REGULATION OF THE CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY OF THE REPUBLIC OF INDONESIA
NUMBER 24 OF 2017 ON
CRITERIA AND PROCEDURES FOR DRUG REGISTRATION

BY THE BLESSINGS OF GOD ALMIGHTY

CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY,
REPUBLIC INDONESIA

Considering : a. that in order to protect the public from the distribution of drugs that do not meet the requirements of efficacy, safety, and quality, it is necessary to register drugs before distribution;

b. that the provisions of the criteria and procedures for drug registration as stipulated in the Regulation of the Chairperson of the Indonesian Food and Drug Authority Number HK.03.1.23.10.11.08481 of 2011 on The Criteria and Procedures for Drug Registration as amended several times by the Regulation of the Chairperson of the Indonesian Food and Drug Authority Number 17 of 2016 on the Second Amendment to the Regulation of the Chairperson of the Indonesian Food and Drug Authority Number HK.03.1.23.10.11.08481 of 2011 on Criteria and Procedures for Drug Registration needs to be adjusted to the latest developments in science and technology;

c. that based on the considerations as referred to in point a and point b, it is necessary to issue the Regulation of the Chairperson of the Indonesian Food and Drug Authority on Criteria and Procedures for Drug Registration;

Observing : 1. Ordinance of Prescription Drugs (*Sterkwerkende Geneesmiddelen Ordonnantie, Staatsblad* 1949:419);

2. Law Number 5 of 1997 on Psychotropic Drugs (State Gazette of the Republic of Indonesia of 1997 Number 10, Supplement to the State Gazette of the Republic of Indonesia Number 3671);
3. Law Number 8 of 1999 on Consumer Protection (State Gazette of the Republic of Indonesia of 1999 Number 42, Supplement to the State Gazette of the Republic of Indonesia Number 3821);
4. Law Number 35 of 2009 on Narcotics (State Gazette of the Republic of Indonesia of 2009 Number 143, Supplement to the State Gazette of the Republic of Indonesia Number 5062);
5. Law Number 36 of 2009 on Health (State Gazette of the Republic of Indonesia of 2009 Number 144, Supplement to the State Gazette of the Republic of Indonesia Number 5063);
6. Presidential Regulation Number 80 of 2017 on the Indonesian Food and Drug Authority (State Gazette of the Republic of Indonesia of 2017 Number 180);
7. Regulation of the Minister of Health Number 1010/MENKES/PER/XI/2008 on Drug Registration as amended by Regulation of the Minister of Health Number 1120/MENKES/PER/XII/2008 on Amendment to Regulation of the Minister of Health Number 1010/Menkes/Per/XI/2008 on Drug Registration;
8. Regulation of the Minister of Health Number 1799/MENKES/PER/XII/2010 on Pharmaceutical Industry as amended by Regulation of the Minister of Health Number 16 of 2013 on Amendment to Regulation of the Minister of Health Number 1799/MENKES/PER/XII/2010 on Pharmaceutical Industry (State Bulletin of the Republic of Indonesia of 2013 Number 442);
9. Regulation of the Chairperson of the Indonesian Food and Drug Authority Number HK.03.01.23.12.11.10217 of

2011 on Compulsory Drugs for Equivalence Test (State Bulletin of the Republic of Indonesia of 2012 Number 120);

10. Regulation of the Chairperson of the Indonesian Food and Drug Authority Number HK.03.1.34.11.12.7542 of 2012 on Technical Guidelines for Good Distribution Practices of Drugs (State Bulletin of the Republic of Indonesia of 2012 Number 1268);
11. Regulation of the Chairperson of the Indonesian Food and Drug Authority Number HK.03.1.33.12.12.8195 of 2012 on Implementation of Guidelines for Good Manufacturing Practices of Drugs (State Bulletin of the Republic of Indonesia of 2013 Number 122);
12. Decision of the Chairperson of the Indonesian Food and Drug Authority Number 02001/SK/KBPOM of 2001 on Organization and Working Procedure of the Indonesian Food and Drug Authority as amended by Decision of the Chairperson of the Indonesian Food and Drug Authority Number HK.00.05.21.4231 of 2004 on Amendment to Decision of the Chairperson of the Indonesian Food and Drug Authority Number 02001/SK/KBPOM of 2001 on The Organization and Working Procedure of the Indonesian Food and Drug Authority;

HAS DECIDED:

To issue : REGULATION OF THE INDONESIAN FOOD AND DRUG AUTHORITY ON CRITERIA AND PROCEDURES FOR DRUG REGISTRATION.

CHAPTER I
GENERAL PROVISIONS

Article 1

In this Chairperson Regulation:

1. Drug Registration hereinafter referred to as Registration means the procedure for registration and evaluation of Drugs to obtain approval.

2. Drug means a finished product including Biological Product, which is a substance or combination of substances used to affect or investigate the physiological system or state of pathology in order to establish diagnosis, prevention, treatment, recovery, and improvement of health, and contraception for humans.
3. Biological Product means a product containing biological materials derived from a human, animal, or microorganisms prepared in a conventional way, including extraction, fractionation, reproduction, cultivation, or through biotechnology methods, among others fermentation, genetic engineering, cloning, including but not limited to enzymes, monoclonal antibodies, hormones, stem cells, gene therapy, vaccines, blood products, DNA recombinant products, and immunosuppressants.
4. Contraceptive mean a Drug or device containing a drug that is intended to prevent conception.
5. Narcotic mean a Drug derived from a plant or non-plant, both synthetic and semi-synthetic, which can cause a decrease or change in consciousness, loss of sense, alleviate and relieve of pain and can create an addiction, which is differentiated into categories as stipulated in the Law on Narcotics.
6. Psychotropic mean a drug both natural and synthetic, non-Narcotics, which has psychoactive properties through selective effect on the central nervous system that causes distinctive changes in mental activity and behavior.
7. Marketing Authorization means a form of Registration approval to be distributed in the territory of Indonesia.
8. Marketing Authorization Holder means an Applicant who has obtained a Marketing Authorization for Drugs submitted for Registration.
9. Label means information printed on the packaging.
10. Summary of Product Characteristics/Brochure means complete information approved by the Chairperson regarding the description of Drugs, efficacy, and safety of

Drugs from the data of clinical trial results, and other information that is considered necessary and serves as a source of information for healthcare professional and a reference in the preparation of Product Information for Patients.

11. Product Information means a complete description of Drugs approved by the Chairperson, including efficacy, safety, route of administration and other information deemed necessary that is listed in the Summary of Product Characteristics/Brochures and/or Patient Information Leaflet.
12. Patient Information Leaflet means information for patients approved by the Chairperson regarding the efficacy, safety, and route of administration and other information deemed necessary by using Indonesian that is easy to understand and comprehended by patients.
13. Applicant means Pharmaceutical Industry that has obtained licensing in Pharmaceutical Industry in accordance with the provisions of legislation.
14. Pharmaceutical Industry means a business entity that has a license from the Minister of Health to carry out Drug product or drug substances manufacturing activities.
15. Domestic Pharmaceutical Industry means a Pharmaceutical Industry located in the territory of Indonesia.
16. New Registration means a Registration for Drugs that have not obtained a Marketing Authorization in Indonesia.
17. Variation Registration means the Registration of changes in aspects of administration, efficacy, safety, quality, and/or Product Information and Drug Labels that have been Marketing Authorization in Indonesia.
18. Major Variation Registration means a Variation Registration that has a significant impact on the aspects of efficacy, safety and/or quality of Drugs.
19. Minor Variation Registration means a Variation Registration that does not belong to the category of Major

Variation Registration or Notification Variation Registration.

20. Notification Variation Registration means a Variation Registration that has minimal or no impact at all on aspects of efficacy, safety, and/or quality of Drugs, and does not change the information on the Marketing Authorization.
21. Renewal registration means the registration of extension of the Marketing Authorization validity period.
22. Biosimilar Product means a Biological Product with a similar profile of efficacy, safety, and quality to approved Biological Products.
23. Good Manufacturing Practice, hereinafter abbreviated as GMP means a method of Drugs manufacturing that aims to ensure that the quality of drugs produced is in accordance with the requirements and purposes of use.
24. Active Pharmaceutical Ingredients means a component of drugs that have pharmacological effects.
25. Excipient means a component of drugs that do not have pharmacological effects.
26. Composition means a qualitative and quantitative arrangement of Active Pharmaceutical Ingredients in Drugs.
27. Formula means a qualitative and quantitative arrangement of Active and Excipient Substances in Drugs.
28. New Drug means a Drug with a New Chemical Entity, new dosage form, new strength, or new combination having never been approved in Indonesia.
29. Branded Generic Drug means a Drug with trade names containing Active Pharmaceutical Ingredients with the same Composition, strength, dosage form, route of administration, indications, and posology with originator drugs that have been approved in Indonesia.
30. Generic Drug means a drug with the name according to International Nonproprietary Names Modified determined by the World Health Organization or the name specified in

the national health program.

31. First Generic Drug means the first Generic Drug registered in Indonesia with the same Active Pharmaceutical Ingredients as the Originator Drug approved in Indonesia.
32. Local Drug mean a drug made or packaged primary by the Pharmaceutical Industry in Indonesia.
33. Contract Giver means the Pharmaceutical Industry that delegates the work of manufacturing drugs based on a contract.
34. Contract Acceptor means the Pharmaceutical Industry that accepts Drug manufacturing works based on a contract.
35. Imported Drug means a drug made by the pharmaceutical industry abroad in the form of a Finished Product or a Bulk Product in primary packaging to be distributed in Indonesia.
36. Finished Product means a product having gone through all stages of the manufacturing process.
37. Bulk Product means an ingredient having been processed and only requiring packaging to become Drugs.
38. Contract Drug mean a drug whose manufacture is delegated to other Pharmaceutical Industries.
39. Licensed Drug mean a Drug made by Domestic Pharmaceutical Industry on the basis of a License.
40. License means the delegation of right and authority to use the results of research and development related to efficacy, safety, quality, and technology transfer in the manufacture, and/or use of trade names and marketing of a Drug.
41. Patent Protected Drug mean a Drug that obtains patent protection based on the applicable Patent Law in Indonesia.
42. Investigational New Drug mean a Drug product or drug substances in the form of a new molecule or new Formula, Biological Product/biotechnology being developed and manufactured by a research institution or

Pharmaceutical Industry in Indonesia and/or abroad for use in the nonclinical and/or clinical trial stages in Indonesia with the aim of obtaining a Marketing Authorization in Indonesia.

43. Orphan Drug means an indispensable Drug for the treatment of rare diseases and have proven their safety and effectiveness.
44. Form means a registration form.
45. Day means a work day.
46. Chairperson means the Chairperson of the Indonesian Food and Drug Authority.

CHAPTER II
REQUIREMENTS AND CRITERIA1

Part One
Requirements

Article 2

(1) Drugs to be distributed in the territory of Indonesia must have a Marketing Authorization.
(2) To obtain a Marketing Authorization as referred to in section (1), registration must be carried out.
(3) Registration as referred to in section (2) is submitted by the Applicant to the Chairperson.

Article 3

(1) Exclusion from the provisions as referred to in Article 2 section (1), is intended for Special Access Scheme Drug.
(2) Special Access Scheme Drug as referred to in section (1) is carried out in accordance with the provisions of legislation.

Part Two

Criteria

Article 4

(1) Drugs that have Marketing Authorization must meet the following criteria:
   a. reassuring efficacy and adequate safety are proven through nonclinical and clinical trials or other evidence in accordance with the status of scientific development;
   b. qualified quality in accordance with the established standards, including the manufacturing process in accordance with GMP and equipped with valid evidence; and
   c. Product Information and Label contain complete, objective, and non-misleading information that can guarantee the proper, rational, and safe use of the Drugs.

(2) In addition to meeting the criteria as referred to in section (1), the Drugs must also meet the following criteria:
   a. specifically for the new Psychotropics, should have advantages compared to Drugs that have been approved to distribute in Indonesia; and
   b. specifically for Drugs for the national health program, must comply with the requirements set by a government institution administering the national health program.

CHAPTER III
REGISTRATION CATEGORY

Article 5

(1) Registration consists of:
   a. New Registration;
   b. Variation Registration; and
   c. Renewal Registration.

(2) New Registration as referred to in section (1) point a consists of:

a. category 1 : Registration of New Drugs and Biological Products, including Biosimilar Products.
b. category 2 : Registration of Generic Drugs and Branded Generic Drugs.
c. category 3 : Registration of other preparations containing Drugs with special technology, can be in the form of transdermal patch, implant, and beads.

