-S1B
	Dose Selection for Carcinogenicity Studies of Pharmaceuticals	ICH-S1C
	Dose Selection for Carcinogenicity Studies of Pharmaceuticals: Addition of a Limit Dose and Related Notes	ICH-S1C(R)
3.5	▪ **Reproductive Toxicity**	
	Detection of Toxicity to Reproduction for Medicinal Products	ICH-S5A
	Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility Studies	ICH-S5B (M)
	▪ **Biotechnology Products**	
	Safety Studies for Biotechnological Products	ICH-S6

ICH No.	PARAMETERS	COMPONENTS	REQUIREMENTS						GP
			NCE	BIOTECH	MaV			MiV	
					RT	S/P	IND		
M3	**1. Pharmacology**	- Studies designed to examine effects other than the primary therapeutic effect of a drug substance.							
	1.1. Primary Pharmacodynamics	- Studies are done to identify the mode of action and/or effects of a substance in relation to its desired therapeutic target	—	—					
	1.2. Secondary Pharmacodynamics	- Studies are done to identify the mode of action and/or effects of a substance not related to its therapeutic target	—	—					
S7A S6	**1.3. Safety Pharmacology**	- Studies focus on identifying adverse effects on physiological functions - Core battery includes the assessment of effects on the vital functions, such as cardiovascular, central nervous and respiratory systems, and these should be evaluated prior to human exposure. - These evaluations may be conducted as addition to toxicity studies or as separate studies.	—	—					
	1.4. Pharmacodynamic Drug Interactions	- If they have been performed, pharmacodynamic drug interaction studies should be briefly summarized in this section.	—	—					
S3B S3A	**2. Pharmacokinetics**	- PK data form the basis for prediction of therapeutic doses and suitable dosage regimen							

ICH No.	PARAMETERS	COMPONENTS	REQUIREMENTS						GP
			NCE	BIOTECH	MaV			MiV	
					RT	S/P	IND		
	2.1. Absorption	- Extent and rate of absorption, in-vivo and in situ studies - Kinetic parameters, bioequivalence and or bioavailability (serum/plasma/ blood PK studies)	__	❖	❖	❖			
	2.2. Distribution	- Tissue distribution studies - Protein binding and distribution in blood cells - Placental transfer studies	__	❖	❖	❖			
	2.3. Metabolism (inter-species comparison)	- Chemical structure and quantities of metabolites in biological samples - Possible metabolic pathways - Pre- systemic metabolism (GI/Hepatic First-Pass Effects) - In vitro metabolism including P450 studies - Enzyme induction and inhibition	__	❖	❖	❖			
	2.4. Excretion	- Route and extent of excretion - Excretion in milk	__	❖	❖	❖			
	2.5. Pharmacokinetic Drug Interaction (Non-clinical)	- If they have been performed, non-clinical pharmacokinetic drug interaction studies (in-vitro and/ or in-vivo) should be briefly summarized in this section.	__						
	2.6. Other Pharmacokinetic Studies	- If studies have been performed in non-clinical models of disease (eg. Renally impaired animals), should be summarized in this section.	__		❖				

ICH No.	PARAMETERS	COMPONENTS	REQUIREMENTS						GP
			NCE	BIOTECH	MaV			MiV	
					RT	S/P	IND		
	3. Toxicology	- The scope of the toxicologic evaluation should be described in relation to the proposed clinical use.							
S4	**3.1.Single Dose Toxicity**	- The single dose data should be briefly summarized, in order by species, by route. - It should be evaluated in two mammalian species prior to the first human exposure - A dose escalation study is considered an acceptable alternative to the single dose design.	__	__					
S4A	**3.2.Repeat Dose Toxicity**	- Studies should be summarized in order by species, by route, and by duration, giving brief details of the methodology and highlighting important findings (e.g. nature and severity of target organ toxicity, dose (exposure)/ response relationships, no observe adverse effect levels (NOEL). - It is performed on rodents and non-rodents with a study duration of 6 months and 9 months respectively - Studies are related to the duration, therapeutic indication and scale of the proposed clinical trial of the pharmaceutical.	__	__					

ICH No.	PARAMETERS	COMPONENTS	REQUIREMENTS						GP
			NCE	BIOTECH	MaV			MiV	
					RT	S/P	IND		
S2A S2B	**3.3.Genotoxicity**	- Brief summaries of in vitro and in vivo tests designed to detect compounds which induce genetic damage directly or indirectly by various mechanisms: ▪ In vitro tests include tests for the detection of bacterial mutagens ▪ In vivo tests include tests for the detection of clastogens (either by chromosomal aberrations or micronuclei polychromatic erythrocytes)	__						

ICH No.	PARAMETERS	COMPONENTS	REQUIREMENTS						GP
			NCE	BIOTECH	MaV			MiV	
					RT	S/P	IND		
S1A S1B S1C S1C (R)	**3.4.Carcinogenicity**	- Studies are conducted to identify a tumorigenic potential in animals and to assess the relevant risk in humans. - The strategy for testing the carcinogenic potential of a pharmaceutical is developed only after acquisition of information : results of genetic toxicology, intended patient population, clinical dosage regimen, pharmacodynamics in animals and in humans, repeated-dose toxicology studies. No single approach can be expected to predict the carcinogenic potential. - Other factors may also be considered : such as the intended patient population, prior assessment of carcinogenic potential, extent of systemic exposure etc. - A brief rationale should explain why the studies were chosen and the basis for high dose selection. - Individual studies should be summarized and comprises : • one long-term rodent studies, • and either, short / medium term studies (in-vivo rodent test systems) or a long term studies in a second rodent species • Other studies	—	♦					

ICH No.	PARAMETERS	COMPONENTS	REQUIREMENTS						GP
			NCE	BIOTECH	MaV			MiV	
					RT	S/P	IND		
S5A S5B (M)	**3.5 Reproductive and Developmental Toxicity**	- Studies are designed to evaluate the effect of the drug on the general reproductive performance of animals starting at implantation and continuing through the weaning period in doses significantly greater than those intended for man or in doses that give greater significantly higher blood and / or other tissue concentration than those achieved in man. - Studies should be conducted in mammalian species, same species and strain as in other toxicological studies, i.e. rats. For embryotoxicity studies, a second mammalian species is required, rabbit being the preferred choice as a non-rodent. - Dosages : choice of high dose should be based on data from all available studies - Route and frequency of administration : similar to the intended route for human usage and usual frequency is once daily or more or less frequent depending on the kinetic profile - Control group : use of vehicle as control group vs test group	—	—					

ICH No.	PARAMETERS	COMPONENTS	REQUIREMENTS						GP
			NCE	BIOTECH	MaV			MiV	
					RT	S/P	IND		
S5A S5B (M)	**3.5.1 Fertility and Early Embryonic Development**	- Studies are conducted to test for toxic effects/disturbances resulting from treatment from before mating (males/females) through mating and implantation. - Effects of a potentially toxic substance could be determined by assessment of: maturation of gametes, mating behavior, fertility, preimplantation stages of the embryo, implantation.	—	—					

ICH No.	PARAMETERS	COMPONENTS	REQUIREMENTS						GP
			NCE	BIOTECH	MaV			MiV	
					RT	S/P	IND		
S5A S5B (M)	**3.5.2 Embryo-fetal Development**	- Studies conducted to detect adverse effects on the pregnant female and development of the embryo and fetus consequent to exposure of the female from implantation to closure of the hard palate. - The potential adverse effects to be assessed include: enhanced toxicity relative to that in non-pregnant females, embryofetal death, altered growth and structural changes - Studies should include: • characterization of the type and incidence of malformations in comparison with the negative and positive controls through detailed skeletal and visceral organ examination • calculation of pregnancy rate, implantation efficiency and fetal viability • evaluation of the effect of treatment or chemical on maternal weight, mortality, behavior, and fetal weight including male / female ratio	—	—					

ICH No.	PARAMETERS	COMPONENTS	REQUIREMENTS						GP
			NCE	BIOTECH	MaV			MiV	
					RT	S/P	IND		
S5A	**3.5.3 Pre-Natal and Post Natal Development including Maternal Function**	- The study determines the adverse effects of drugs or chemical on the pregnant/lactating female and on development of the conceptus and the offspring following exposure of the female from implantation through weaning. Since manifestations of effect induced during this period may be delayed, observations should be continued through sexual maturity. - The potential adverse effects to be assessed shall include: enhanced toxicity relative to that in non-pregnant females, pre- and postnatal death of offspring, altered growth and development, functional deficits in offspring, including behavior, maturation (puberty) and reproduction (F1). - studies should provide data on : a. labor - as to the presence of dystocia, duration of labor, onset of labor b. gestation - as to duration and weight gain of dams during pregnancy c. litter - as to number of pups (litter size), weight of pups, bursing behavior of pups, physiologic and anatomic parameters (food and water consumption, length, etc.) and effect of cross over nursing of pups - concurrent negative control of animal must be run together with the treated groups (at least 3 dose levels)	—	—					

ICH No.	PARAMETERS	COMPONENTS	REQUIREMENTS						GP
			NCE	BIOTECH	MaV			MiV	
					RT	S/P	IND		
	4 Local Tolerance	- Studies are summarized in order by species, by route and by duration on the following: ▪ Eye irritation test ▪ Dermal toxicity testing	❖	❖	❖	❖	❖		
	5 Other Toxicity Studies	- Rationale for conducting the studies should be provided - Other studies may include : antigenicity, immunotoxicity, mechanistic studies , dependence, studies on metabolites, impurities and other studies	❖	❖	❖	❖	❖		
	6 List of Key Literature Reference	List of key references must be submitted.	—	—	❖	❖	❖		

❖ [1] When applicable, especially for major variation (i.e. change of route of administration due to change of formulation, change of formulation and posology such as immediate release to sustained released) and /or for products with narrow margin of safety or variable kinetics

♦ Generally inappropriate for biotechnology-derived products, however, product-specific assessment of carcinogenic potential may be needed depending upon duration of clinical dosing, patient population and /or biological activity of the product (eg. Growth factors, immunosuppressive agents, etc.)