(3) Variation Registration as referred to in section (1) point b consists of:
a. category 4 : Major Variation Registration.
b. category 5 : Minor Variation Registration.
c. category 6 : Notification Variation Registration.

(4) Renewal Registration as referred to in section (1) point c falls into category 7.

CHAPTER IV
REGISTRATION REQUIREMENTS

Part One
Drug Names

Article 6

(1) The registered drug names can use:
a. generic names; or
b. trade names.

(2) The generic names as referred to in section (1) point a are in accordance with International Nonproprietary Names Modified, determined by the World Health Organization or the names specified in the national health program.

(3) The trade names as referred to in section (1) point b is the names given by the Applicant as the identity of the Drug.

(4) The granting of trade names as referred to in section (1) point b is based on an self-assessment and is the responsibility of the Applicant.

(5) Self-assessment as referred to in section (4) refers to the General Guidelines for Drug Names as contained in Annex I as an integral part of this Agency Regulation.

(6) In the event that the self-assessment as referred to in section (5) is not in accordance with the General Guidelines for Drug Names as in Annex I, the proposal for the name of the Drug cannot be approved.

(7) If in the future there is another party who is more entitled to the name of the drug listed in the Marketing Authorization in accordance with the provisions of legislation, the Applicant must change the name of the Drug

Part Two
Registration

Article 7

(1) Registration is carried out by Applicants by submitting registration documents.

(2) The registered drugs are in the form of:
   a. Local Drugs; or
   b. Imported Drugs.

Part Three
Registration of Local Drugs

Article 8

(1) Applicants submitting for Registration of Local Drugs must meet the following requirements of:
   a. having a license in Pharmaceutical Industry; and
   b. holding a valid GMP certificate in accordance with the registered type and dosage form.

(2) Exemption from the provisions as referred to in section (1) point a and point b, is for Registration of Local Drugs carried out by a prospective Pharmaceutical Industry that is under construction.

(3) Exemption from the provisions as referred to in section (1)

point b, for Registration of Local Drugs carried out by the Pharmaceutical Industry which adds facilities for new dosage forms or the Pharmaceutical Industry which expands manufacturing facilities.

(4) Requirements for Registration of Local Drugs as referred to in section (2) and section (3) are in the form of recommendations based on the results of inspection on the fulfillment of GMP requirements.

(5) In the event that the Registration is carried out based on the provisions as referred to in section (2) and section (3), Marketing Authorization will be issued after the Applicant meets the requirements as referred to in section (1).

Part Four
Registration of Local Contract Drug

Article 9

(1) Registration of Local Contract Drugs can only be submitted by the Contract Giver as the Applicant.

(2) Registration as referred in section (1) must meet the following requirements of:
   a. having a license in Pharmaceutical Industry;
   b. having at least 1 (one) manufacturing facility that has met the GMP requirements; and
   c. having a contract agreement document.

(3) The Contract Giver Pharmaceutical Industry and Contract Acceptor Pharmaceutical Industry are responsible for aspects of the efficacy, safety, and quality of the Contract Drug, with the main responsibility being the Contract Giver Pharmaceutical Industry as the Marketing Authorization Holder.

(4) The Contract Acceptor Pharmaceutical Industry must have a valid GMP certificate in accordance with the manufactured dosage form.

(5) The Contract Acceptor Pharmaceutical Industry cannot outsource the manufacturing of Contract Drugs to third

parties.

Article 10

(1) Manufacture of local contract drugs is in the form of:
    a. whole stages of manufacture; or
    b. partial stages of manufacture.
(2) Formula of local Contract Drugs as referred to in section (1) is in the form of:
    a. Formula from the Contract Giver; or
    b. Formula from the Contract Acceptor.
(3) Local Contract Drugs as referred to in section (1) can be manufactured in more than 1 (one) manufacturing site by providing justification.
(4) Local Contract Drugs as referred to in section (3) must have the same quality, including Formula and product specifications.

Part Five

Imported Drug Registration

Article 11

(1) Imported drugs are in the form of:
    a. Imported Drugs in the form of Bulk Products; or
    b. Imported Drugs in the form of Finished Products.
(2) Imported Drug Registration is prioritized for:
    a. Drugs for national health program;
    b. Investigational new drugs; and/or
    c. Drugs that are needed but cannot be manufactured locally.

Article 12

Drugs for national health program as referred to in Article 11 section (2) point a are stipulated by the government institution administering the national health program.

Article 13

(1) Investigational new drugs as referred to in Article 11 section (2) point b consists of:
   a. Patented drug; or
   b. Originator drug.

(2) The originator drug as referred to in section (1) point b is the first Drug to be given a Marketing Authorization in Indonesia based on complete data on efficacy, safety, and quality.

Article 14

(1) Drugs needed but cannot be manufactured locally as referred to in Article 11 section (2)point c are:
   a. Drugs that require special technology and manufacturing facilities that are not yet owned by the Pharmaceutical Industry in Indonesia;
   b. Drugs that require special technology and manufacturing facilities that are already available in Indonesia, but the production capacity is inadequate to meet local demands;
   c. Drugs that are economically impossible to manufacture domestically because of the need in small quantities; can be in the form of drugs for rare diseases (Orphan Drug) in Indonesia; or
   d. Drugs centrally manufactured overseas by the multinational pharmaceutical industry that owns the Pharmaceutical Industry in Indonesia by showing a balance of export and import activities.

(2) Registration of Imported Drugs as referred to in section (1) must be supplemented with the justification that the Drug in question cannot be manufactured in Indonesia.

Article 15

(1) Registration of Imported Drugs can only be submitted by Applicants that obtain written approval from the pharmaceutical industry abroad.

(2) Exemption from the provisions of obtaining written

approval from the pharmaceutical industry abroad as referred to in section (1) is for Applicants that are affiliates of the parent company.

(3) Written approval as referred to in section (1) must include the validity period of partnership.

(4) The pharmaceutical industry abroad as referred to in section (1) must have a license in Pharmaceutical Industry and meet the GMP requirements as evidenced by:

a. license in pharmaceutical industry from a local state authority;

b. a valid GMP certificate or other equivalent document issued by a local Drug regulatory authority and/or another country's Drug regulatory authority; and

c. report on the results of the latest inspections and related changes not later than 2 (two) years issued by a local Drug regulatory authority and/or another country's Drug regulatory authority.

(5) If necessary, to ensure the fulfillment of GMP requirements as referred to in section (4), on-site inspection can be conducted at Drug manufacturing facilities in accordance with the provisions of legislation.

(6) In the event that Imported Drugs as referred to in section (1) whose partial or whole stages of manufacture are carried out by more than 1 (one) Pharmaceutical Industry, whole stages of manufacture must meet the requirements as referred to in section (4).

Article 16

(1) Registration of Imported Drugs as referred to in Article 14 section (1) must be carried out in stages for technology transfer to be manufactured locally.

(2) Technology transfer as referred to in section (1) can be in the form of transfer of knowledge/ability in the field of:

a. product development;

b. production procedures and methods/processes; and/or

c. quality control.

(3) The transfer of technology as referred to in section (1) may be given to affiliates of the overseas pharmaceutical industry in Indonesia or other Pharmaceutical Industries in Indonesia based on an agreement between the owner and recipient of the technology.

Part Six
Narcotic Registration

Article 17

(1) Narcotic registration can only be submitted by Applicants who have a special license to manufacture Narcotics from the Minister of Health.

(2) Narcotic Registration as referred to in section (1) is carried out in accordance with the requirements and procedures for registration as stipulated in this Agency Regulation.

Part Seven
Licensed Drug Registration

Article 18

(1) Licensed Drug Registration is carried out by the Applicants who have obtained the letter of authorization from the licensor.

(2) Registration as referred to in section (1) must meet the following requirements of:
   a. having a license in Pharmaceutical Industry;
   b. having a valid GMP certificate in accordance with the registered type and dosage form; and
   c. having a license agreement document.

(3) The license agreement document as referred to in section (2) point c must contain at least:
   a. information on licensed matters; and
   b. license validity period.

(4) The licensor as referred to in section (1) may be:
   a. Local Pharmaceutical Industry or overseas pharmaceutical industry; or

b. a domestic or overseas research agency owning Formula and technology.

(5) The licensor as referred to in section (4) must have proof of status as a Pharmaceutical Industry or research agency.

Part Eight

Registration for Export-Only Drug

Article 19

(1) Registration for Export-Only Drug is carried out submitted by Applicants.

(2) Export-Only Drug as referred to in section (1) consist of:
   a. Local Drugs intended for export only; and
   b. Imported Drugs for export only

(3) Applicants of Registration for Local Drugs intended for export only as referred to in section (2) point a must meet the following requirements of:
   a. having a license in Pharmaceutical Industry; and
   b. having a valid GMP certificate in accordance with the type and dosage form registered.

(4) Applicants of Registration for Imported Drugs for export only as referred to in section (2) point b must meet the following requirements of:
   a. having a license in Pharmaceutical Industry;
   b. having a valid GMP certificate in accordance with the registered type and dosage form; and
   c. having obtained written approval from overseas pharmaceutical industry.

(5) Exported drugs as referred to in section (2) are prohibited to be distributed in the territory of Indonesia.

Part Nine

Patent Protected Drug Registration

Article 20

(1) Registration for Drugs with Active Pharmaceutical Ingredients that are patented in Indonesia can only be carried out by:
   a. The Applicant as the Patent holder; or
   b. Applicants appointed by patent holder.
(2) The patent as referred to in section (1) must be proven by a patent certificate.

Article 21

(1) Registration for the First Generic Drugs with Active Pharmaceutical Ingredients that are still patented in Indonesia can be submitted by Applicants which are not patent holders in accordance with the provisions of legislation.
(2) Registration as referred to in section (1) can be submitted 5 (five) years Prior to the expiry of patent protection.
(3) Applicants of the First Generic Drug Registration as referred to in section (1), must submit the following documents:
   a. information on the expiration date of the patent protection period from the authorized institution; and
   b. data equivalence and/or other data to ensure equality of efficacy, safety, and quality.
(4) The Marketing Authorization for the submission of the First Generic Drug Registration as referred to in section (1) is issued after the patent protection period expires.

Part Ten

Investigational New Drug Registration

Article 22

(1) Registration for Drugs with clinical trials conducted in Indonesia must go through the assessment of Investigational New Drugs.
(2) The assessment of Investigational New Drugs as referred to in section (1) is carried out in accordance with the

provisions of legislation.

Part Eleven
Registration of Generic Drug

Article 23

(1) Registration of Generic Drug is submitted by Applicants using the generic name as referred to in Article 6 section (2).
(2) Whole stages of Generic Drug manufacture are carried out locally.
(3) Exemption from the provisions as referred to in section (2) is for Drugs of which their partial stages of manufacture cannot be carried out domestically.
(4) In the event that the Applicants already have Branded Generic Drugs with the same Active Pharmaceutical Ingredients, the registered Generic Drugs must be made with the same Formula, source of raw materials, Drug specifications, quality, packaging specifications, manufacturing process, and use the same manufacturing facility.
(5) The specifications as referred to in section (4) include:
    a. size;
    b. form;
    c. color;
    d. odor; and
    e. flavor.
(6) Generic Drug Labels must include the following information:
    a. the highest retail price in accordance with the provisions of legislation; and
    b. green generic logo using the following format:

(7) The generic logo as referred to in section (6) point b is attached proportionally according to the packaging size.
(8) In the event that the Applicants submit a Generic Drug

Registration with more than 1 (one) Active Pharmaceutical Ingredients strength, the strength of the Active Pharmaceutical Ingredients must be listed after the dosage form on the packaging with the font size in accordance with the generic name font size.

Part Twelve
Orphan Drug Registration

Article 24

Further provisions regarding Orphan Drug Registration are specifically regulated by the Indonesian FDA Regulation.

CHAPTER V
REGISTRATION PROCEDURES

Part One
General

Article 25

(1) Registration consists of:
    a. pre-registration stage; and
    b. registration stage.
(2) The application for pre-registration and registration as referred to in section (1) is submitted by Applicants in writing to the Chairperson by attaching the pre-registration and registration documents.
(3) The application as referred to in section (2) is submitted by filling out the Form in accordance with the example as contained in Annex II as an integral part of this Agency Regulation.
(4) Instructions for filling the Form as referred to in section (3) are listed in Annex III as an integral part of this Agency Regulation.
(5) Pre-registration and registration documents must be in Indonesian or English.
(6) Pre-registration and registration applications can be

submitted electronically in accordance with applicable regulations.

(7) In the event that electronic Registration cannot be submitted or the electronic system does not work, the Registration submitted manually.

Article 26

(1) The application for pre-registration and registration as referred to in Article 25 section (1) is subject to a fee as non-tax state revenue in accordance with the provisions of legislation.

(2) The fee as referred to in section (1) must be paid not later than 10 (ten) Days from the date of the Public Service Payment Order (*Surat Perintah Bayar-Layanan Publik*, SPB-LP) is issued.

(3) Applicants must confirm the payment of SPB-LP and submit pre-registration or registration documents not later than 3 (three) Days from the date of payment.

(4) In the event that the Applicants do not confirm the payment of SPB-LP and submit the pre-registration or registration documents as referred to in section (3), the application will be declared canceled.

Paragraph One
Registration Documents

Article 27

(1) Registration documents as referred to in Article 25 section (2) consists of:

a. part I : administrative documents, Product Information and Labels.
b. part II : quality documents.
c. part III : nonclinical documents.
d. part IV : clinical documents.

(2) The registration documents as referred to in section (1) are prepared in accordance with the ASEAN Common Technical Dossier (ACTD) format and refer to the

procedures for preparing the registration documents as contained in Annex IV as an integral part of this Agency Regulation.

(3) The registration documents as referred to in section (1) are in accordance with the example as contained in Annex V as an integral part of this Agency Regulation.

(4) The registration documents as referred to in section (1) are confidential documents used only for evaluation purposes by the competent authority.

Article 28

(1) The administrative documents as referred to in Article 27 section (1) point a are in accordance with the example as contained in Annex VI as an integral part of this Agency Regulation.

(2) Quality documents as referred to in Article 27 section (1) point b are contained in Annex VII as an integral part of this Agency Regulation.

(3) Nonclinical documents as referred to in Article 27 section (1) point c are contained in Annex VIII as an integral part of this Agency Regulation.

(4) Clinical documents as referred to in Article 27 section (1) point d are contained in Annex IX as an integral part of this Agency Regulation.

Article 29

(1) Product Information documents as referred to in Article 27 section (1) point a consist of:
   a. Summary of Product Characteristics/Brochure; and
   b. Patient Information Leaflet.

(2) Patient Information Leaflet as referred to in section (1) point b, for the Over the Counter (OTC) Drug must be included in the smallest packaging; it can be catch cover/envelope, blister, or brochure that is firmly attached to the smallest package, which is legible during the use of Drugs.

(3) The Product Information documents as referred to in

section (1) must at least include the information as contained in Annex X as an integral part of this Agency Regulation.

Article 30

(1) Label Documents as referred to in Article 27 section (1) point a include tags, strip/blister, ampoule/vial, catch cover/ envelope, and outer wrap.
(2) The label as referred to in section (1) must include traceable identity to guarantee the validity of the product.
(3) Further provisions regarding traceable identity to guarantee the validity of the product as referred to in section (2) are regulated in a Agency Regulation.
(4) The minimum information that must be included on the Label as referred to in section (1) is contained in Annex XI as an integral part of this Agency Regulation.

Article 31

(1) Patient Information Leaflet as referred to in Article 29 section (1) point b must use Indonesian, Latin, and Arabic numerals.
(2) The use of a language other than Indonesian as referred to in section (1) may be carried out as long as there is no Indonesian equivalent.
(3) In addition to using Indonesian as referred to in section (1), Patient Information Leaflet can be added in English according to the agreed information.
(4) Exemption from the provisions as referred to in section (1) for Export-Only Drugs.

Paragraph Two

Responsibilities of Applicants

Article 32

(1) Applicants are responsible for:
   a. the completeness of the submitted documents;
   b. the correctness and validity of all information contained in the registration documents; and
   c. changes in data and information on products that are in the process of registration or already have a Marketing Authorization.
(2) The Applicant's responsibility as referred to in section (1) must be stated in writing in a statement letter as contained in Annex XII as an integral part of this Agency Regulation.
(3) Any changes to data and/or Product Information as referred to in section (1) point c must obtain the approval of the Chairperson.

Part Two

Pre-registration

Article 33

The application for Drug pre-registration is made for registration screening, including determining the Registration category, the evaluation path, the evaluation fee, and the registration documents.

Article 34

Exemption from the provisions as referred to in Article 33 for:

a. Registration of Local manufactured Generic Drugs category 2 as referred to in Article 5 section (2) point b;
b. Registration of Variations Category 4 that does not require clinical trials as referred to in Article 5 section (3) point a, category 5, and category 6 as referred to in Article 5 section (3) point b and point c; and
c. Renewal registration category 7 as referred to in Article 5 section (4).

Article 35

Application as referred to in Article 33 is submitted by:

a. filling out the Form as contained in Annex II as an integral part of this Agency Regulation.
b. submitting proof of payment of pre-registration fees; and
c. attaching the documents as contained in Annex XIII as an integral part of this Agency Regulation.

Article 36

(1) Pre-registration results (*Hasil Praregistrasi,* HPR) are published within a maximum period of 40 (forty) days from the receipt of the application as referred to in Article 33.
(2) HPR as referred to in section (1) is binding and valid for 1 (one) year from the date of issuance.
(3) In the event that additional data is required, the request for additional data is submitted in writing to Applicant.
(4) In the event that Applicants are given a letter requesting additional data as referred to in section (3), the calculation of the evaluation timeline as referred to in section (1) is terminated (clock off) until the Applicants submit the requested additional data.
(5) Not later than 20 (twenty) Days from the date of the letter requesting additional data, the Applicants must submit additional data.
(6) The calculation of the evaluation timeline will be resumed (clock on) after the Applicants submit the complete additional data.
(7) In the event that the Applicants are unable to submit additional data within the period of 20 (twenty) Days as referred to in section (5), the Applicants may request an extension of the fulfillment of additional data 1 (one) time accompanied by justification.
(8) In the event that the Applicants are unable to submit additional data as referred to in section (7), the pre-registration is declared canceled and the fee will not be refunded.

Part Three

Evaluation Pathway

Article 37

(1) Evaluation pathway consists of:
   a. 7 (seven) Days pathway covering Registration for Export-Only Drug;
   b. 10 (ten) Days pathway covering Renewal registration;
   c. 40 (forty) Days pathway covering Minor Variation Registration;
   d. 100 (one hundred) Days pathway covering:
      1) New Registration of New Drugs and Biological Products indicated for the treatment of serious diseases that threaten human life (lifesaving), and/or are easily transmitted to others, and/or there is no or lack of other safe and effective therapeutic options;
      2) New Registration of New Drugs and Biological Products based on justification indicated for serious and rare diseases (Orphan Drug) in Indonesia;
      3) New Registration of New Drugs, Biological Products, Generic Drugs, and Branded Generic Drugs is intended for national health programs equipped with supporting documents for program requirements or the results of prequalification of the World Health Organization;
      4) New Registration of New Drugs and Biological Products that have gone through the Investigational New Drugs developed by a research institution or the Pharmaceutical Industry in Indonesia, made by the Pharmaceutical Industry in Indonesia and at least 1 (one) clinical trial conducted in Indonesia;
      5) New Registration of Generic Drugs that have the same Formulas, source of raw materials, Drug

specifications, quality, packaging specifications, manufacturing process, that have and use the same manufacturing facility as Branded Generic Drugs that have been approved;

6) Major Variations Registration with new indications/posology for Drugs intended as referred to in point 1) to point 4);

7) Major Variation Registration regarding quality and Product Information.

e. 120 (one hundred and twenty) Days pathway covering New Registration of New Drugs and Major Variations Registration with new indications/posology that have been approved in at least 3 (three) countries with an established evaluation system;

f. 150 (one hundred and fifty) Days pathway covering New Registration of Generic Drugs and Branded Generic Drugs that are not included in the evaluation path as referred to in point d;

g. 300 (three hundred) Days pathway covering New Registration of New Drugs and Biological Products as well as Major Variations Registration with new indications/posology that are not included in the evaluation path as referred to in point d and point e.

(2) The criteria for determining 120 (one hundred and twenty) Days pathway as referred to in section (1) point e as contained in Annex XIII as an integral part of this Agency Regulation.

Part Four
New Registration

Article 38

(1) Applications for New Registration are submitted by filling in the form as shown in the example in Annex II and attaching registration documents.

(2) New Registration document requirements as referred to in

section (1) as contained in Annex XIV as an integral part of this Agency Regulation.

(3) Exemption from the provisions as referred to in section (2), for the exported Drug Registration in accordance with the requirements as contained in Annex XV as an integral part of this Agency Regulation.

Article 39

(1) In addition to completing the New Registration documents as referred to in Article 38 section (2), for New Registration category 1 as referred to in Article 5 section (2) point a, Applicants must also submit a risk management plan.

(2) Further provisions regarding the assessment of risk management plans as referred to in section (1) are regulated in a Indonesian FDA Regulation.

Part Five

Variation Registration

Article 40

(1) Changes to Drugs that have obtained a Marketing Authorization can be in the form of changes in aspects of administration, efficacy, safety, quality, and/or Product Information and Label.

(2) The changes as referred to in section (1) must be reported to the Chairperson through the Variation Registration mechanism.

(3) Application for Variation Registration as referred to in Article 5 section (3) is submitted by filling out the Form as shown in the example as contained in Annex II and attaching the Variation Registration documents in accordance with the proposed changes as referred to in Annex XVI as an integral part of this Agency Regulation.

Article 41

(1) Exemption from the provisions as referred to in Article 40

section (1) for Notification Variations Registration as referred to in Article 5 section (3) point c, Applicants can make changes and report to the Chairperson not later than 6 (six) months after the changes are made.

(2) If the reported changes are not in accordance with the type of change as contained in Annex XVI point B point 3, the notification is rejected and the Applicants must submit registration in accordance with the specified Variation Registration category.

(3) The implementation of changes as referred to in section (1) is carried out through a change control mechanism.

(4) The changes as referred to in section (1) may be verified directly and the Applicants must be able to show documentation regarding the proposed changes.

(5) If the verification results are not in accordance with the type of notification change reported, the notification is rejected and the Applicants may be subject to sanctions in accordance with the provisions of legislation.

Part Six
Renewal Registration

Article 42

(1) Renewal Registration is submitted not sooner than 12 months and not later than 2 (two) months before the expiration of the Marketing Authorization.

(2) Exemption from the provisions as referred to in section (1), the application for Renewal Registration without changes can be submitted not later than 1 (one) month before the end of the Marketing Authorization period.

(3) Application for Renewal Registration as referred to in section (1) and section (2) is submitted by filling out the Form as shown in the example in Annex II and attaching the Renewal Registration documents as contained in Annex XVII as an integral part of this Agency Regulation.

(4) The extension of the Marketing Authorization as approval of the application for Renewal Registration as referred to

in section (1) and section (2) is valid since the end of the old Marketing Authorization period, as long as there is no:

a. changes in Active Pharmaceutical Ingredients;
b. changes in Drug manufacturers;
c. changes in Applicant;
d. changes in dosage form;
e. changes in formula;
f. changes in type and size of packaging; and/or
g. violation of the provisions of legislation.

(5) In case of the application for Renewal Registration containing any of the matters as referred to in section (4) point a to point f, the Registration is processed in accordance with the Variation Registration category.

(6) Drugs that fail to be re-registered until the time period as referred to in section (1) and section (2), can be re-submitted as New Registration by following the procedures as regulated in Article 25 to Article 39.

Part Seven
Samples of Drugs and Reference Standards

Article 43

The Chairperson may require the Applicants to submit samples of Drugs, pharmaceutical substances, and reference standards as needed.

CHAPTER VI
EVALUATION AND ISSUANCE OF DECISIONS

Part One
Evaluation

Article 44

(1) Submission of Registration applications that has been declared fulfilling the completeness of the documents as referred to in Article 27 section (1), is evaluated.

(2) The evaluation as referred to in section (1) is an

assessment of the aspects of efficacy, safety, quality, Product Information, and/or Label in accordance with the criteria and categories of Registration as referred to in Article 4 and Article 5.

(3) The evaluation as referred to in section (1) is carried out in accordance with the evaluation pathway as referred to in Article 37.