FINAL DRAFT

ASEAN COMMON TECHNICAL REQUIREMENTS FOR PHARMACEUTICAL REGISTRATION : CLINICAL DATA [ASEAN CTR: CLINCAL DATA]

No.	PARAMETERS	COMPONENTS	REQUIREMENTS *						
			NCE	BIOTECH	MaV			MiV	GP
					RT	ST/P	IND		
1	**Bioavailability (BA) and Bioequivalence (BE) Studies**	BA studies evaluate the rate and extent of absorption of the active substance from the medicinal product. Comparative BA or BE studies may use PK, PD, clinical, or in vitro dissolution endpoints, and may be either single dose or multiple dose.							
	a) BA Studies		✓	✓	✓	-	-	-	-
		1) Studies comparing the rate and extent of absorption of a drug substance from a non-intravenous dosage form compared to intravenous injection (Absolute BA study) or compared to that of non-intravenous clear solution dosage form (Relative BA study)	✓	✓	✓	-	-	-	-
		2) Dosage form proportionality studies	✓	✓	✓	-	-	-	-
		3) Food-effect studies							

No.	PARAMETERS	COMPONENTS	REQUIREMENTS *						
			NCE	BIOTECH	MaV			MiV	GP
					RT	ST/P	IND		
	b) Comparative BA or BE Studies	Studies compare the rate and extent of absorption of the drug substance from similar drug products (e.g., tablet to tablet, tablet to capsule etc.) Comparative BA or BE studies may include comparison between :						(see Quality Part)	(see Quality Part)
		1) The drug product used in clinical studies supporting effectiveness and the to-be-marketed drug product if applicable.	✓	✓	✓	✓	-		
		2) The drug product used in clinical studies supporting effectiveness and the drug product used in stability batches if applicable.	✓	✓	✓	✓	-		
		3) Same drug products from different manufacturers if applicable.	**(see Quality Part)**	**(see Quality Part)**	✓	✓	-		
2	**Studies Pertinent to Pharmacokinetics Using Human Biomaterials**	To study metabolic pathways relative to drug absorption and elimination and to assess drug-drug interactions with these pathways							
	a) Plasma Protein Binding Studies	Ex vivo protein binding study	✓	✓	✓	♦	-	-	-
	b) Hepatic Metabolism and Drug Interaction Studies	Hepatic metabolism and metabolic drug interaction studies with hepatic tissue	✓	✓	✓	♦	-	-	-
	c) Studies Using Other Human Biomaterials	Studies with other biomaterials	✓	✓	✓	✓	-	-	-

♦ if non-linear PK

No.	PARAMETERS	COMPONENTS	REQUIREMENTS *						
			NCE	BIOTECH	MaV			MiV	GP
					RT	ST/P	IND		
3	**Human Pharmacokinetic (PK) Studies**								
	a) Healthy Subject PK and Initial Tolerability Studies	Studies of PK and initial tolerability in healthy subjects	✓	✓	✓	♦	-	-	-
	b) Patient PK and Initial Tolerability Studies	Studies of PK and initial tolerability in patients	✓	✓	✓	♦	-	-	-
	c) Intrinsic Factor PK Studies	PK studies to assess intrinsic factors such as age, gender, racial, weight, height, disease, genetic polymorphism, and organ dysfunction	✓	✓	✓	♦	-	-	-
	d) Extrinsic Factor PK Studies	PK studies to assess extrinsic factors such as drug-drug interactions, diet, smoking, and alcohol use.	✓	✓	✓	♦	-	-	-
	e) Population PK Studies	Population PK studies based on sparse samples obtained in clinical trials including efficacy and safety trials	✓	✓	✓	♦	-	-	-
4	**Human Pharmacodynamic (PD) Studies**								
	a) Healthy Subject PD and PK/PD studies	PD and/or PK/PD studies	✓	✓	✓	-	-	-	-
	b) Patient PD and PK/PD studies	**PD and/or PK/PD studies in patients**	✓	✓	✓	♦	-	-	-

No.	PARAMETERS	COMPONENTS	REQUIREMENTS *						
			NCE	BIOTECH	MaV			MiV	GP
					RT	ST/P	IND		
5	**Efficacy and Safety**								
	a) Controlled Clinical Studies Pertinent to the Claimed Indication	The controlled clinical studies should be sequenced by type of control: – Placebo control (could include other control groups, such as an active comparator or other doses) – No-treatment control – Dose-response (without placebo) – Active control (without placebo) – External (Historical) control, regardless of the control treatment	✓	✓	✓	✓	✓	-	-
	b) Uncontrolled Clinical Studies	uncontrolled clinical studies (e.g., open label safety studies)	✓	✓	✓	✓	✓	-	-
6	**Post Marketing Data** (If available)		✓	✓	✓	✓	✓	-	-
7	**References**		✓	✓	✓	✓	✓	-	-

* = All studies should be complied to ICH guideline on Efficacy Topics (currently E 1 – E 12)

NCE = New Chemical Entity

BIOTECH = Biotechnological Product

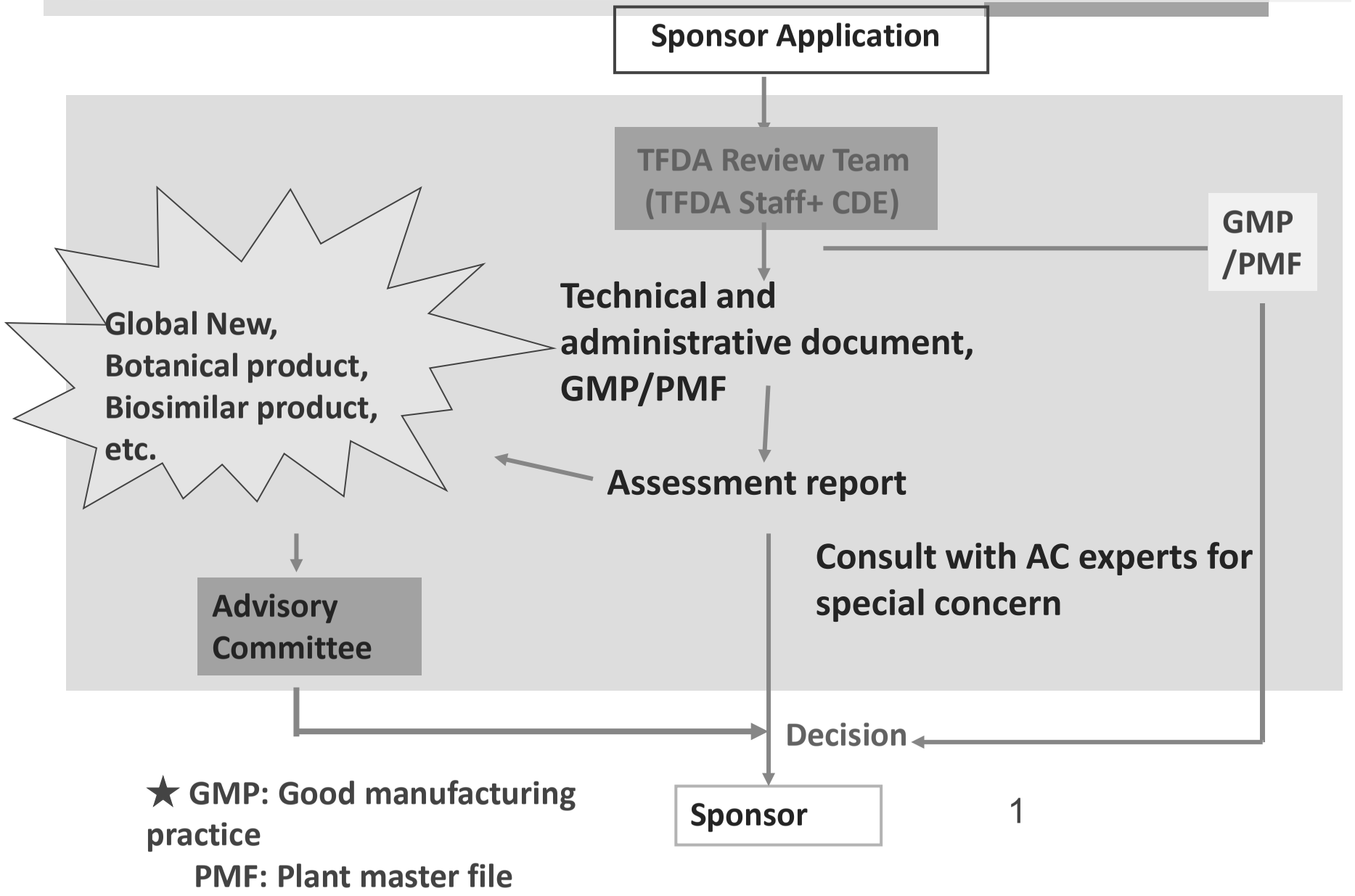
MaV = Major Variation

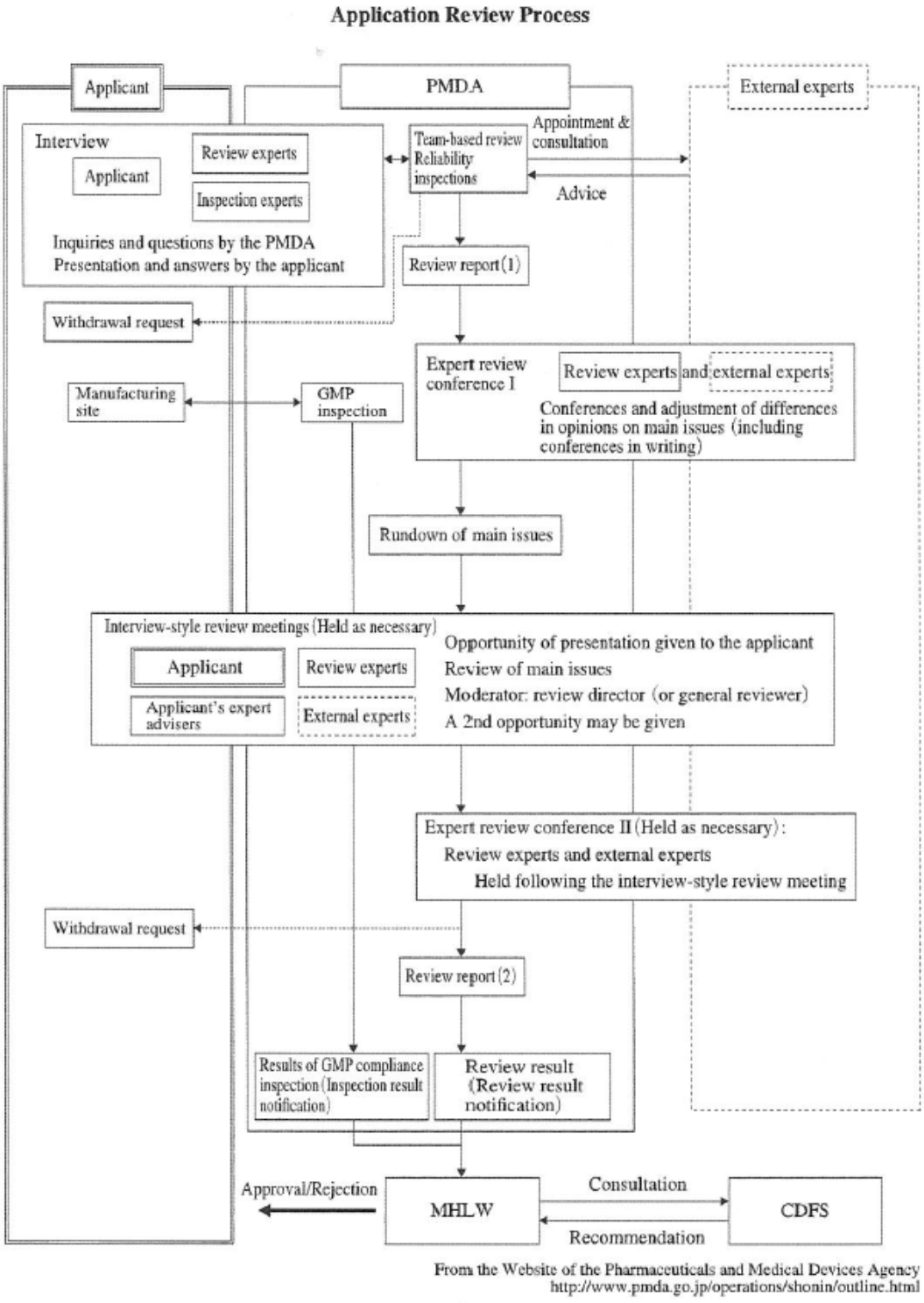
- **RT** = Route of Administration
- **ST/P** = Strength & Posology
- **IND** = Indication

MiV = Minor Variation

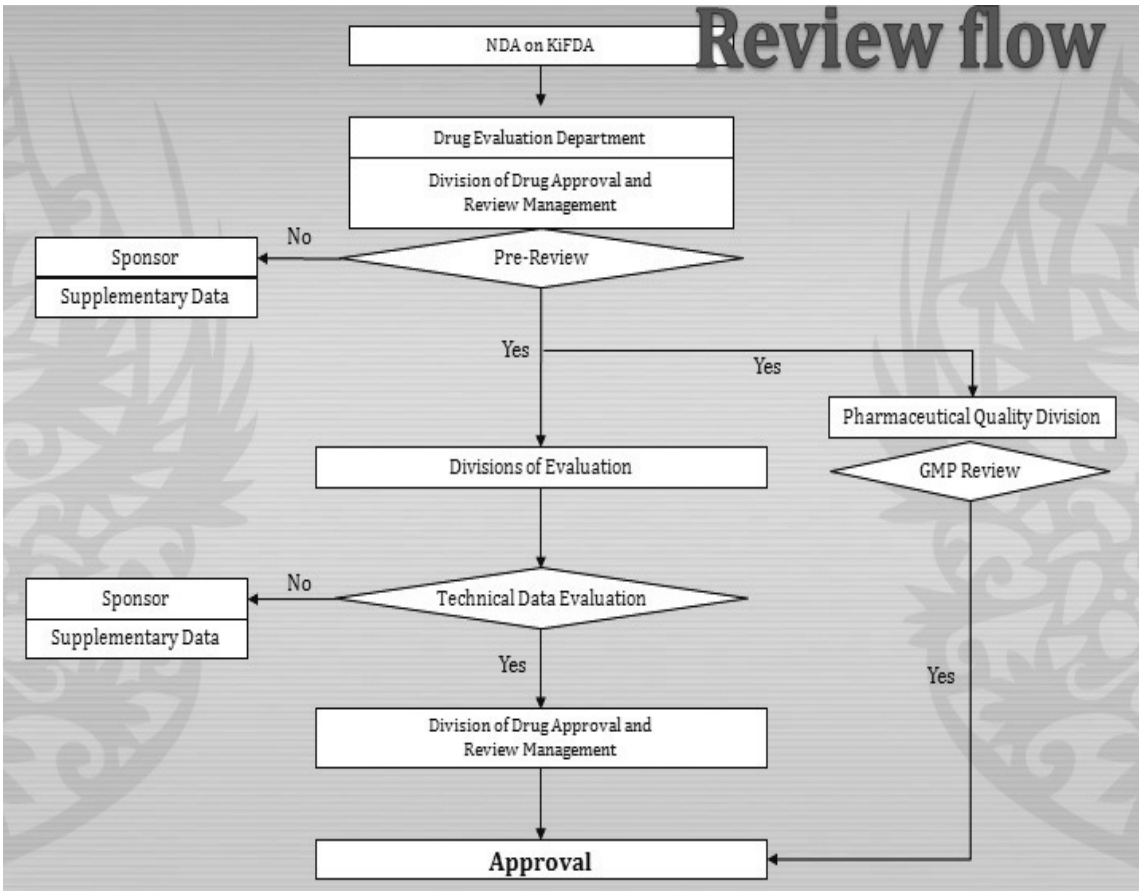
GP = Generic Product

Review Process for NDA





(Source: Jiho. DRUG APPROVAL AND LICENSING PROCEDURES IN JAPAN 2012. Tokyo: Jiho, Inc, 2013; P525)



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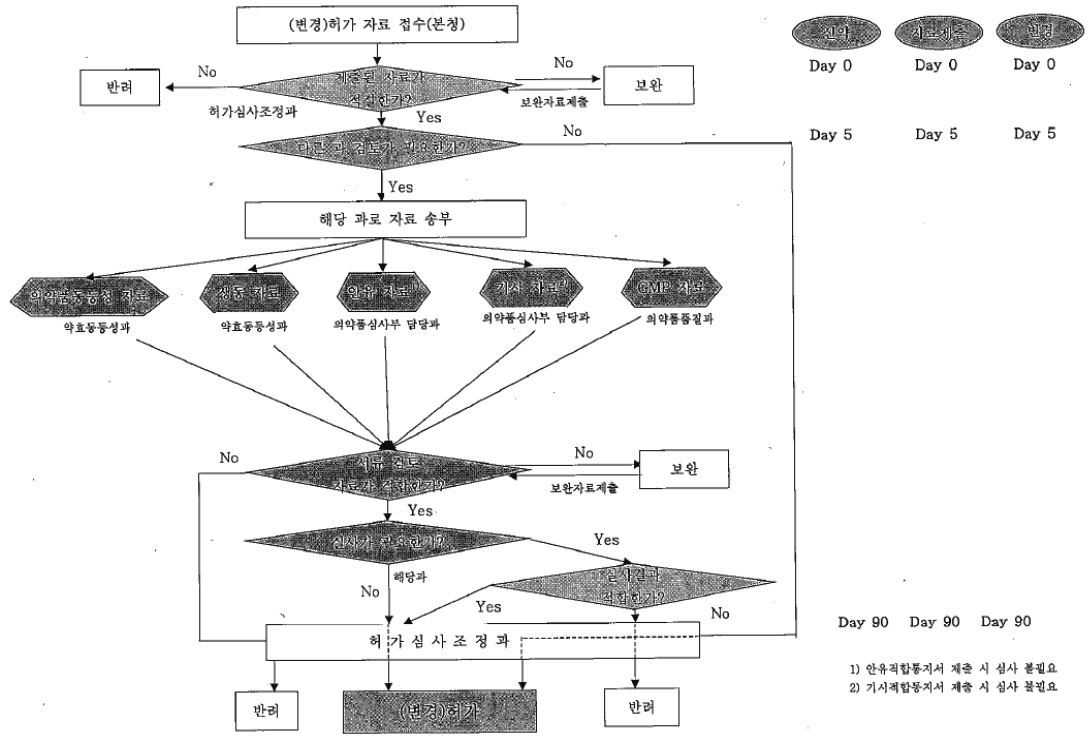


Number of reviewers	New Drugs							New Generic (NG)	Generic (G)	Biologics		
	NCE	NI	NCO	ND	NR	NDOS	NS			NB	BF	B
CMC	2	-	2	2	2	2	2	2	2	2	2	1
Clinical	2	2	2	2	2	2	2	1 (BA/BE)	-	2	–	1
Non-clinical	2	2*	2*	2*	2*	-	2*	-	-	2	2	1