(4) The calculation of the evaluation timeline as referred to in section (2) in accordance with the evaluation pathway as referred to in Article 37 is counted from the receipt of the registration documents as referred to in Article 27 section (1).

Article 45

(1) The evaluation as referred to in Article 44 is carried out on efficacy and safety data based on scientific evidence and guidelines for the assessment of safety efficacy by the Efficacy-Safety Evaluation Team.

(2) The National Drug Evaluation Team (*Tim Penilai Obat Nasional*, TPON) conducts discussions on the results of the evaluation as referred to in section (1) and provides recommendations for decisions to the Chairperson.

(3) In the event that a detailed technical clarification and/or explanation is needed on the registration documents as referred to in Article 27 section (1), TPON can request clarification from the Applicants through a hearing.

(4) For the implementation of the hearing as referred to in section (3), the Chairperson delivers a written notification to the Applicants.

(5) The Chairperson submits the decision on the results of the evaluation as referred to in section (2) in writing to the Applicants not later than 30 (thirty) Days from the implementation of the TPON periodic meeting.

Article 46

(1) Evaluation of quality data is carried out by the Quality Evaluation Team according to the criteria as referred to in

Article 4 section (1) point b based on the validity of document information and the latest GMP inspection data.

(2) The information in the quality document as referred to in section (1) must use valid and actual data, the Formula is in accordance with the Formula to be marketed, and the manufacturing process has been validated.

(3) If necessary, to ensure the validity of the document information as referred to in section (1), a local inspection is carried out at the Drug manufacturing facility (in situ).

Article 47

(1) Evaluation of Product Information and Label is carried out by the Product Information and Label Evaluation Team to ensure that the information contained in the Product Information and Label is in accordance with the criteria as referred to in Article 4 section (1) point c.

(2) Evaluation of Product Information and Label as referred to in section (1) refers to:
   a. the results of the evaluation of efficacy, safety, and quality as referred to in Article 45 and Article 46;
   b. Information on New Drug Products that have been approved by the Chairperson; or
   c. Drug information standards set by the Chairperson.

Article 48

(1) In the event that additional data is required, the Chairperson delivers a written request for additional data to Applicants.

(2) The Applicants must submit additional data as referred to in section (1) not later than 100 (one hundred) Days from the date of request for additional data.

(3) In the event that Applicants are unable to submit additional data within the period of 100 (one hundred) Days as referred to in section (2), the Applicants may submit a justification for extension to fulfill the additional data 1 (one) time accompanied by justification.

(4) In the event that additional data is required as referred to in section (1), the calculation of the evaluation timeline is terminated (clock off).

(5) The calculation of the evaluation timeline will be resumed (clock on) after the Applicants submit the complete additional data.

(6) In the event that Applicants fail to comply with the provisions as referred to in section (2) and section (3), the Registration is declared canceled and the fee will not be refunded.

(7) Registration declared canceled as referred to in section (6), can be re-submitted by following the procedure as regulated in Article 25 to Article 43.

Part Two

Issuance of Decisions

Article 49

(1) The decision of the Chairperson on Registration is given by considering:
   a. evaluation results of registration documents and/or recommendations of TPON/Efficacy-Safety Evaluation Team/Quality Evaluation Team/Product Information and Label Evaluation Team; and/or
   b. results of on-site inspection at the Drug manufacturing facility (in situ).

(2) The decision as referred to in section (1) is in the form of:
   a. granting of approval; or
   b. rejection:

(3) Granting of approval as referred to in section (2) point a is only issued to Applicants who meet the administrative requirements and provisions as referred to in in Article 4.

(4) Rejection as referred to in section (2) point b is given if the registration document does not fulfill the provisions as referred to in Article 4.

Paragraph One

Approval

Article 50

(1) Prior to the issuance of the approval as referred to in Article 49 section (2) point a, an approvable letter may be issued.

(2) In the event that an approvable letter is issued as referred to in section (1), Applicants may:
   a. Conduct manufacturing Drugs of commercial scale Drugs; or
   b. Conduct importation of imported Drugs.

(3) In the event that the Applicant conduct importation of Imported Drugs as referred to in section (2) point b, the requirement must have a Marketing Authorization to use the approvable letter for the issuance of import certificate or import approval letter.

(4) The approvable letter as referred to in section (1) is not intended as a substitute for Marketing Authorization and can only be used for 1 (one) time importation.

(5) The approvable letter as referred to in section (1) is valid for no longer than 2 (two) years since the date the approvable letter is issued.

Article 51

(1) The approval as referred to in Article 49 section (2) point a is notified in writing to the Applicants in the form of:
   a. Marketing Authorization;
   b. Export-only approval; or
   c. Variation Registration approval.

(2) The Marketing Authorization as referred to in section (1) point a is issued if the results of commercial scale Drug manufacture meet the requirements or have submitted proof of importation.

Article 52

(1) Variation Registration Approval as referred to in Article 51 section (1) point c is in the form of:

a. New Marketing Authorization; or
b. Variation Registration approval letter which is an addendum of Marketing Authorization.

(2) Variation Registration Approval as referred to in section (1) is carried out not later than 6 (six) months since the date the approval is issued.

(3) The old agreement can still be produced not later than 6 (six) months after the issuance of a new agreement as long as the new agreement has not been implemented.

(4) The Drugs in accordance with the old approval manufactured before the implementation of the Variation Registration approval as referred to in section (3) can be distributed as long as they still meet the quality requirements.

(5) The Applicants are obligated to report the quantity, batch number, and expiration date of the last batch distributed prior to the implementation of the Variation Registration as referred to in section (3) to the Chairperson.

(6) Exemption from the provisions as referred to in section (2) to section (4) is for changes of:
a. Applicant; or
b. tightening of safety aspects as a follow-up to the results of surveillance, implemented in accordance with the provisions stipulated.

Paragraph Two
Rejection

Article 53

(1) The Chairperson delivers the rejection as referred to in Article 49 section (2) point b in writing to the Applicants.

(2) In the event that the Registration application is rejected, the Registration paid fee will not be refunded.

(3) The rejected registration as referred to in section (1) can be re-submitted by following the procedures as regulated in Article 25 to Article 43.

Part Three

Appeal

Article 54

(1) In the event of any objection to the rejection decision as referred to in Article 49 section (2) point b, the Applicants may submit a written request for appeal to the Chairperson.

(2) The appeal as referred to in section (1) may be submitted within a period of not later than 6 (six) months as of the date of rejection letter and can only be applied for 1 (one) time.

Article 55

In the event of any objection to the results of the evaluation of efficacy and safety as referred to in Article 49 section (1) point a, the Applicants may submit a written request for appeal to the Chairperson not later than 20 (twenty) Days from the date of notification letter of the results of the evaluation of efficacy and safety and can only be applied for 1 (one) time.

Article 56

(1) A request for appeal as referred to in Article 54 and Article 55 may be conducted through the mechanism of hearing and/or submitting documents in the form of new data and/or existing data with justification.

(2) Discussion on the request for appeal as referred to in Article 54 and Article 55 is conducted not later than 100 (one hundred) Days from the date the document is received.

Part Four

Re-submission of Registration

Article 57

(1) In the event that the Registration is rejected, the Applicants may re-submit the Registration by following the procedures as regulated in Article 25 to Article 43.

(2) In the event that the Registration is rejected due to failed

to meet the criteria of efficacy and safety, in addition to having to follow the provisions as referred to in section (1), the resubmission of registration can only be submitted with new data and not sooner than 1 (one) year after the date of rejection letter.

CHAPTER VII
MARKETING AUTHORIZATION VALIDITY PERIOD

Article 58

(1) Marketing Authorization and export only approvals are valid for a maximum of 5 (five) years as long as they meet the provisions of legislation.
(2) In the event that the Marketing Authorization is not re-registered as referred to in Article 42 section (1) and section (2), the Drugs cannot be manufactured and/or distributed, and the marketed drugs must be recalled.
(3) Exemption from the provisions as referred to in section (1), is for Drug Registration based on the agreement/appointment with a validity period of less than 5 (five) years, the validity period of the Marketing Authorization in accordance with the validity period of cooperation in the agreement document.
(4) The Expired Marketing Authorization may be renewed as long as they meet the criteria as regulated in Article 42.

Article 59

In the event that the agreement/appointment as referred to in Article 58 section (3) is terminated before the expiration of the Marketing Authorization period, the relevant Drug Marketing Authorization is revoked.

CHAPTER VIII
IMPLEMENTATION OF MARKETING AUTHORIZATION

Article 60

(1) Pharmaceutical Industry that has obtained Marketing Authorization is required to make and send manufacturing reports or reports on the import of Imported Drugs to the Chairperson.
(2) Manufacturing reports or reports on the import of Imported Drugs as referred to in section (1) is carried out in accordance with the provisions of legislation.
(3) The manufacturing reports or reports on the import of Imported Drugs as referred to in section (1) do not eliminate the obligation for the Pharmaceutical Industry to submit other reports in accordance with the provisions of legislation.

Article 61

(1) Drug Marketing Authorization holder is obligated to monitor the efficacy, safety, and quality of the Drugs during the Drugs are distributed and is obligated to report the results to the Chairperson.
(2) Monitoring the efficacy, safety, and quality of the Drugs during the Drugs distributed as referred to in section (1) is carried out in accordance with the provisions of legislation.

CHAPTER IX
RE-EVALUATION

Article 62

(1) Drugs that have been granted a Marketing Authorization may be subject to re-evaluation.
(2) The re-evaluation as referred to in section (1) is conducted if based on the monitoring results as referred to in Article 61 section (2), there is the latest data and information on the efficacy, safety, and quality of the Drugs.
(3) The re-evaluation implementation as referred to in section (1) as contained in Annex XVIII as an integral part of this Agency Regulation.

(4) The decision on the re-evaluation as referred to in section (2) is in the form of:
   a. Label changes;
   b. Composition/Formula improvements;
   c. the provision of usage restrictions;
   d. changes in the Drug category;
   e. recall of Drugs from distribution; and/or
   f. Marketing Authorization suspension/revocation.

(5) The decision as referred to in section (4) is submitted in writing to the Marketing Authorization holder for follow-up.

CHAPTER X
SANCTIONS

Article 63

(1) Violations of the provisions in this Agency Regulation may be subject to administrative sanctions in the form of:
   a. written warning;
   b. cancellation of the Registration process;
   c. suspension of Drug Marketing Authorization;
   d. revocation of Drug Marketing Authorization; and/or
   e. prohibition to register for 2 (two) years.

(2) Administrative sanctions as referred to in section (1) point b and/or point e may be imposed based on or in the case of:
   a. not complying with the provisions as referred to in Article 4;
   b. not complying with the provisions as referred to in Article 32 section (1) point b; and/or
   c. invalid data as referred to in Article 46.

(3) Administrative sanctions as referred to in section (1) point c and/or point d may be imposed based on or in the case of:
   a. not performing obligations as referred to in Article 60 section (1) and section (2);
   b. Pharmaceutical Industry License of Marketing

Authorization holder is revoked; and/or

c. Marketing Authorization holder commits violations in the field of production, distribution, promotion, and/or Drug Label.

CHAPTER XI
MISCELLANEOUS PROVISIONS

Article 64

(1) To ensure the stability of the drugs in the form of solid oral dosage forms, the registration of Drugs in a bottle contains a maximum of 100 (one hundred) pills.

(2) Registration of Drugs in bottle packaging as referred to in section (1) can only be done for Drugs with stable Active Pharmaceutical Ingredients.

Article 65

If Applicants carry out a Registration that has more than 1 (one) Active Pharmaceutical Ingredients strength, then it must have different specifications such as size, shape, and/or color.

CHAPTER XII
TRANSITIONAL PROVISION

Article 66

Registrations that have been submitted prior to the enforcement of this Agency Regulation are still being processed based on the Regulation of the Chairperson of the Indonesian Food and Drug Authority Number HK.03.1.23.10.11.08481 of 2011 on Criteria and Procedures for Drug Registration as amended several times, and last by the Regulation of the Chairperson of the Indonesian Food and Drug Authority Number 17 of 2016 on the Second Amendment to the Regulation of the Chairperson of the Indonesian Food and Drug Authority Number HK.03.1.23.10.11.08481 of 2011 on Criteria and Procedures for Drug Registration.