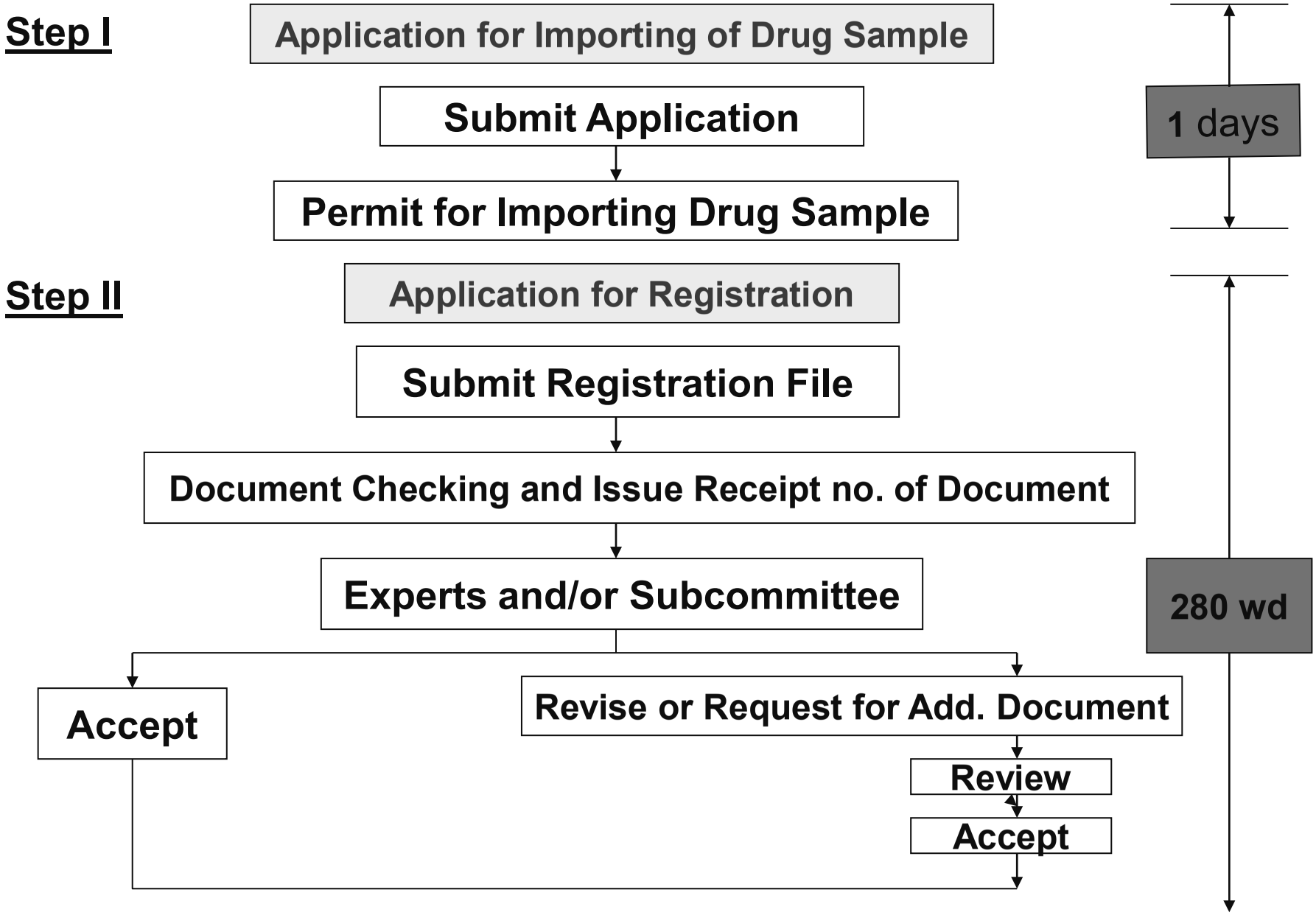
* If applicable

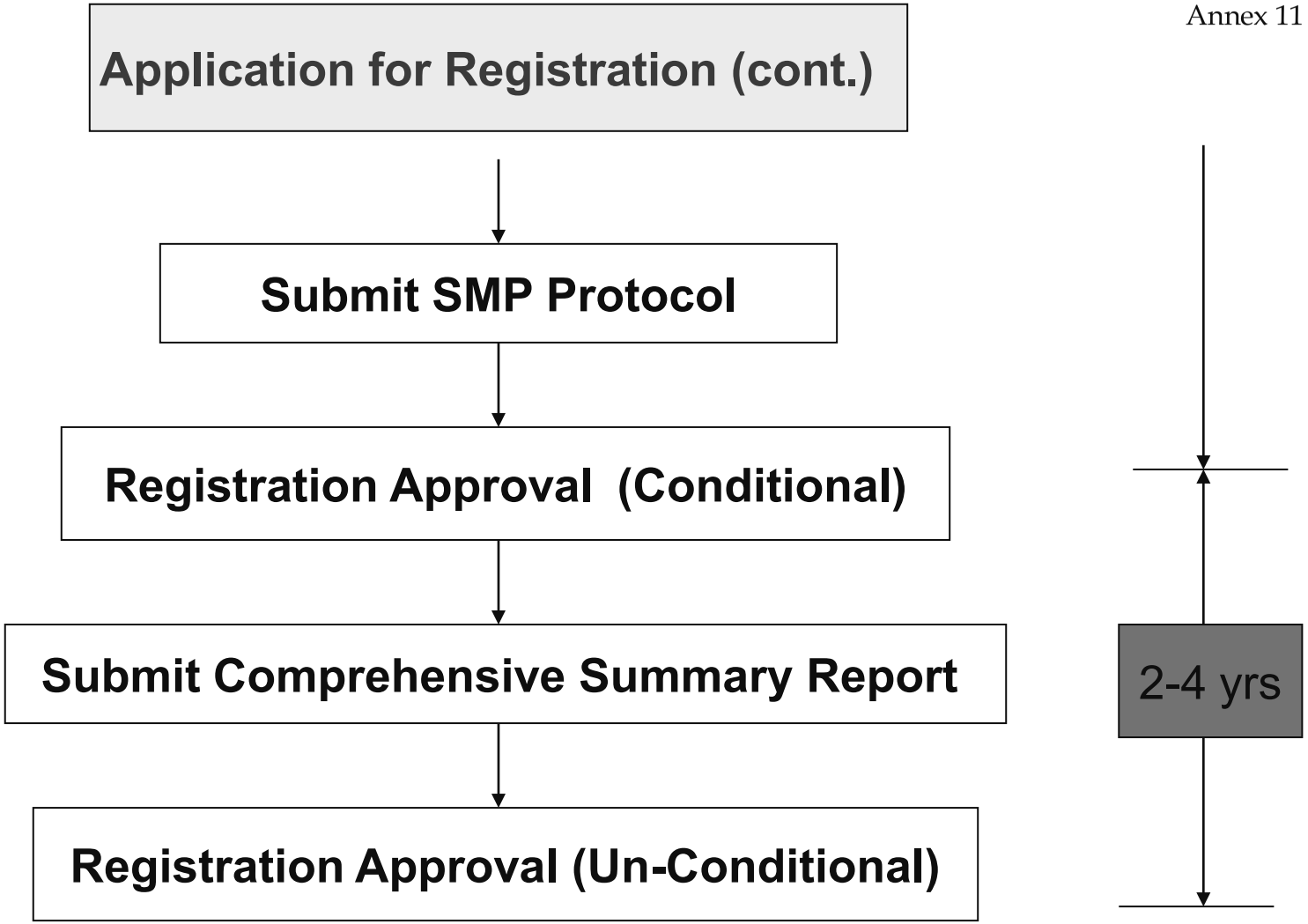
NCE = New Chemical Entity,
NI = New Indication,
NCO = New Combination,
ND = New Delivery system,
NR = New Route of administration,
NDOS = New Dosage form of Approved New Drug,
NS = New Strength of Approved New Drug
NB = New Biological

New Drug Registration
Thailand

REGISTRATION PROCEDURE

FDA Drug Control Division




Application for Registration (cont.)
Submit SMP Protocol
Registration Approval (Conditional)
Submit Comprehensive Summary Report
Registration Approval (Un-Conditional)
2-4 yrs

GUIDELINES FOR APPLICATION OF CLINICAL TRIAL IMPORT LICENCE AND CLINICAL TRIAL EXEMPTION IN MALAYSIA

National Pharmaceutical Control Bureau

Ministry of Health

Malaysia

Fifth Edition (Version 3.3)

June 2009

Guidelines for Application of Clinical Trial Import Licence and Clinical Trial Exemption in Malaysia

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THESE GUIDELINES ARE ISSUED BY THE DIRECTOR OF PHARMACEUTICAL SERVICES UNDER REGULATION 29, CONTROL OF DRUG AND COSMETICS REGULATION 1984. HE/SHE RESERVES THE RIGHT TO AMEND ANY PART OF THE GUIDELINES WHICHEVER IT DEEMS FIT

FOREWORD

Since the last update of the Guidelines for the Application of Clinical Trial Import License (CTIL) and Clinical Trial Exemption (CTX) in Malaysia in 2004, there has been significant changes in regulatory environment for clinical trial. Thus, it is timely and appropriate to streamline the existing guidelines in accordance with the current needs, regulatory requirements and international standards.

The significant changes in this guideline amongst others include changes in the format of the guidelines, application forms for CTIL and CTX, reporting of serious adverse events, pharmaceutical data requirements for herbal/ natural products (Annex B1), responsibility of license holders, conditions for CTIL / CTX, labelling requirements, guidance for the application of variation, processing fee for CTIL renewal and product accountability and disposal. The updated guidelines shall assist sponsors, contract research organisations (CROs), local investigators and others in their applications for CTIL/ CTX. Adherence to these updated guidelines will facilitate the CTIL/ CTX applications leading to timely approval by the Drug Control Authority.

I would like to take this opportunity to extend my deepest appreciation to all the committee members who have contributed in one way or another to making this 5th edition of the guidelines (June 2009) a reality. It is my hope that with these guidelines will further contribute towards strengthening and promoting Malaysia as a clinical trial hub in this region.

Selvaraja Seerangam
Director of Pharmacy Regulatory
National Pharmaceutical Control Bureau
Ministry of Health, Malaysia

June 2009

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    National Pharmaceutical Control Bureau
26. Mr. Khoo Jeng Yih
    National Pharmaceutical Control Bureau

CONTENTS

4.5 Product Particulars, Data and Supporting Documents

No.	Particular	Notes
4.5.1	Annexes	All applications for CTIL/CTX must be accompanied with the **product particulars and data necessary** for the evaluation of the product The product particulars and data shall be presented with supporting documentation in **the form of Annexes** (Please refer to Appendix A, B and C for the Structure of the respective Annexes).
4.5.2	Presentation	**i. Compilation** A content page should be provided. Each Annex shall be original copy and compiled with a label in a well-presented orderly manner.
		ii. Pages Every page of documents should be well annoted and numbered sequentially with separate series for each Annex. Drawings, tables, graphs etc must be appropriately captioned and referenced.
		iii. Binding Each copy of Annex shall be clearly separated.
		iv. Paper size A4 size paper.
4.5.3	Language	Application form, current Borang BPFK 442 and Borang BPFK 443 must be written in Bahasa Melayu or English. All other data, supporting documents, labels and package inserts can be in Bahasa Melayu or English. In cases where supporting documents is not originally in Bahasa Melayu or English, a copy of the document in its original language, accompanied by authenticated translation in Bahasa Melayu or English shall be submitted.

SECTION II: **GUIDELINES ON ANNEXES**

INTRODUCTION

1. Section II comprises recommended formats for Annexes A, B and C.

2. Details of particulars and supporting documentations should be enclosed as specified.

   Failure to enclose necessary details and supporting documents may result in delay in the processing, or rejection of an application.

3. Headings set out for each Annex are minimum general requirements. These may not be applicable in all circumstances, neither are they exhaustive.

   Interpretation of these guidelines should be flexible and related to the nature and proposed use of the product.

4. Where a heading is not applicable or information is not available, indicate clearly in the appropriate sections.

5. Data in addition to those specified in the guidelines may be submitted to support the application for import licence for clinical trial / clinical trial exemption. Such data must be presented in a well compiled manner, with a summary of the particulars.

6. These guidelines do not preclude any other information required by the Drug Control Authority (DCA). Such additional information should be supplied to the DCA on request.

Appendix A

ANNEX A: FORMAT FOR CLINICAL STUDY PROTOCOL

Note: The protocol should contain the following particulars, where applicable.

1. **Name and Dosage form of Product**

   - State the **name or code number** under which the product will be imported and known during the trial or study

   - State clearly the **pharmaceutical dosage form** of the product e.g. tablet, capsule, injection, etc

   * A separate application is required for each trial.

2. **Title of the Trial**

3. **Objective(s) of the Trial**

   - State the specific objective(s) and rationale of study or trial

4. **Description of the Trial Design**

   - State
     - **Type** of the trial, e.g. controlled, open-labelled
     - **Trial design**, e.g. parallel group, cross-over technique
     - **Blinding technique**, e.g. double-blind, single-blind
     - **Randomisation** method and procedure

   - State **total number of subjects** involved to achieve the trial objective(s) based on statistical consideration (sufficient to allow drop-out, variability effect, etc.)

5. **Description of trial Subjects**

   - **Inclusion and exclusion criteria** of potential trial subjects and process of recruitment types, methods and allocation time of subjects.

Appendix A

6. Treatment profile

- State the **dose**: including justification for route of administration, dosage, dosage interval and treatment period for pharmaceutical product being tested and the product being used as a control.
- State previous treatment, **concomitant treatment** may be permitted or give, or subsequent therapy, if any.
- **Washout period**, where applicable.

7. Study Parameters

- **Indices, variables**, etc. that were selected for measuring parameter under study (effect, reactions etc.)
- **Methods of measurements & assessment of observations** including details of measuring techniques, assessment, qualification of response, clinical and laboratory tests, pharmacokinetic analysis, etc.
- **Rationale** for choice of indices, variables and their methods determination specificity, sensitivity and the precision of the method selected.

8. Operational Aspects

- Information on the establishment of the trial code where it will be kept and when, how by whom it can be broken in the event of an emergency.
- Measures to be implemented to ensure the safe handling and storage of pharmaceutical products.

9. Adverse Event

- Methods of recording and reporting adverse events/ reactions, provisions for dealing with complications.