CHAPTER XIII
CLOSING PROVISIONS

Article 67

At the time this Agency Regulation comes into force:

1. Regulation of the Chairperson of the Indonesian Food and Drug Authority Number HK.03.1.23.10.11.08481 of 2011 on Criteria and Procedures for Drug Registration (State Bulletin of the Republic of Indonesia of 2011 Number 634);
2. Regulation of the Chairperson of the Indonesian Food and Drug Authority Number 3 of 2013 on Amendment to the Regulation of the Chairperson of the Indonesian Food and Drug Authority Number HK.03.1.23.10.11.08481 of 2011 on Criteria and Procedures for Drug Registration (State Bulletin of the Republic of Indonesia of 2013 Number 540);
3. Regulation of the Chairperson of the Indonesian Food and Drug Authority Number 17 of 2016 on the Second Amendment to the Regulation of the Chairperson of the Indonesian Food and Drug Authority Number HK.03.1.23.10.11.08481 of 2011 on Criteria and Procedures for Drug Registration (State Bulletin of the Republic of Indonesia of 2016 Number 1140);

are repealed and declared ineffective.

Article 68

This Agency Regulation comes into force on the date of its promulgation.

In order that every person may know hereof, it is ordered to promulgate this Agency Regulation by its placement in the State Bulletin of the Republic of Indonesia.

Issued in Jakarta
on 24 November 2017

CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY OF THE REPUBLIC OF INDONESIA

signed

PENNY K. LUKITO

Promulgated in Jakarta
on 24 November 2017

DIRECTOR GENERAL OF LEGISLATION
OF THE MINISTRY OF LAW AND HUMAN RIGHTS
OF THE REPUBLIC OF INDONESIA

signed

WIDODO EKATJAHJANA

STATE BULLETIN OF THE REPUBLIC OF INDONESIA OF 2017 NUMBER 1692

Jakarta, 30 March 2022
Has been translated as an Official Translation
on behalf of Minister of Law and Human Rights
of the Republic of Indonesia
DIRECTOR GENERAL OF LEGISLATION,

BENNY RIYANTO

ANNEX I
REGULATION OF THE CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY OF THE REPUBLIC OF INDONESIA
NUMBER 24 OF 2017
ON
CRITERIA AND PROCEDURES FOR DRUG REGISTRATION

GENERAL GUIDELINES FOR DRUG NAMES

Drug names must consider to the following provisions:

1. Trade names must be objective and not misleading.
2. The same trade name can only be used by one Pharmaceutical Industry of Marketing Authorization holder for Drugs with the same Active Pharmaceutical ingredients, indications, and category.
3. Trade names may not use the whole or part of generic names of the Active Pharmaceutical ingredients that is not contained.
4. Trade names must not be the same or very similar in sound or writing with trade name of a Drug that has been registered with a different Active Pharmaceutical ingredients.
5. Trade names of drug category over the counter containing at least one of the same Active Pharmaceutical ingredients and/or the same therapeutic class may use the same trade name as the umbrella brand.
6. Trade names may not use the same or similar name to a Drug which the Marketing Authorization has been revoked due to safety issues, misuse, and other violations.

CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY,
signed.

PENNY K. LUKITO

ANNEX II
REGULATION OF THE CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY OF THE REPUBLIC OF INDONESIA
NUMBER 24 OF 2017
ON
CRITERIA AND PROCEDURES FOR DRUG REGISTRATION

REGISTRATION FORM

BADAN POM RI

CONFIDENTIAL DOCUMENT

INDONESIAN FOOD AND DRUGAUTHORITY OF THE REPUBLIC OF INDONESIA

DRUG AND BIOLOGICAL PRODUCT REGISTRATION FORM

Filled By TheINDONESIAN FDA

No. Registration

Date of Admission (dd/mm/yyyy) Evaluation Code Evaluation Subcode

A. DRUG DESCRIPTION #)

Registration category

Types of drug*) New Generic Biological Products

Types of Product*) Single Product Combination Product Combipack Product

Drug category *) Prescription OTC Limited Free Narcotics Psychotropics

Drug name

Dosage Form Strength Unit of measure

Therapy Class ATC Code

Packaging (Type and Description)

Package Size

*): Choose one

Other Dosage Form, Strength, packaging

Dosage Form	Strength	Packaging Type	Packaging Size	MA*)	Validity Period of MA

*):MA: Marketing Authorization Number

B. APPLICANT'S FULL DESCRIPTION #)

Applicant's Name

Applicant's Address Street Name and Number City Country

Address for Correspondence Street Name and Number City Country

Telephone &Fax Numbers E-mail

C. MANUFACTURE STATUS #)

Manufacture Status *) Local Manufacture Self-manufacturing

Contract manufacturing

License-based manufacturing

Import ☐

Drugs are intended for export only *) Yes ☐ No ☐

Name of Licensor ▼

Licensor's Address | Street Name and Number | City ▼ | Country ▼

Manufacturer

Name	Address: Street and Number	Address: City	Address: Country	SMF **)	GMP	Function/Role

*): Choose one **): Submission receipt

D. FORMULA #)

1. Unit Dose Active Pharm Ingredient

CAS NO	Name	Numbers	Unit		Animal/human sources	Manufacturer	DMF**)	Manufacturing Country
▼	▼		▼			▼		▼
▼	▼		▼			▼		▼
	▼		▼			▼		▼

2. Excipient

CAS NO	Name	Numbers	Unit		Animal/human sources	Function	Manufacturer	Manufacturing Country
▼	▼		▼			▼	▼	▼
▼	▼		▼			▼	▼	▼
▼	▼		▼			▼	▼	▼
▼	▼		▼			▼	▼	▼

3. Solvent

CAS NO	Name	Numbers	Unit		Animal/human sources	Manufacturer	Manufacturing Country
▼	▼		▼			▼	▼
▼	▼		▼			▼	▼
▼	▼		▼			▼	▼
▼	▼		▼			▼	▼

**): Filled in if DMF is required and available.

E. DRUG INFORMATION

Drug Administration ##)

Drug Specifications and Analysis Methods ##) | Drug Specifications | Drug Analysis Methods

Indications #)

Posology#)

Drug Administration Route #)

F. PRE-REGISTRATION INFORMATION

Pre-registration results (HPR)*) Yes ☐ No ☐

Issuance Date of HPR

Registration Category ☐

Evaluation Fee | In words

Evaluation Pathway*) 300 WD ☐ 150 WD ☐ 120 WD ☐ 100 WD ☐ 40 WD ☐ 10 WD ☐ 7 WD ☐

*): Choose one

G. STORAGE CONDITION AND EXPIRATION DATE

Storage Condition	
Expiration Date	
Expiration Date after packaging is opened/reconstitution *)	

*): Filled for certain dosage forms, for example eye drops (after opening the package) or lyophilization powder for reconstitution (after the drug is reconstituted)

H. REGISTRATION STATUS IN OTHER COUNTRIES *) ##)

Country	Registration Status	Date of Approval	Drug Category

*) : Filled in only for New Drugs, Biological Products, and Imported Generic Drugs

I. PATENT INFORMATION *) ##)

Patent Title	Patent Admission	Patent Filing Date

): If any

J. HISTORY OF REGISTRATION ##)

Registration category	Submission Date	Date of Approval	MA	Validity Period of MA

K. DESCRIPTION OF THE BATCH NUMBERING SYSTEM

L. PRICE INFORMATION

Packaging	HNA *)	HET **)

*): HNA: Pharmacy Net Price
**) : HET : Highest Retail Price

M. COMMITMENTS TO BE FULFILLED

N. TECHNICAL DOCUMENTS

Document Format Type *) ACTD ☐ ICH CTD ☐

	Number of ring binder/folder	Number of Copies
SECTION I : Administrative Documents and Product Information		
SECTION II : Quality Documents		
SECTION III : NonclinicalDocuments		
SECTION IV : Clinical Documents		

*): Choose one

O. DESCRIPTION OF REGISTRATION OFFICERS

Name	
Positin	
Address	
Telephone & fax numbers	

Mobile phone number	
E-mail	

Notes:

1. #) : Must be filled in when submitting pre-registration and cannot be updated at the time of submitting Registration.

   ##) : Must be filled in when submitting pre-registration and canbe updated at the time of submitting Registration.

2. For Variation Registration and Registration Renewal submitted along with certain changes, all information contained in the Registration Form must be filled in as approved, except for the part where changes are to be made, the information can be updated.
3. For Registration Renewal, all information contained in the Registration Form must be filled in as approved.

CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY,

signed.

PENNY K. LUKITO

ANNEX III
REGULATION OF THE CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY OF THE REPUBLIC OF INDONESIA
NUMBER 24 OF 2017
ON
CRITERIA AND PROCEDURES FOR DRUG REGISTRATION

REGISTRATION FORM FILLING INSTRUCTIONS

A. DRUG DESCRIPTION #)

1. Registration Category
   Filled in according to the Registration category submitted or according to the one listed in the Pre-registration Results (HPR).

2. Types of Drug
   Filled with a check mark (√) on one of the options according to the types of Drug registered, namely New Drugs, Generic Drugs (for Generic Drugs and Branded Generic Drugs), or Biological Products (for Biological Products and Biosimilar Products).

3. Types of Product
   Filled with a check mark (√) on one of the options according to the types of product, namely:
   a. Single Product, if the product consists of Drugs only;
   b. Combination Product, if the product consists of Drugs and Solvents or aids for the use of Drugs (for example syringes, aerosols, sprays, implants); or
   c. Combipack Product, if the product consists of two or three Drugs packed in one packaging with the aim to be given to patients simultaneously.

4. Drug Category
   Filled with a check mark (√) on one of the options according to the Drug category, namely Prescription Drugs, Over the Counter Drugs, Limited Over the counter, Narcotics, or Psychotropic Drugs.

5. Drug name
   Filled with the name of the registered Drug.

6. Dosage form, strength, and unit of measure
   The dosage form is listed in detail, complete with dosage strength and unit of measure. Example: 5 mg sugar coated tablet.

   6.1. Dosage form:
   Aerosol foam, aerosol metered dose, aerosol spray, oral spray, buccal spray, transdermal spray, topical spray, powder spray, elixir, emulsion, enema, gas, gel, eye gel, granule effervescent, granule, intra uterine device (IUD), implant, capsule, soft capsule, sustained release capsule, caplet, film coated caplet, enteric coated caplet, sugar coated caplet, slow release caplet, immediate release caplet, chewable caplets, film coated chewable caplets,cream, lipophilic cream, solution, inhalation solutions, injection solutions, infusions, mouthwashes, ovules, pastes, pills, patch, pessary, ointments, eye ointments,

shampoo, nasal spray, aerosol powder, oral powder, inhaler powder, injection powder, lyophilized injection powder, infusion powder, external medicine powder/sow powder, sterile powder, effervescent powder, syrup, dry syrup, slow release dry syrup, subdermal implants, suppositories, suspensions, injection suspensions, external drug suspensions/fluids, sterile fluids, eye fluids, diagnostic fluids, tablets, effervescent tablets, lozenges, chewable tablets, immediaterelease tablets, Sustained-release tablets, oral disintegrating tablets, dispersible tablets, fast dissolving tablets, sugar coated tablets, enteric coated tablets, film coated tablets, sublingual tablets, slow release sublingual tablets, vaginal tablets, coated tablets, release coated tablets, chewing gum, eye drops, nose drops, ear drops, oral drops, eye and ear drops, transdermal, transdermal urethral, tulle/plaster, vaginal cream, vaginal gel, vaginal douche, vaginal ring, or vaginal tissue.

6.2. Dosage strength:

The dosage strength can be expressed by weight or volume for:

6.2.1. per one unit dosage form for tablets, capsules, pills, suppositories, and ovules.
6.2.2. per g or% w/w for ointments and creams.
6.2.3. per mL or each packaging for the injection solution.
6.2.4. each pack in g or mg for powder injection.
6.2.5. every 5 mL or 15 mL for syrups, suspensions, emulsions, elixirs, mouthwashes.
6.2.6. per mL or % w/v for drops.
6.2.7. each pack for powder for oral use.
6.2.8. per g for external use powder.
6.2.9. each dose for aerosol/inhalation/spray, and so on.
6.2.10. per unit surface area or per unit weight for gauze or plaster.
6.2.11. per unit measuring device/dose for Biological Products.