10. Evaluation of Results

- Description of methodology on evaluation of results, (e.g. statistical method) and on the report on patients/ subjects withdrawn from the trial.

11. Name of the investigator

- Designation of investigator

Appendix B

ANNEX B: FORMAT FOR PHARMACEUTICAL DATA ON DOSAGE FORM

Note: This is the recommended format for Annex B for individual drug. Spacing should be adjusted by applicant where necessary. Extension sheets for details and supporting documents should be numbered and referenced appropriately.

Product: Ref:

1. Finished Product

- Description (Physical Characteristics)

- Composition (Complete Formula)
    - Active Ingredient(s)
        - Name of Active Ingredient(s)

    - Other Ingredient(s), e.g. adjuncts, exicipients, preservative, colour, flavor, etc.
        - Name of other ingredient(s)

    - Packing/Pack Size (brief)

2. Manufacture of Product

Note: If desired, enclosed in sealed envelope marked 'CONFIDENTIAL'.

- Name and address and responsibilities of all manufacturer(s)/ repacker(s), including contractors, and each proposed production sites involved in manufacture and testing

- Certificate of GMP for all the manufacturer(s)/ repacker(s)

- Complete Batch Manufacturing Master Formula
    - Name of Ingredients (Active and otherwise)

- Manufacturing Process
    - Brief Description and Principles

    - A flow chart of the successive steps indicating the components used for each step and including any relevant in-process controls

Appendix B

3. Quality Control

- State whether quality control is done in part or solely by the manufacturer's own quality control department or an external laboratory.

- If quality control tests are done by an external laboratory, state
  - Name and address of the laboratory
  - Tests done by the external laboratory
  - Reasons why the tests are not done by the manufacturer

- Specifications for active ingredient and others

  Example:

Name of Ingredients	**Acceptance Limits** (State whether derived from British Pharmacopoeia (BP) or European Pharmacopoeia (Ph. Eur.) or United States Pharmacopoeia (USP) or Manufacturer's)	**Result**

- In-process quality control
  - Tests performed during manufacturing process and sampling protocols. Example:

Tests	**Stages at which test is done**	**Frequency of Sampling**	**Quantity of sample taken each time**

- Finished Product Quality Control
  - Tests and Specification Limits (Check and Release Specifications)

Test	**Test Method**	**Acceptance Limits/ Release Specifications** (State whether derived from BP or Ph. Eur. or USP or Manufacturer's)

- Certificate of Analysis (CoA) must be certified by Quality Assurance Manager. CoA for the recent batch should be submitted (**minimum of 1 batch**)

Appendix B

4. Stability of Product

- **Storage condition** to be included on the label

- **Proposed Shelf life**
  - In the events if the extension of shelf life for clinical trial materials is required, industry will provide supportive data in the form of retest results will be considered.

- **Stability Studies**
  - Completed stability studies/ accelerated stability studies
    (Summary of stability studies, characteristic and degradation products monitored results and conclusions of completed stability studies).
  - Stability studies results of at least one batch are required.

  - On-going/ Proposed Stability Studies
    - Outline of on-going or proposed stability studies

*Stability studies must be carried out in accordance to ASEAN/ ICH Stability Studies Guidelines.

5. Containers/ Packaging

- **Immediate containers/ packaging**
  - Type
  - Material
  - Capacity, where applicable
  - Closure and liner (type and material), where applicable

- **Other container(s)/ packaging(s)**

- **Dose-measuring device/ applicators/ administration set/ etc., if any**
  - Description/ Type
  - Material
  - Capacity, where applicable

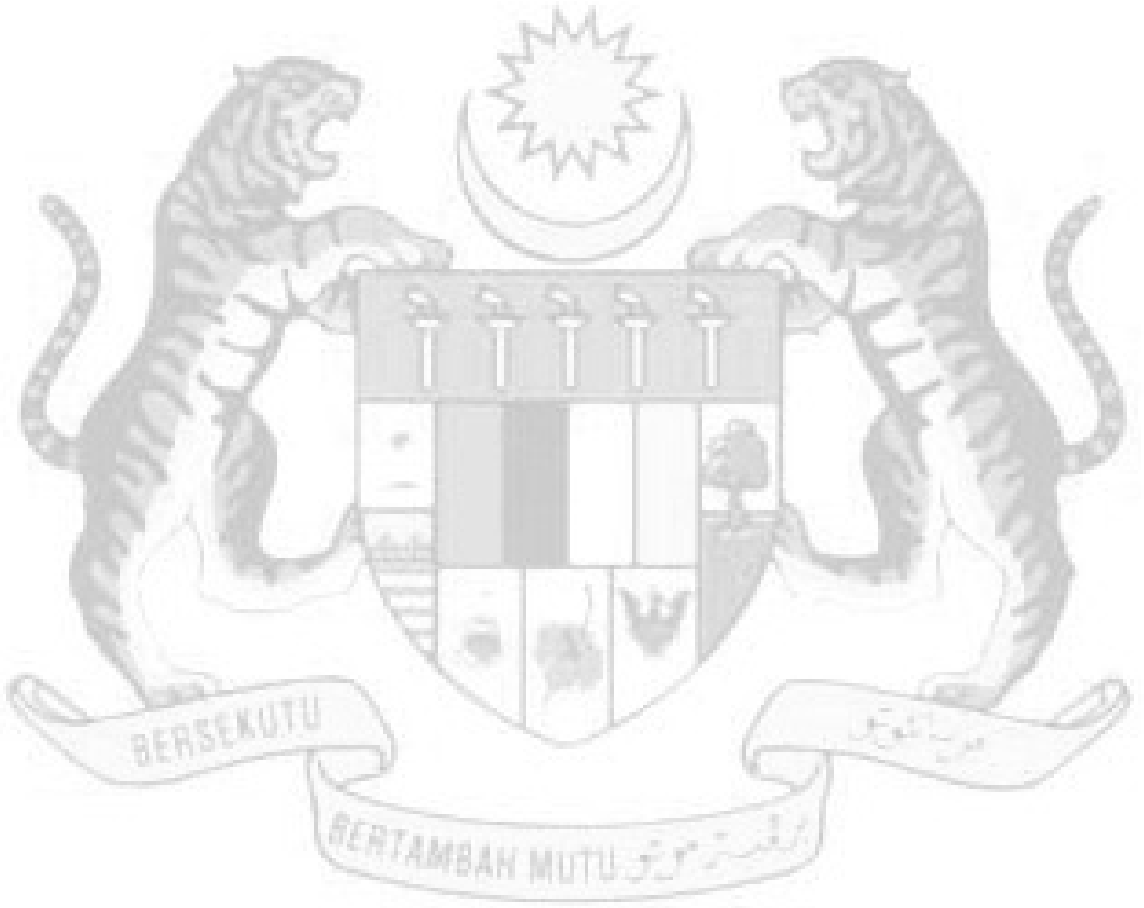
- **Packaging inclusions (desiccant, filler, etc), if any**
  - Description and compositions

- Is there any known interaction between the product and packaging material? [Yes /No]

Appendix B

6. Labelling

- Please refer to Appendix D
- Samples or proposed drafts of the following are required to be submitted:
    - Label(s) for immediate package/container of product
    - Label(s) for outer package/container of product
    - Original Package insert(s) for comparator drug



Appendix B1

ANNEX B1: FORMAT FOR QUALITY DATA ON HERBAL/ NATURAL PRODUCTS

Note: This is the recommended format for Annex B1 for clinical trials involving herbal/ natural products with therapeutic claims. Spacing should be adjusted by applicant where necessary. Extension sheets for details and supporting documents should be numbered and referenced appropriately.

Product: Ref:

1. Finished Product

- Description (Physical Characteristics)

- Composition (Complete Formula)
  - Active Ingredient(s)/ Standardised Extract(s)
    - Name of Active Ingredient(s) / Standardised Extract(s)
  - Other Ingredient(s), e.g. adjuncts, excipients, preservative, colour, flavor, etc.
    - Name of other ingredient(s)
  - Packing/Pack Size (brief)

2. Standardisation Of Extract

For Example:
The extract is standardised to contain:
- X% of compound A (assayed by e.g. HPLC, UV Spectrophotometry etc.)
- Y% of compound B (assayed by e.g. HPLC, UV Spectrophotometry etc.)

3. Manufacture of Product

Note: If desired, enclosed in sealed envelope marked 'CONFIDENTIAL'.

- Name and address and responsibilities of all manufacturer(s)/ repacker(s), including contractors, and each proposed production sites involved in manufacture and testing

- Certificate of GMP for all the manufacturer(s)/ repacker(s)

- Complete Batch Manufacturing Master Formula
  - Name of Ingredients (Active and otherwise)

- Manufacturing Process
  - Brief Description and Principles
  - A flow chart of the successive steps indicating the components used for each step and including any relevant in-process controls

4. Quality Control

- State whether quality control is done in part or solely by the manufacturer's own quality control department or an external laboratory.

- If quality control tests are done by an external laboratory, state
  - Name and address of the laboratory
  - Tests done by the external laboratory
  - Reasons why the tests are not done by the manufacturer

4.1 Specifications of the Standardised Extracts

Test/Criteria	Acceptance Limits/Specifications	Methodology (Manufacturers/ etc)
▪ Appearance		
▪ Qualitative Assay: o Chemical fingerprint		
▪ Quantitative Assay		
▪ Loss on drying/Moisture		
▪ Solubility		
▪ Microbial limits o Total bacterial count o Yeast and mould o Salmonella o *E. coli*		
▪ Heavy metal limits o Arsenic o Mercury o Lead o Cadmium		
▪ Other Tests (if applicable)		

- Certificate of Analysis for The Standardised Extracts need to be attached (**minimum of 1 batch**).

4.2 Method of Identification of Marker Compounds in the Standardised Extracts

Appendix B1

4.3 Method of Analysis of Marker Compounds in the Standardised Extracts

- Both of the method used for identification and analysis need to be explained.

4.4 Finished Product Quality Control

- Tests and Specification Limits (Check and Release Specifications)

Test/Criteria	Acceptance Limits/Specifications	Methodology (Manufacturers/ etc)
▪ Appearance (e.g. capsules/tablets)		
▪ Appearance of content		
▪ Quantitative Assay		
▪ Microbial limits o Total bacterial count o Yeast and mould o Salmonella o *E. coli*		
▪ Heavy metal limits o Arsenic o Mercury o Lead o Cadmium		
▪ Uniformity of Weight		
▪ Disintegration/Dissolution test		

- Certificate of Analysis (CoA) must be certified by Quality Assurance Manager. CoA for the recent batch should be submitted (**minimum of 1 batch**)

4.5 Validation of Analytical Method (Quantitative Assay of the Finished Product)

- Validation Reports need to be submitted
  - Contents of Validation Reports :
    - Introduction
    - Specificity
    - Repeatability
    - Reproducibility
    - Linearity
    - Accuracy
    - Detection Limit
    - Quantitation Limit
    - Conclusions

Appendix B1

5. Stability of Product

- **Storage condition** to be included on the label

- **Proposed Shelf life**
  - In the events if the extension of shelf life for clinical trial materials is required, industry will provide supportive data in the form of retest results will be considered.

  - **Stability Studies***Completed stability studies/ accelerated stability studies
    (summary of stability studies, characteristic and degradation products monitored, results and conclusions of completed stability studies).
  - Stability studies results of at least one batch is required.
  - On-going/ Proposed Stability Studies

- Outline of on-going or proposed stability studies

*Stability studies must be carried out in accordance to ASEAN/ ICH Stability Studies Guidelines.

6. Containers/ Packaging

- **Immediate containers/ packaging**
  - Type
  - Material
  - Capacity, where applicable
  - Closure and liner (type and material), where applicable

- **Other container(s)/ packaging(s)**

- **Dose-measuring device/ applicators/ administration set/ etc., if any**
  - Description/ Type
  - Material
  - Capacity, where applicable

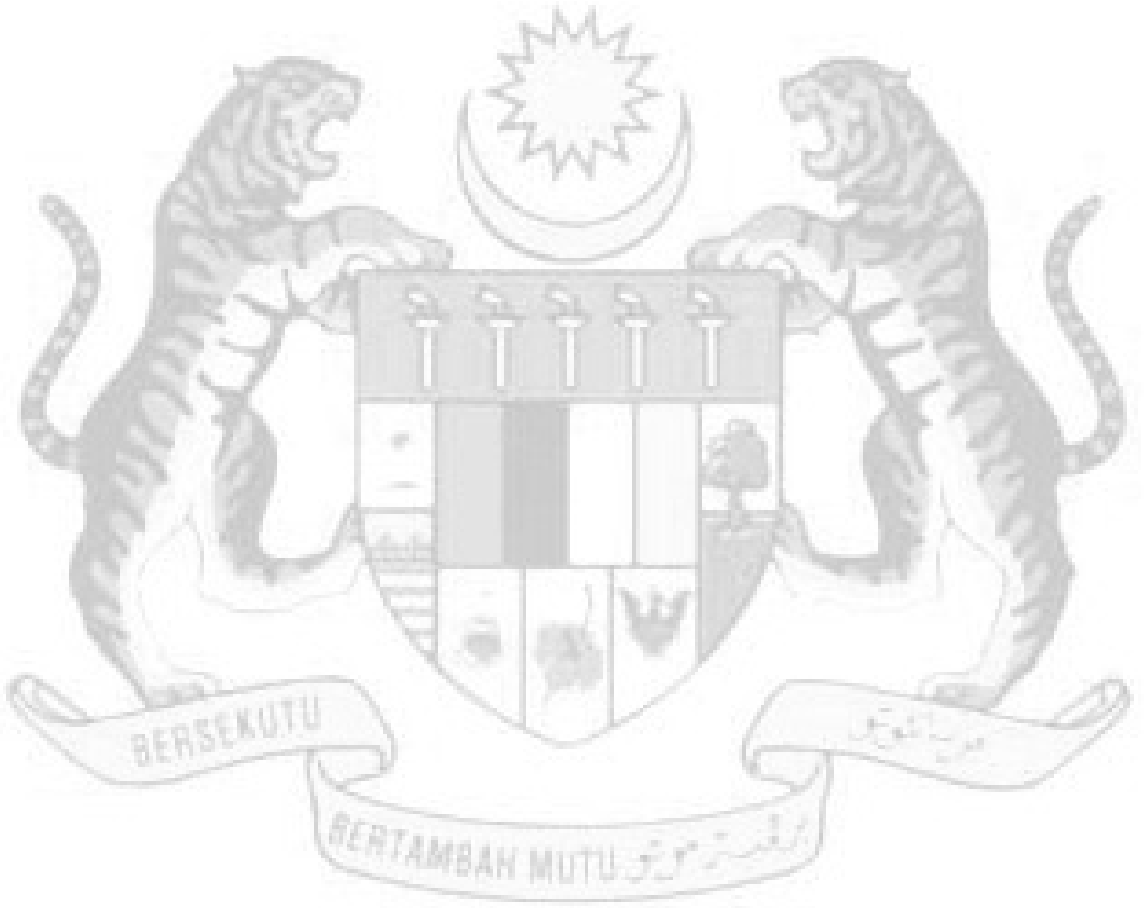
- **Packaging inclusions (desiccant, filler, etc), if any**
  - Description and compositions

- Is there any known interaction between the product and packaging material? [Yes /No]

Appendix B1

7. Labelling

- Please refer to Appendix D
- Samples or proposed drafts of the following are required to be submitted:
    - Label(s) for immediate package/container of product
    - Label(s) for outer package/container of product
    - Original Package insert(s) for comparator product



Appendix C

ANNEX C: FORMAT FOR INVESTIGATOR'S BROCHURE

1. **Title Page**
2. **Sponsor's Name**
3. **Product Name(s) – Chemical, Generic (if approved)**
4. **Trade Name(s) – if legally permissible and desired by the sponsor)**
5. **Investigator's Brochure**
6. **Edition Number**
7. **Release Date**
8. **Replaces Previous Edition Number**
9. **Date**
10. **Confidentiality Statement (Optional)**
11. **Signature page (Optional)**

Appendix C

Investigator's Brochure Table of Contents

1. **Summary**
2. **Introduction**
3. **Physical, Chemical and Pharmaceutical Properties Formulation**
4. **Non-clinical Studies**
    a. **Non-clinical Pharmacology**
    b. **Pharmacokinetics and Product Metabolism in Animals**
    c. **Toxicology**
5. **Effects in Human**
    a. **Pharmacokinetics and Product Metabolism in Humans**
    b. **Safety and Efficacy**
    c. **Marketing Experience**
6. **Summary of Data and Guidance for the Investigator**
7. **References on Publications and Reports.**
    a. **These references should be found at the end of each chapter.**
8. **Appendices (if any)**

Appendix D

LABELLING REQUIREMENTS FOR UNIT CARTON, INNER AND BLISTER/ STRIPS

The following information should present on the label of the products for clinical trial:

Parameters	**Unit Carton/ Patient Kit**	**Inner Labels**	**Blister/ Strips**
Study No./ Protocol	√	√	√
Visit	√**	√**	√**
Patient No./ Patient Initials	√	√*	√
Product Name/ Code	√	√	√
Dosage Form	√**	√**	NA
Name of Active Substance(s)	√**	√**	√**
Strength of Active Substance(s)	√**	√**	√**
Instruction for use	√	√*	√
Batch number	√	√	√
Expiry Date /Retest date	√	√	√
For Clinical Trial Use Only	√	√*	√
Name and address of manufacturer/ final release/ Product Owner (corporate address)/ Sponsor	√	√**	√**
Route of Administration	√	√	√
Storage Condition	√	√	NA
Pack Sizes	√	√*	NA
Sources of gelatin capsule (Porcine/ Bovine)	√**	√**	√**
Keep Out of Reach of Children	√	√**	√**

Please take note that if the product is supplied without an outer carton, the information that is required on the outer carton should be stated on the inner label.

Source of gelatin capsule must be stated in the Informed Consent Form.

NA Not Applicable
* Exempted for small label such as ampoule and vial
** Optional

Appendix E

STRUCTURE OF LETTER OF AUTHORISATION

LETTER OF AUTHORISATION

Date:

……
(Company's Name)

a company operating under the laws of ……., located in …… do hereby authorise

Local Company's Name and Address
Tel no.:
Facsimile no.:

to represent us in Malaysia for the application of the Clinical Trial Import Licence for :-

Title of the Clinical Trial : ……
Protocol No : ……
Release Date : ……

…… (Local company's name and address) is authorised to be the Clinical Trial Import Licence Holder and will be responsible for all matters pertaining to the Clinical Trial Import Licence for the above mentioned study protocol.

Yours faithfully,

……
(Responsible Signatures)

APPENDIX F

STRUCTURE OF INTERIM REPORT & END OF STUDY SUMMARY REPORT

Date:

Deputy Director,
Centre for Investigational New Product,
National Pharmaceutical Control Bureau,
Ministry of Health,
Lot 36, Jalan University,
46200 Petaling Jaya,
Selangor.

Dear <Insert Name>,

INTERIM/ END OF STUDY SUMMARY REPORT (whichever applicable)
<Title of the trial>, <Protocol Number>, <Name of trial site>, <Name of PI>

The following is a summary of the <Trial Title> trial conducted in <insert institution name>;

First Patient In (FPI): <**insert date**>
Last Patient In (LPI): <**insert date**>
Last Patient Out (LPO): <**insert date**>
Number of patients screened: <**insert number**>
Number of patients randomized: <**insert number**>
Number of patients discontinued: <**insert number**>
Reason of discontinuation: <**List of individual discontinued patient**>
Number of patients completed study: <**insert number**>
Number of Suspected, Unexpected Serious Adverse Events (SUSAR): <**insert number**>
Number of patients reach study Endpoints: <**insert number- if applicable, if not, to be removed**>
Last batch of drug supplies collected back from site: <**insert date**>
Last batch of drug supplies sent back to <**originating site**> for destruction <**insert date**>
(Note: if drug are destruct locally, replace this with relevant information)

Thank you.

Best Regards,

<Insert Clinical Research Associate's Name>
Clinical Research Associate

APPENDIX G

FORMAT FOR CLINICAL STUDY REPORTS (ICH TOPIC E3, STRUCTURE & CONTENT FOR CLINICAL STUDY REPORTS CPMP/ICH/137/95)

(Please refer to Malaysia Guidelines for GCP, Section 5.22)

1. **Title page**
2. **Synopsis**
3. **Table of Contents for the Individual Study Report**
4. **List of Abbreviations and Definition of Terms**
5. **Ethics**
6. **Investigators and Study Administrative Structure**
7. **Introduction**
8. **Study Objectives**
9. **Investigational Plan**
10. **Study Patients**
11. **Efficacy Evaluation**
12. **Safety Evaluation**
13. **Discussion and Overall Conclusions**
14. **Tables, Figures and Graphs referred to but not included in the text**
15. **Reference List**
16. **Appendices**

APPENDIX H

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	4-6. REACTION ONSET			8-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year			Day	Month	Year	
7 + 13. DESCRIBE REACTION(S) (including relevant tests/lab data)										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRO-DUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) From/To Dates Type of History/Notes Description

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH ☐ LITERATURE PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOW UP	

APPENDIX I

DATA ELEMENTS FOR INCLUSION IN EXPEDITED REPORTS OF SERIOUS ADVERSE DRUG REACTIONS

The following list of items has its foundation in several established precedents, including those of CIOMS-I, the WHO International Drug Monitoring Centre, and various regulatory authority forms and guidelines. Some items may not be relevant depending on the circumstances. The minimum information required for expedited reporting purposes is: an identifiable patient, the name of a suspect medicinal product, an identifiable reporting source, and an event or outcome that can be identified as serious and unexpected and for which, in clinical investigation cases, there is a reasonable suspected causal relationship. Attempts should be made to obtain follow-up information on as many other listed items pertinent to the case.