6.3. Unit of measure:

The levels of Active Pharmaceutical Ingredientsand Excipients are expressed in the unit of measure:

6.3.1.	Kilogram	abbreviate kg
6.3.2.	Grams	abbreviate g
6.3.3.	Milligram	abbreviate mg
6.3.4.	Microgram	abbreviate mcg
6.3.5.	Liter	abbreviate L
6.3.6.	Milliliter	abbreviate mL
6.3.7.	Centimeter	abbreviate cm
6.3.8.	Gram equivalent	abbreviate grek
6.3.9.	Milligram equivalent	abbreviate mgrek
6.3.10.	International unit	abbreviate IU
6.3.11.	Micromole	abbreviate mcmol
6.3.12.	Mole	abbreviate mol
6.3.13.	Nanogram	abbreviate ng
6.3.14.	Square centimeter	abbreviate cm_2
6.3.15.	Colony forming units	abbreviate CFU
6.3.16.	Plaque forming units	abbreviate PFU
6.3.17.	Cell Culture Infectious Dose 50%	abbreviate $CCID_{50}$

6.3.18. The number of D antigen abbreviate D Antigen Unit

7. Therapy Class and ATC Code
Filled in accordance with WHO Anatomical Therapeutic Chemical Code published by WHO Collaborating Centre for Drug Statistics Methodology (www.whocc.no/atc_ddd_index/).

8. Packaging (Type and Description)
The first column lists the types of packaging, for example blisters, ampoules, vials, bottles, and others.

The second column contains a specific description and composition of the primary packaging, including the type of material, color, size and so on, for example:
- Vial, 20 mL brown borosilicate glass type I with rubber cap.
- Blister, PVC/PE with aluminum foil.

9. Packaging Size
The number of container closure system in secondary packaging and the number of dosage forms per packaging system are indicated, for example:
- Box, 1 blister @ 10 tablets.
- Box, 1 vial @ 5 mL.

The solvent and/or aids for the use of Drugs included in the packagingis also listed.

10. Other Dosage form, strength, and packaging
Filled with the dosage form, strength, type of packaging, and other packaging registered and/or currently registered. The latest Marketing Authorization number is stated for registered drugs, along with the validity period of the Marketing Authorization.

B. APPLICANT'S FULL DESCRIPTION #)

1. Applicant's Name
Filled with the name of the Applicant Pharmaceutical Industry in accordance with that stated in the Pharmaceutical Industry license.

2. Applicant's Address
Filled with the address of the Applicant Pharmaceutical Industry in accordance with that stated in the Pharmaceutical Industry license complete with street name, number, city, and country.

3. Address for Correspondence
Filled with the applicant pharmaceutical industry address for correspondence, complete with street name, number, city, country, telephone and fax numbers, as well as E-mail of the Applicant.

C. MANUFACTURING STATUS #)

1. Manufacturing Status
Filled with a check mark (√) on one of the options according to the registered Drug manufacturing status, namely local and import manufacture. If local manufacture, tick (√) on one

of the options, i.e., self-manufacturing, contract manufacturing, or license-based manufacturing.

2. Drugs intended for export only
Filled with a check mark (√) on one of the options, namely "Yes" if the Drug is intended only for export and "No" if the Drug is not intended for export only.

3. Name of Licensor
Filled with the name of the Pharmaceutical Industry that gives the license.

4. Licensor's Address
Filled with the address of the Pharmaceutical Industry that gives the license, complete with street name, number, city, and country.

5. Manufacturer
Filled with complete information of the manufacturer, namely the pharmaceutical industry involved in the production process, for example the manufacture of Active Pharmaceutical Ingredients(specifically for biological products), semi-finished products/granulations/semi-finished dosage forms (bulk) or finished drugs and/or solvents and/or auxiliary devices, primary and/or secondary packaging, responsible for batch release or others.

5.1. Name
Filled with the name of the Pharmaceutical Industry that manufactures Drugs.

5.2. Address
Filled with the complete address with street name, number, city, and country.

5.3. SMF (Site Master File) ##)
Filled with a check mark (√) if SMF is required and available.

5.4. GMP
Filled with the expiration date of the GMP certificate according to the registered product dosage form.

5.5. Function/Role
Filled with the type of activity (manufacturing stage) carried out by the manufacturer, for example the manufacture of Active Pharmaceutical Ingredients(specifically for biological products), semi-finished products/granulation/semi-finished dosage forms (bulk)or finished Drugs and/or solvents and/or auxiliary device, primary and/or secondary packaging, the manufacturer in charge for batch release or others.

D. FORMULA #)

1. Active Pharmaceutical Ingredients

1.1 Dosage unit
Filled with a measure and a unit of measure, for example "every 5 mL of syrup contains:" or "each tablet contains:". For the Active Pharmaceutical Ingredients in the form of salt/ester, the equivalence of the base must be written if the Active Pharmaceutical Ingredients are in the form of a base.

1.2 CAS No.
Filled according to the Active Pharmaceutical Ingredients used.

1.3 Name

1.3.1 Active Pharmaceutical Ingredients are written according to International Nonproprietary Names Modified (INNM).

If the name has not been listed in the INNM, it should be written according to United States Adopted Names (USAN) or British Approved Name Modified (BANM).

1.3.2 The active pharmaceutical ingredientsin the form of ester or salt are written in the form of their ester or salt.

1.3.3 Active Pharmaceutical Ingredients in the form of inorganic salt containing crystalline water must have their chemical names written appropriately, including the crystalline water contained.
Example: Amoxicillin trihydrate.

1.3.4 A trace element (*seseporalogam*) is written with the chemical name of the correct salt including the crystalline water it contains, in addition to the metal.

1.4 Numbers
Filled according to the number of Active Pharmaceutical Ingredients used per unit dose.

1.5 Unit
Filled in according to the Active Pharmaceutical Ingredients unit used (see the procedures for writing the unit of measure in section A.6.3).

1.6 Animal/human sources
In the first column, it is stated "Yes" if the Active Pharmaceutical Ingredients derived from animals/humans and "No" if the Active Pharmaceutical Ingredients do not derive from animals/humans.

The second column lists the types of animal or human as the source of the Active Pharmaceutical Ingredients.
Example: Yes; bovine.
Yes; human.

1.7 Manufacturer
Filled with the name of the Active Pharmaceutical Ingredients manufacturer along with the complete address with street name, number, and city.

1.8 DMF (Drug Master File)##)
Filled with a check mark (√) if DMF is required and available.

1.9 Manufacturing Country
Filled with the country where the Active Pharmaceutical Ingredients are manufactured.

2. Excipient

2.1 CAS No.
Filled according to the Excipient used.

2.2 Name
Excipients and excipients in combination are written according to the International Nonproprietary Names (INN) and International Nonproprietary Names Modified (INNM).

The excipients used must be in accordance with the applicable additive provisions.

The Coloring Agents is written with a simple common name, the color index number must be written (CI number) and includes the solubility in water (Dye), or in oil (Lake). Example: Brilliant Blue FCF C142090 (Dye).

The Coloring Agents used must comply with the applicable excipient provisions.

2.3 Numbers
Filled according to the number of Excipients used per unit dose.

2.4 Unit
Filled in according to the Excipient unit used (see the procedures for writing the unit of measure in item A.6.3).

2.5 Animal/human sources
In the first column, it is stated "Yes" if the Excipients derived from animals/humans and "No" if the Excipients do not derive from animals/humans.

The second column lists the types of animal or human as the source of the Excipients.
Example: Yes; bovine.
Yes; human.

2.6 Function
Filled according to the function/usefulness of Excipients used.

2.7 Manufacturer
Filled with the name of the Excipient manufacturer along with the complete address with street name, number, and city.

2.8 Manufacturing Country
Filled with the country where the Excipients are manufactured.

3. Solvents

3.1. CAS No.
Filled with solvents used.

3.2. Name
Solvents are written according to the International Nonproprietary Names (INN) and International Nonproprietary Names Modified (INNM).

3.3. Numbers
Filled according to the number of solvents used per unit dose.

3.4. Unit
Filled in according to the solvent unit used (see the procedures for writing the unit of measure in section A.6.3).

3.5. Animal/human sources
In the first column, it is stated "Yes" if the Solvents derived from animals/humans and "No" if the Solvents do not derive from animals/humans.

The second column lists the types of animal or human as the source of the solvents.
Example: Yes; bovine.
Yes; human.

3.6. Manufacturer
Filled with the name of the solvent manufacturer along with the complete address with street name, number, and city.

3.7. Manufacturing Country
Filled with the country where the solvents are manufactured.

E. DRUG INFORMATION

1. Drug Administration ##)
It explains the shape, color, size, weight, and special signs found on the Drug according to the Drug's specifications.

2. Drug Specifications and Analytical Methods ##)
Drug specifications are stated by describing the administration (including identification marks on tablets, capsules, etc.), weight/volume of drugs, physical and chemical characteristics, limits of content or potency and other requirements (sterility, pyrogenicity, etc.).

The method of Drug analysis when following one of the Pharmacopoeia is simply to write down Pharmacopoeia used which is equipped with the edition number and page number. If you do not follow any of the Pharmacopoeia, it can be written in-house. Analytical methods that need to be explained include methods of identification, determination of levels or potentials, and methods of specific analysis (sterility, pyrogenicity, and so on).

3. Indications #)
Proposed or fully approved indications should be stated. It is an indication for the use of Drugs in therapy, listed the types of diseases indicated.

4. Posology #)
Proposed or fully approvedposologyshould be stated, includinghowto use, amount, frequency, and length of use. The route of administration must be clearly mentioned, for example intravenous injection, intramuscular, or others. The amount of use must be stated in the usual measure and limits for both adults and children. The dosage regimen is the frequencyof the drug ~~is~~ given in one day or every hour.

The length of use is described by stating how long the drug must be/can be given, how long the use must be stopped before reuse or how long the Drug must be minimally used.

5. Drug administration route #)
It explains how to administer Drugs e.g., per oral, parenteral, e.g., intravenous injection, topical, and others.

F. PRE-REGISTRATION INFORMATION

1. Pre-registration Results (HPR)
Filled with a check mark (√) on one of the options according to the existing/absence of HPR.

2. HPR Issuance Date
Filled with HPR issuance date.

3. Registration Category
In the first column listed registration category as submitted or as stated in HPR.

The second column contains detailed information on the type of Registration category.

Example: - New Drugs with new chemical entity.

- Generic Drugs that require bioequivalence study.

4. Evaluation Fee
Filled with nominal numbers and in words according to the submitted category or as stated on the HPR or according to applicable regulations (if not through the pre-registration process).

5. Evaluation Pathway
Filled with a check mark (√) on one of the evaluation pathway options according to the category of Registration submitted, or as stated on the HPR, namely 300WD, 150WD, 120WD, 100WD, 40WD, 10WD or 7WD.

G. STORAGE CONDITION AND EXPIRATION DATE

1. Storage Condition
It states proposed or approved storage condition equipped with temperature and humidity.

2. Expiration Date
It includes the proposed or approved expiration date.

3. Expiration Date After First Opening/Reconstitution
The expiration date for certain dosage forms is stated, for example eye drops (after first opening) or lyophilized powder for reconstitution (after the Drug is reconstituted).

H. REGISTRATION STATUS IN OTHER COUNTRIES ##)

Filled in only for New Drugs, Biological Products, and imported Generic Drugs

1. Country
Filled with the name of other countries where the Drugs are registered.

2. Registration Status
   Filled with Registration status in other countries.

3. Date of Approval
   Filled with the date of approval in other countries if the Drugs have been approved in that country.

4. Drug Category
   Filled with Drug category in other countries.

I. PATENT INFORMATION ##)

Filled if any.

1. Patent Title
   Filled with patent title issued by relevant institutions in Indonesia.

2. Patent Admission Number
   Filled with patent acceptance numbers issued by relevant institutions in Indonesia.

3. Patent Filing Date
   Filled with date of patent acceptance issued by relevant institutions in Indonesia.

J. HISTORY OF REGISTRATION##)
Filled in for Variation Registration and addition of indications/posology. All Registrations that have been approved and which are in the evaluation process (if any) must be listed.

1. Registration Category
   Filled with Registration Category that has been approved and is in the process of evaluation (if any).

2. Submission Date
   Filled with the date of Registration submission that is in the evaluation process (if any).

3. Date of Approval
   Filled with the date of approval for the Drug that was previously approved.

4. Marketing Authorization Number
   Filled with Marketing Authorization Number of approved Marketing Authorization.

5. Validity Period of Marketing Authorization
   Filled with the validity period of approved Marketing Authorization

K. DESCRIPTION OF THE BATCH NUMBERING SYSTEM

Filled with code consisting of Latin letters or Arabic numerals or a combination of both which are identifiers of a batch, for a re-search of the complete history of the batch's creation, including stages of manufacture, control, and distribution.