1. Patient Details

- Initials
- Other relevant identifier (clinical investigation number, for example)
- Gender
- Age and/or date of birth
- Weight and Height

2. Suspected Medicinal Product(s)

- Brand name as reported
- International Non-Proprietary Name (INN)
- Batch number
- Indication(s) for which suspect medicinal product was prescribed or tested
- Dosage form and strength
- Daily dose and regimen (specify Units - e.g., mg, ml, mg/kg)
- Route of administration
- Starting date and time of day
- Stopping date and time, or duration of treatment

3. Other Treatment(s)

For concomitant medicinal products (including non-prescription/OTC medicinal products) and non-medicinal product therapies, provide the same information as for the suspected product.

4. Details of Suspected Adverse Drug Reaction(s)

Full description of reaction(s) including body site and severity, as well as the criterion (or criteria) for regarding the report as serious should be given. In addition to a description of the reported signs and symptoms, whenever possible, attempts should be made to establish a specific diagnosis for the reaction.

- Start date (and time) of onset of reaction
- Stop date (and time) or duration of reaction
- Dechallenge and rechallenge information
- Setting (e.g., hospital, out-patient clinic, home, nursing home)

Outcome: information on recovery and any sequelae; what specific tests and/or treatment may have been required and their results; for a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction should be provided. Any autopsy or other post-mortem findings (including a coroner's report) should also be provided when available. Other information: anything relevant to facilitate assessment of the case, such as medical history including allergy, drug or alcohol abuse; family history; findings from special investigations.

5. Details on Reporter of Event (Suspected ADR)

- Name and Address
- Contact number
- Profession (specialty)

6. Administrative and Sponsor/Company Details

- Source of report
- Date event report was first received by sponsor/manufacturer
- Country in which event occurred
- Type of report filed to authorities: initial or follow-up (first, second, etc.)
- Name and address of sponsor/manufacturer/company
- Name, address, telephone number, and Fax number of contact person in reporting company or institution
- Sponsor/ manufacturer's identification number for the case (this number must be the same for the initial and follow-up reports on the same case).

Appendix J

SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS REPORTING REQUIREMENTS AND TIMELINES TO THE CENTRE FOR **INVESTIGATIONAL NEW PRODUCT**

Nature of Report		Report ? (Y/N)	Timeframe of Report	Form Preferred	Content of Submission	Responsibility for Reporting to CRACS
Clinical trial not conducted in Malaysia		**NO**	Not Applicable			
Suspect drug is known to be other than trial drug (e.g. Other treatments, placebo or comparator drug)		**NO**	Not Applicable			
Serious Adverse Events and Not drug related		**NO**	Not Applicable			
Suspected Expected Serious Adverse Reactions		**NO**	Not Applicable			
For clinical trials conducted in Malaysia and other multi-centres overseas	Suspected unexpected Serious Adverse Reactions Death / Life Threatening Events	**YES**	<u>Expedited Reporting:</u> Initial report as soon as possible but not later than 7 calendar days Follow by as complete a report as possible within 8 additional calendar days	CIOMS-I	Where applicable: Covering Letter Sponsor's comments	Sponsor
	Suspected unexpected Serious Adverse Reactions Non Fatal/ Non Life Threatening Events	**YES**	<u>Expedited Reporting:</u> Initial report: as soon as possible but not later than 15 calendar days Follow-up information should be actively sought and submitted as it becomes available	CIOMS-I	Where applicable: Covering Letter Sponsor's comments	Sponsor

Appendix K

SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS REPORT

LETTERHEAD

<insert date>

Deputy Director,
Centre for Investigational New Product,
National Pharmaceutical Control Bureau,
Ministry of Health,
Lot 36, Jalan University,
46200 Petaling Jaya,
Selangor.

Dear <Insert Name>,

Submission of Clinical Drug Trial Suspected Unexpected Serious Adverse Reactions (SUSARs) Report(s)

Study Drug:
Study/Protocol ID/No.:
Study Title:
Location of Event: ☐ **Local** ☐ **Foreign**

With reference to the above matter, we would like to submit the following SUSARs report(s) for DCA to review:

No	SUSARs	Country	Type of Report (Initial/Follow up)	Date of SUSARs	Date of Report

Please find the enclosed copy of the SUSARs Report(s).

Thank you.

Yours Sincerely,
<Insert Name and Designation>

APPENDIX L

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially

information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be

informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for

the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

Guidance for Industry

Post-marketing Safety Reporting Requirements for Human Drug and Biological Products Including Vaccines

Food and Drug Administration

13 July 2011

Table of Contents

Guidance for Industry

Post-marketing Safety Reporting Requirements for

Human Drug and Biological Products Including Vaccines

1. Introduction

Although drugs approved by the Thai FDA have undergone extensive studies on efficacy and safety, from preclinical testing to clinical trials in phases I-III, there are still adverse reactions that are not detected during these studies, and are known only after marketing. This is the result of limitations in clinical studies, e.g. small number of patients, exclusion of children, the elderly and pregnant women as well as patients with liver or kidney abnormalities, and short duration of study. Therefore reporting and monitoring of adverse reactions following the marketing of a drug is crucial to pharmacovigilance. The Thai FDA has put in place a requirement upon registration of a new drug: that market authorization holders (MAHs) have to report adverse reactions/ events as a condition for a conditional approval. Subsequently, the Thai FDA also imposed a requirement for such reporting for all vaccines and has received good cooperation.

To improve effectiveness and standardize the pharmacovigilance requirements, the Thai FDA, representing by the Health Product Vigilance Center (HPVC), in cooperation with the Pharmaceutical Research and Manufacturers Association (PReMA) has issued the guidance document. This document serves as a guide for MAHs to implement pharmacovigilance activities after a drug is marketed. This guidance covers purpose and scope, individual case safety reports, reporting requirements in special situations, reporting flow charts, glossary, and reporting forms.

2. Purpose and Scope

The purpose of this document is to guide Marketing Authorization Holders (MAHs) on the submission of relevant safety information to Health Product Vigilance Center (HPVC) of the Food and Drug Administration, Ministry of Public Health. However, this guidance does not include medicinal products which are imported under the remit of the Bureau of Drug Control, the Thai FDA, for clinical studies.

This guidance consists of the following topics:

- Reporting requirements for individual case safety report
- Spontaneous or unsolicited AE report
- Scientific literature report
- Reporting requirements in special situations
- Solicited report

- Periodic Safety Update Report (PSUR)

3. Reporting Requirements for Individual Case Safety Reports (ICSRs)

The MAH should report AEs of registered drugs and biological products Including vaccines that are spontaneously received to HPVC. Only serious suspected AEs should be reported to HPVC according to the process and time frame shown in Annex 1.

3.1 Essential Information in AE Reports

AE reports should be as complete as possible and contain essential information to facilitate assessment.

The minimum information required for submission of an initial AE report is:

1. An identifiable patient
2. An identifiable reporting source
3. At least one adverse event
4. At least one suspected product

3.2 Follow-up Reports

Additional information should be provided in the form of follow-up reports which should be clearly stated as such with reference to the initial report.

3.3 Expedited Reporting

Upon the first knowledge of a fatal adverse event associated with use of a vaccine or a new drug with conditional approval (NC), or death from unexpected/unlabelled ADRs, the MAH should notify the FDA by phone, fax within 24 hours and send a complete report within 7 calendar days of the first knowledge.

3.4 AE Reporting Channels

(1) the online reporting system which is available at:
http://www.fda.moph.go.th/vigilance (passwords required)

(2) the Thai FDA AE reporting form with or without the CIOMS I form, and submit the reports via fax, email, mail to HPVC.

(3) The Thai FDA AE reporting form can be downloaded from:

http://www.fda.moph.go.th/vigilance/

The CIOMS I form is available at: http://www.cioms.ch/

3.5 Time Frames for Reporting

The time frame depends on type of AE reports. Please see the table below:

Adverse Events	Reporting Time Frame
Death	As soon as possible but not later than 7 calendar days, except the following circumstances whereby the FDA should be notified by phone, fax, email within 24 hours, followed by a complete report within 7 days of the first knowledge: (1). Death after use of • Vaccine • New drug with conditional approval (NC) (2) Death from unexpected/unlabelled ADRs
Serious	15 calendar days*
Non-serious	2 months

*****Calendar Day from the MAH's receipt date of the report.

4. Spontaneous or Unsolicited AE Reports

4.1 Serious Adverse Events

Only serious adverse event reports that are suspected to be associated with drugs, biological products or vaccines should be submitted.

4.2 Non-Serious Adverse Events

(1) Non-serious AE reports, originated in Thailand, for all vaccines and for drugs and biological products under conditional approval should be submitted.

(2) Other such reports, originated in Thailand, should not be submitted, except upon request by the Thai FDA.

(3) AE reports originated in foreign countries should not be submitted except that the AE involves a product purchased from Thailand or occurs to a Thai citizen.

5. Scientific Literature Reports

Cases of AEs reported in scientific and medical literature, including relevant published abstracts from meetings, may qualify for reporting if the source country is Thailand, the minimum information for reporting (see 3.1) is met, and the AEs are serious. The publication reference (s) should be given as the report source.

If multiple products are mentioned in the article, a report should be submitted only by the applicant whose product is suspected. The suspected product is identified as such by the article's author.

6. Safety Reporting in Special Situations

6.1 Lack of Efficacy

Synonyms: lack of effect, failure of expected pharmacological actions, etc.

Lack of efficacy is considered an adverse event. The underlying principle is that if a drug fails to produce the expected pharmacological, therapeutic or preventive benefit, there may be an adverse outcome for the patient, including a worsening of the condition for which the medication is being taken.

6.2 Exposure During Pregnancy

In the event that a MAH is aware that its product which is not recommended for use during pregnancy has been received by a pregnant patient, the MAH should follow up with the doctor on the pregnancy outcome. If a pregnancy results in a serious or an abnormal outcome which the reporting doctor considers might be due to the product, the MAH must submit the AE report to the HPVC within 15 calendar days.

6.3 Drug Overdoses

The MAH does not need to report cases of drug overdoses unless these lead to adverse events.

7. Solicited Reports

Solicited AE reports derived from organized data collection systems including studies e.g. phase IV clinical studies, may qualify for reporting to HPVC if the following is fulfilled:

(1) The medicinal product is used according to the approved label and prescribing information, and
(2) The medicinal product used in the study does not require an import permit from the Bureau of Drug Control
(3) Only serious adverse events from such studies need to be submitted.

8. Periodic Safety Update Reports (PSURs)

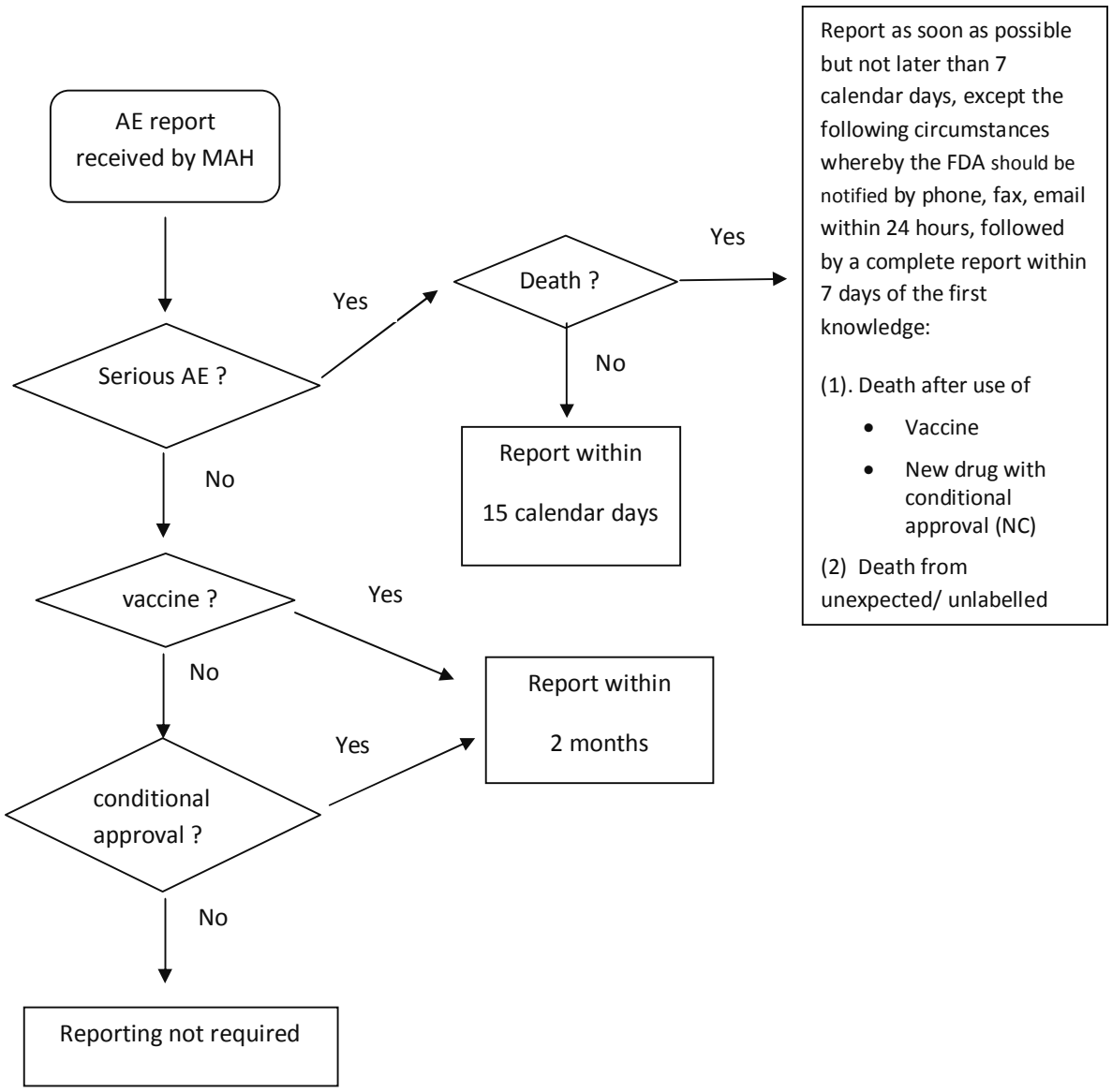
MAHs are not required to submit PSURs except when requested by the Thai FDA.

9. Other Safety Information

When the MAH receives product safety information which may warrant changes in risk management measures, the MAH should send the information to HPVC as soon as possible.

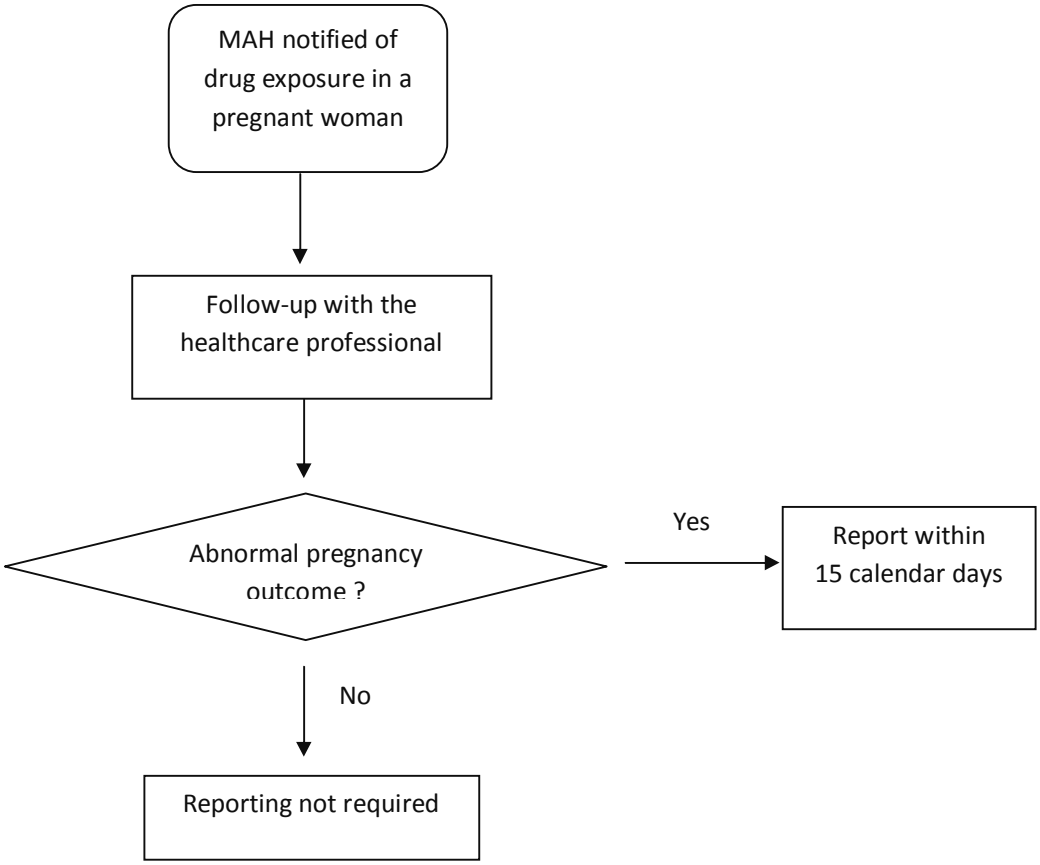
Annex I

Flow Chart A: Post-Marketing Adverse Event Reporting to HPVC



Annex I

Flow Chart B: Reporting of Drug Exposure During Pregnancy to HPVC



Annex II

The Thai FDA AE Reporting Form in Thai (See the HPVC website)

Annex III CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	4-6 REACTION ONSET			8-12 CHECK ALL
(first, last)		Day	Month	Year	Years		Day	Month	Year	APPROPRIATE TO ADVERSE REACTION
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING ☐ CONGENITAL ANOMALY ☐ OTHER MEDICALLY IMPORTANT CONDITION

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRO-
17. INDICATION(S) FOR USE		DUCTION? ☐ YES ☐ NO ☐ NA
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnoses, allergies, pregnancy with last menstrual period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		26-26a. NAME AND ADRESS OF REPORTER (INCLUDE ZIP CODE)
RIGINAL REPORT NO.	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ REGULATORY AUTHORITY ☐ OTHER	
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOW-UP	

Annex IV : Glossary

Adverse event or Adverse Experience (AE:

Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse Drug Reaction (ADR) :

A response to a medicine which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

An adverse drug reaction, contrary to an adverse event, is characterized by the suspicion of a causal relationship between the drug and the occurrence, i.e. judged as being at least possibly related to treatment by the reporting or a reviewing health professional.

For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse drug reaction.

Causality assessment:

Causality assessment is the systemic review of data about an adverse reaction case to determine the likelihood of a causal association between the event and the medicinal product received.

CIOMS I form:

An adverse reaction reporting form developed by the Council for International Organisations of Medical Sciences (CIOMS), intended for notifying the regulatory authorities of countries other than the country where the report originated.

Labelled/ Unlabelled adverse reaction

An adverse reaction, the nature or severity of which is/is not consistent with domestic labeling or market authorization.

Periodic Safety Update Report (PSUR):

A systematic review of the global safety data which became available to the manufacturer of a marketed drug during a specific time period, produced in an internationally agreed format.

Serious AE :

A serious adverse event is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- results in congenital anomaly/birth defect,
- is a medically important event or reaction.

To ensure no confusion or misunderstanding of the difference between the terms 'serious' and 'severe', the following note of clarification is provided:

The term 'severe' is not synonymous with serious. In the English language, 'severe' is used to describe the intensity (severity) of a specific event (as in mild, moderate or severe); the event itself, however, may be of relatively minor medical significance (such as severe headache). Seriousness (not severity) which is based on patient /event outcome or action criteria serves as guide for defining regulatory reporting obligations.

Marketing Authorization (MA) :

The approval granted by the Thai FDA for marketing in the Kingdom of Thailand.

Marketing Authorization Holder (MAH):

The company named on the Marketing Authorization for manufacturing in or importing into the Kingdom of Thailand

Solicited reports

Solicited reports are those derived from organized data collection systems, which include clinical trials, registries, post-approval named patient use programs, other patient support and disease management programs, surveys of patients or healthcare providers, or information gathering on efficacy or patient compliance. Adverse event reports obtained from any of these should not be considered spontaneous.

Safety Monitoring Program (SMP):

A specific form of post-marketing adverse event reporting required for new drugs. For at least 2 years after a drug is marketed, it is marked on the label with a triangle within which is written 'must monitor' and the registration number is also labelled 'NC' (new drug with conditions), indicating that all suspected AEs associated with the drug should be reported to the Thai FDA according to specific reporting timelines. The distribution of such drugs is limited to hospitals and clinics. In certain circumstances, distribution is limited to only hospitals, and the words "for hospital use only" must

appear on the label. At the end of the SMP period, the MAH has to submit a summary of sales, distribution and AE information and comprehensive summary on the safety profile of the new drug which includes domestic adverse event reports in relation to usage, and safety information from foreign countries, i.e. PSUR, to the Thai FDA. If the safety information is sufficient to demonstrate safety profile of the drug, the Thai FDA may grant an unconditional approval. The drug registration number will be labeled 'N', and the triangle showing monitoring status will be removed. The drug can be available in drugstores if it is classified as a "Dangerous Drug" or "Non-Dangerous Drug" and not a "Special Controlled Drug".

Spontaneous or unsolicited report:

Any unsolicited communication by healthcare professionals or consumers to a company, regulatory authority or other organization (e.g., WHO, Regional Center, Poison Control Center) that describes one or more adverse events in a patient who was given one or more medicinal products and that does not derive from a study or organized data collection scheme.