L. PRICE INFORMATION

1. Packaging
   Filled according to the size of the packaging to be registered.

2. HNA
   Filled with The Net Price of Pharmacies (*Harga Netto Apotek*, HNA) for each unit of packaging up to the smallest packaging that will apply throughout Indonesia.

3. HET
   Filled with the Highest Retail Price (*Harga Eceran Tertinggi*, HET) for each unit of packaging up to the smallest packaging that will apply throughout Indonesia.

M. COMMITMENTS TO BE FULFILLED

Filled with commitments that must be fulfilled if there are requirements that cannot be submitted.

N. TECHNICAL DOCUMENTS

1. Types of Document Format
   Filled with a check mark (√) on one of the options according to the types of document format used for Registration, namely ACTD format or ICH CTD format.

2. Section I (Administrative Documents and Product Information)
   Filled according to the number of ring binder/folder and the number of copies for Section I

3. Section II (Quality Documents)
   Filled according to the number of ring binder/folder and the number of copies for Section II

4. Section III (Nonclinical Documents)
   Filled according to the number of ring binder/forlder and the number of copies for Section III

5. Section IV (Clinical Documents)
   Filled according to the number of ring binder/folder and the number of copies for Section IV

O. DESCRIPTION OF REGISTRATION OFFICERS ##)

Filled with Registration officer's personal data.

1. Name
   Filled with full name of the Registration officer of Applicant.

2. Position
   Filled with position of Registration officer in the Applicant.

3. Address
   Filled with the address of the Registration officer that can be contacted.

4. Telephone and fax numbers
   Filled with telephone and fax number of the Registration officer that can be contacted.

5. Mobile phone number
   Filled with mobile phone number of the Registration officer that can be contacted.

6. E-mail
   Filled with active E-mail address of the Registration officer.

Notes:

#) : Must be filled when submitting pre-registration and cannot be updated at the time of submitting Registration.

##) : Must be filled in when submitting pre-registration and can be updated at the time of submitting Registration.

For Variation Registration or Renewal Registration submitted along with certain changes, all information contained in the Registration Form must be filled in as approved, except for the part where changes are to be made, the information can be updated.

For Renewal Registration without changes, all information contained in the Registration Form must be filled in according to what has been approved.

CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY,

signed

PENNY K. LUKITO

ANNEX IV
REGULATION OF THE CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY OF THE REPUBLIC OF INDONESIA
NUMBER 24 OF 2017 ON
CRITERIA AND PROCEDURES FOR DRUG REGISTRATION

PROCEDURES FOR PREPARING REGISTRATION DOCUMENTS

The registration documents consist of four parts as follows:

1. Section I: Administrative Documents and Product Information consist of:
   A. Entire Table of Contents
   B. Administrative Documents
   C. Product Information and Label

2. Section II: Quality Documents consist of:
   A. Quality Overall Summary (QOS)
   B. Quality Documents
   C. References

3. Section III: Nonclinical Documents consist of:
   A. Nonclinical Overview
   B. Summary and Matrix of Nonclinical Studies
   C. Report on Nonclinical Studies (if necessary)
   D. References

4. Section IV: Clinical Documents consist of:
   A. Review of Clinical Studies
   B. Summary of Clinical Studies
   C. Matrix of Nonclinical Studies
   D. Report on Clinical Studies
   E. References

Registration documents should be in the form of hardcopy or softcopy.

I. Registration Document Hardcopy
   Each part of the registration document must be completed with a table of contents showing the location of each document and divider paper between sections and between documents. The divider paper between the sections is given a title according to the section name (for example: Section IV.A. Review of Clinical Studies) or the document title according to the registration document format.
   Each part of the registration document must be bundled in a separate ring binder/folder or several parts of the registration document can be combined in anring binder with divider paper between each of these documents. The use of ring binder/folder is adjusted to the number of registration documents.

A. Number of copies of registration documents

	New Drugs & Biological Products	Generic Drugs	Variations	Renewal Registration
Section I – Documents Administrative and Product Information - Certificate and other administrative documents	1 copy	1 copy	1 copy	1 copy
- Registration form	3 copies	3 copies	3 copies	3 copies
- Label	1 copy*)	1 copy*)	1 copy*)	3 copies
- Product Information	1 copy*)	1 copy*)	1 copy*)	4 copies
Section II – Quality Documents	1 copy	1 copy	1 copy (if necessary)	1 copy
Section III – Nonclinical Documents	1 copy	-	1 copy (if necessary)	-
Section IV – Clinical Documents	1 copy (except for Review of Studies and Matrix of Clinical Study Report, 2 copies)	1 copy (If necessary)	1 copy (if necessary)	1 copy (if necessary)

*) If the documents are in accordance with the evaluation results, the Applicants must submit as many as 4 (four) copies.

B. Paper size

If the registration document is in the form of hardcopy, it must use International standard size paper (A4: 8.27 x 11.69 inches). For certain cases the use of paper larger than the standard size is allowed, among others floor plans, synthesis diagrams, batch Formula, or Drug manufacturing flows. These paper pages must be folded and viewable without opening the ring binder cover and can be folded back without causing any damage during storage.

C. Letters

Font size for narratives and tables must be sufficiently large and legible type and size, even after being duplicated or displayed electronically.

Example: for narration, use the letter Times New Roman with a size of 12. For tables, flows, and charts letters size 9 – 10 can be used.

D. Ring binder or folder color

For hardcopy documents, follow the following conditions:

Registration Type	Col
New Registration, Variation Registration, and Renewal-Registration of New Drugs	Blue
New Registration, Variation Registration, and Renewal -Registration of Biological Products	Gray
New Generic Drug Registration	Black
Variation Registration and Renewal -Registration of Generic Drugs	Green
Renewal-Registration Without Changes	Yellow
Exported Drug Registration	Red
Notification Variation Registration.	Transparent White

E. Ring binder/folder numbering

Each ring binder/folder must be assigned a different number in its order.

F. Ring binder/folder identification

In the middle of the front cover for each ring binder/folder, the following information must be written:

- Drug Name.
- Dosage Form.
- Composition.
- Type and Size of Packaging.
- Applicant's Name.
- Manufacturer's Name.

On the front and side of the ring binder must be written ring binder number, unless the folder is only listed on the front in the following format: x of y where x is the specific ring binder number and y is the total number of ring binders for the related section. Example: the 6th ring binder for the Safety Section with a total of 50 ring binders for all sections is written 6 out of 50 on the lower-right corner.

G. Document identification

Each document must include the following information:

- The document name or code must be printed on the upper-right corner of the divider paper.
- The subsection numbering system must be indicated in the lower-right corner, for example:
  Part x, Ord. X, Subsection x.x

Where:

Section x	: Document section
Ord. X.	: ring bindernumber
Subsection x.x	: Subsection number

For example: In the Quality section, the subsection Control on Active Pharmaceutical Ingredients must be written Section II, Ord. 2, Subsection B.S4 on the lower right corner.

H. Page numbering

All documents must have page numbers. The numbering is based on subsections or sub-subsections of documents, not by ring binder or section. All registration documents must not be numbered sequentially based on the page. A set of page numbering for each subsection only.

If there is a document inserted in the document, such as the protocol in the study report, the inserted document is included as an attachment. Each attachment must be separated by a properly named divider paper.

On the lower-right corner of each page, a page numbering system must be written in the following format:

Sect. x, Ord. X, SubSect.x.x, Pg. xx

Where:
Sect. x : part of adocument (Section).
Ord. X : specific ring binder number
SubSect.x.x : subsection or sub-subsection numbers of the related part (subsection)
Pg. xx : page of the related subsection

For example, the Active Pharmaceutical Ingredient specification document from the quality section is written: Sect. II, Ord.2, SubSect. B.S4.1, Pg. 7 on the lower-right corner.

I. Page numbering for additional data documents

Additional data must not change the page numbering order. If the number of additional data pages exceeds the existing page number, it can be added with letters a – z as subpage numbers.

Example: pages 6a, 6b, 6c ... etc.,

J. Documents with ICH CTD format

Documents with ICH CTD format may be submitted in accordance with the applicable ICH CTD provisions, but document Section I must be adapted to the provisions of this Regulation.

II. Registration Document Softcopy
Registration document softcopy can refer to the Technical Manual of Electronic Application Registration of Drugs.

III. Additional Data
In addition to the New Registration, guidelines for the preparation of registration documents can also be for the preparation of additional data documents. General correspondence must be included in Section I.

CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY,

signed

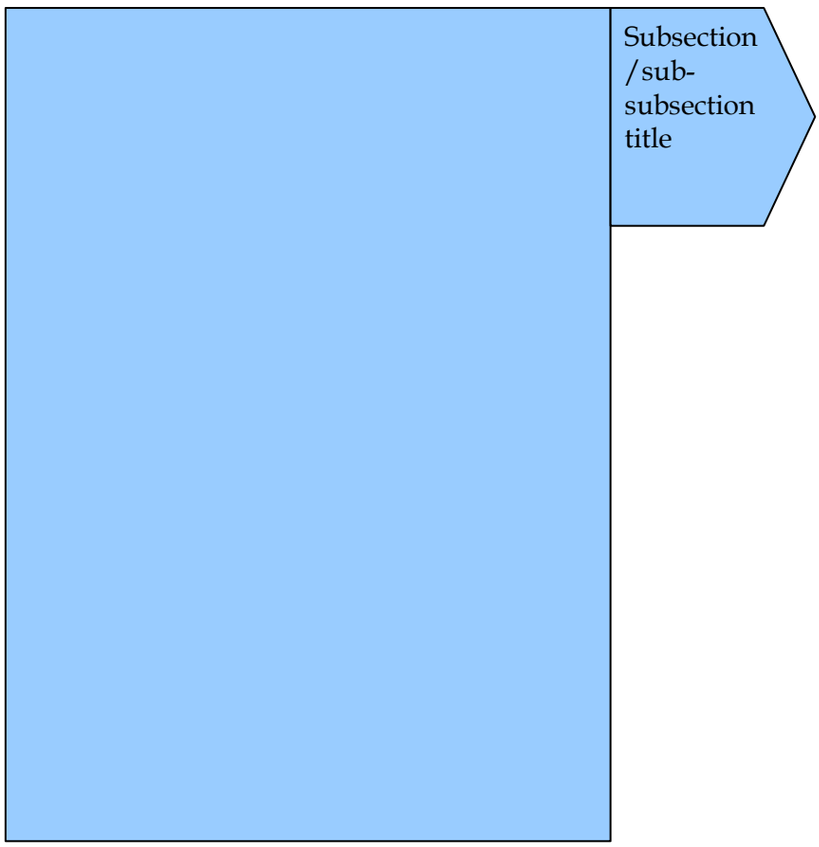
PENNY K. LUKITO

ANNEX V
REGULATION OF THE CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY OF THE REPUBLIC OF INDONESIA
NUMBER 24 OF 2017
ON
CRITERIA AND PROCEDURES FOR DRUG REGISTRATION

EXAMPLE OF DRUG REGISTRATION DOCUMENT

Drug Name	:
Dosage Form	:
Composition	:
Type and Size of Packaging	:
Applicant's Name	:
Manufacturer's Name	:

EXAMPLE OF DIVIDER PAPER



Drug Name	:
Dosage Form	:
Composition	:
Type and Size of Packaging	:
Applicant's Name	:
Manufacturer's Name	:

SECTION I:
ADMINISTRATIVE DOCUMENTS

Ring binder.... from....

ENTIRE TABLE OF
CONTENTS

Drug Name	:
Dosage Form	:
Composition	:
Type and Size of Packaging	:
Applicant's Name	:
Manufacturer's Name	:

SECTION II:
QUALITY DOCUMENTS

Ring binder.... from....

Drug Name	:
Dosage Form	:
Composition	:
Type and Size of Packaging	:
Applicant's Name	:
Manufacturer's Name	:

SECTION III:
NON-CLINICAL DOCUMENTS

Ring binder.... from....

Drug Name	:
Dosage Form	:
Composition	:
Type and Size of Packaging	:
Applicant's Name	:
Manufacturer's Name	:

SECTION IV:
CLINICAL DOCUMENTS

Ring binder.... from....

CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY,

signed

PENNY K. LUKITO

ANNEX VI
REGULATION OF THE CHAIRPERSON OF INDONESIAN FOOD AND DRUG AUTHORITY OF THE REPUBLIC OF INDONESIA
NUMBER 24 OF 2017
ON
CRITERIA AND PROCEDURES FOR DRUG REGISTRATION

ADMINISTRATIVE DOCUMENTS

1. Cover Letter.
2. Registration Form.
3. Applicant's Statement.
4. Certificates and Other Administrative Documents.
   - 4.1. Local Drugs
     - 4.1.1. Pharmaceutical Industry License.
     - 4.1.2. Valid GMP certificate for registered dosage form.
     - 4.1.3. GMP Certificate of Active Pharmaceutical Ingredients manufacturer.
     - 4.1.4. The latest GMP inspection data and related changes are not later than two years issued by the Indonesian Food and Drug Authority.
   - 4.2. Licensed Drugs.
     - 4.2.1. Pharmaceutical Industry License or supporting documents with sufficient evidence for research bodies/institutions as licensors.
     - 4.2.2. Pharmaceutical Industry License as license acceptor.
     - 4.2.3. GMP Certificate of Pharmaceutical Industry licensees that is still valid for the dosage form registered.
     - 4.2.4. GMP Certificate of Active Pharmaceutical Ingredient manufacturer.
     - 4.2.5. License Agreement.
   - 4.3. Local Contract Drugs
     - 4.3.1. Pharmaceutical Industry License of Applicants or Contract Givers.
     - 4.3.2. Pharmaceutical Industry License as Contract Acceptor.
     - 4.3.3. GMP Certificate of Pharmaceutical Industry held by Applicants or Contract Givers which is still valid.
     - 4.3.4. GMP Certificate of Contract Acceptor Pharmaceutical Industry which is still valid according to the dosage form of the contracted Drugs.
     - 4.3.5. GMP Certificate of Active Pharmaceutical Ingredients manufacturer.
     - 4.3.6. Contract Agreement,
   - 4.4. Export Only Drugs.
     - 4.4.1. Pharmaceutical Industry License.
     - 4.4.2. Applicant's GMP Certificate.

4.4.3. GMP certificate or other equivalent documents from the manufacturer according to the registered dosage form (for exported Imported Drugs).

4.4.4. GMP Certificate of Active Pharmaceutical Ingredients manufacturer.

4.5. Imported Drugs.

4.5.1. Pharmaceutical Industry License of manufacturers and Applicants.

4.5.2. Appointment letters from the pharmaceutical industry or overseas product owners are excluded for Applicants who are affiliates of the parent company.

4.5.3. Certificate of Pharmaceutical Product (CPP) or any other equivalent documents from the manufacturing country and/or country where the batch release certificate is issued (if necessary).

4.5.4. A valid GMP certificate from the manufacturer for the registered dosage form or other equivalent documents (including the GMP certificate of the manufacturer of Active Pharmaceutical Ingredientsfor Biological Products).

4.5.5. The latest GMP inspection data and related changes not later than 2 (two) years issued by a local Drug regulatory authority and/or another country's Drug regulatory authority.

4.5.6. GMP Certificate of Pharmaceutical Ingredients manufacturer.

4.5.7. Import justification.

4.5.8. Proof of balance of export and import activities (if necessary).

5. Pre-registration Results

6. Receipt/Proof of Payment.

7. Other Documents.

CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY,
signed.

PENNY K. LUKITO

ANNEX VII
REGULATION OF THE CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY OF THE REPUBLIC OF INDONESIA
NUMBER 24 OF 2017
ON
CRITERIA AND PROCEDURES FOR DRUG REGISTRATION

QUALITY DOCUMENTS

The format in this guide applies to New Registration and Variation Registration which include New Drugs, Biological Products, and Generic Drugs. The quality documents in this guide only show the structure and place where the information mustbe included. The type and scope of supporting data refers to the guidelines/provisions that apply nationally and internationally such as Pharmacopoeia, ICH Guidelines, and others. Requirements for Drugs with New Chemical Entity and Biological Products may refer to the ICH Guidelines or other related guidelines.

Quality documents consist of:

1. Subsection A :Quality Overall Summary/QOS
2. Subsection B :Body of Data

SUBSECTION A :QUALITY OVERALL SUMMARY

Quality Overall Summary (QOS) is a summary according to the scope and format of the complete body of data. The information, data, or justification contained in the QOS must be consistent with the complete body of data submitted.

QOS must include an appropriate summary of information from each subsection of the complete quality document QOS must also include an explanation of the main critical parameters of the quality of the Drugs and justification if there is a procedure deviation from the applicable guidelines QOS must contain an integrated explanation regarding the relationship between the information contained in the body of data and supporting information from other sections. For example, the relationship between data on impurities in Active Pharmaceutical Ingredientsand the results of toxicology studies.

In general, the information contained in the QOS does not exceed forty pages (excluding tables and figures). For Biological or Drug Products manufactured using more complex processes, the information contained in the QOS may be more but not exceeding eighty pages (excluding tables and figures).

The order and information listed in QOS are as follows:

S ACTIVE PHARMACEUTICAL INGREDIENTS

S1 General Information
Summary of information from S1 subsection B.

S2 Manufacturing Process and Source of Active Pharmaceutical Ingredients
Summary of information from S2 subsection B, include:
- Manufacturer's name and address.
- Summary of the manufacturing process and process control. Biological Products must include information ranging from cell banks, including cell culture, harvesting, purification and reaction modification, filling, storage and shipping conditions.

- Control over all materials (including starting materials, solvents, reagents, catalysts) used in the manufacture of Active Pharmaceutical Ingredients, including materials derived from Biological Products.
- Control of critical steps and intermediate substances, including stability data that supports storage conditions for Biological Products.
- Process validation and/or study and evaluation for sterilization and aseptic processes.
- Description and development history of the manufacturing process as described in S2.2.

S3 Characterization

New Chemical Entity:

Confirmation of structures based on synthesis routes and spectral analysis, as described in S3.1.

Biological Products:

Description on primary, secondary, and higher order structures, and information on biological activity, purity, and immunochemical properties (if necessary), as described in S3.2.

New Chemical Entity and Biological Products:

Summary of impurities monitored or tested during or after the manufacture of Active Pharmaceutical Ingredients, as described in S3.2.

Generic Drugs:

Justification from pharmacopeia requirements or appropriate information from the manufacturer.

S4 Specifications and Analytical Methods for Active Pharmaceutical Ingredients

A brief description of the justification for the determination of specifications, methods of analysis, and validation.

The specifications described in point S4.1 subsection B must be included, likewise, if there is a summary table of the batch analysis results included in point S4.4.

Generic Drugs:

Justification from pharmacopeia requirements or appropriate information from the manufacturer.

S5 Reference Standards

The information from point S5 subsection B (in table form, where appropriate) must be included.

Generic Drugs:

Reference standards used are in accordance with the Pharmacopoeia or equivalent information from the manufacturer.

S6 Specifications and Testing Method of Container Closure System

Brief description and discussion in point S6 subsection B must be stated.

S7 Stability

This section must include a summary of the studies conducted (testing conditions, batches, analytical methods) and a brief discussion of the study results and conclusions, proposed storage conditions, retest periodorshelf life if relevant.

Post approval stability test protocols and commitments to monitor stability as stated in item P8 subsection B need to be included.

Summary of stability test results in the form of a table with a graphical overview if necessary.

Generic Drugs:

The justification for setting a retest date or shelf life may refer to literature.

P DRUGS

P1 Description and Formula

The information in point P1 of subsection B and composition must be included in this section.

P2 Product Development

Discussion of information and data from point P2 subsection B, including information from development studies, components of Drug Products, Finished Product, development of manufacturing processes, container closure systems, microbiological attributes, specifications and packaging testing systems, and compatibility must be included.

Generic Drugs:

Justification can use literature data.

P3 Manufacturing Process

Information from point P3 of subsection B, including:

- Manufacturer information for each step of manufacture.
- Name and number of Active Pharmaceutical Ingredients and Excipients.
- A brief description of critical step manufacturing and control processes and intermediate products aimed at producing consistent routine production and quality products.
- A brief description of the process validation results as described in point P3.4 subsection B.

P4 Specifications and Testing Methods for Excipients

The summary of Excipient quality as described in point P4 of subsection B needs to be included.

Generic Drugs:

According to the requirements of Pharmacopeia or equivalent information from the manufacturer.

P5 Specifications and Testing Methods for Drugs

A summary of the justification for the determination of specifications, analysis procedures, and validations and the characterization of impurities must be included.

Specifications listed in point P5.1 subsection B and the summary of the batch analysis results listed in point P5.4 subsection B must be included.

Generic Drugs:

Characterization of impurities and specifications of the Drug according to the requirements of Pharmacopoeia or equivalent information from the manufacturer.

P6 Reference Standards

Information from point P6 subsection B (if appropriate can be in the form of a table), need to be included.

Generic Drugs:

According to the requirements of Pharmacopoeia or equivalent information from the manufacturer.

P7 Specifications and Testing Method for Container Closure System

A brief description of the information contained in point P7 subsection B and discussion must be included.

P8 Stability

A summary of the studies conducted (test conditions, tested batches, and analysis methods), a brief description of the results of the stability study as well as analysis of the data and its conclusions, must be stated.

Conclusions about storage conditions and shelf life and storage conditions after the packaging is opened (if necessary) must be stated.

A summary of the results of the stability study in the form of tables and/or charts of point P8 subsection B if any, needs to be included.

Post-approval stability test protocol Registration and commitments to monitor stability as stated in point P8 subsection B need to be included.

P9 Equivalence Data

A brief description of the dissolution test (in vitro) and the bioequivalence study (in vivo), if required.

SUBSECTION B: QUALITY DOCUMENTS

S ACTIVE PHARMACEUTICAL INGREDIENTS

S1 General Information

S1.1 Nomenclature

- International Nonproprietary Name Modified (INNM).
- Pharmacopeia Name if relevant.
- Registration number of Chemical Abstract Service (CAS).
- Laboratory code (if any).
- Chemical name.

S1.2 Chemical Formulas

New Chemical Entity:
Structural formulas, including relative and absolute stereochemistry, molecular formulas, and relative molecular mass, must be indicated.

Biological Products:
The schematic sequence of amino acids indicating the site of glycosylation or modification of another post-translational and relative molecular mass, should be indicated if any.

Generic Drugs:
According to the requirements of Pharmacopeia or other information from the manufacturer.

S1.3 General Characteristics

Physicochemical properties or other relevant properties of Active Pharmaceutical Ingredient including biological activities for Biological Products must be listed.

References: ICH Guidelines, New Drugs: Q6A; Biological Products: Q6B.

S2 Manufacturing Process and Source of Active Pharmaceutical Ingredients

S2.1 Manufacturer

Full name and address including the city and country of the Active Pharmaceutical Ingredient manufacturer need to be listed.

S2.2 Description and Control of Manufacturing Process

Description of the process of manufacturing Active Pharmaceutical Ingredients that includes information on the manufacturing process and control over the manufacturing process needs to be included.

New Chemical Entity:

- A schematic flow diagram of the synthetic process(es) should be provided that includes molecular formulas, weights and yields, chemical structures of starting materials, intermediates, reagents and Active Pharmaceutical Ingredients reflecting stereochemistry, and identifies operating conditions and solvents.
- A sequential procedural narrative of the manufacturing process that provides quantities of raw materials, solvent, catalysts and reagent reflecting the representative batch scale, and includes process controls, equipment and operating conditions, such as temperature, pressure, pH, time etc.
- Alternative process should be explained and described with the same level of details as the primary process. Reprocessing steps should be identified and justified

Biological Products:

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.
Reference: ICH Guidelines: Q5A, Q5B and Q6

S2.3 Control of Material

Material used in the manufacture of the Active Pharmaceutical Ingredients (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process.

Information on the quality and control of these materials should be provided. Information demonstrating that materials (including biologically-sourced materials, e.g., media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically-sourced materials, this can include information regarding the source, manufacture, and characterization.

References: ICH Guidelines, New Drugs: Q6A; Biological

Products: Q6B.

Biological Products:

- Control of source and starting materials of biological Origin. Summaries of viral safety information for biologically -sourced materials should be provided.
- Source, history and generation of the cell substrate.
  Information of the source of the cell substrate and analysis of the expression construct used to genetically modify cells and incorporated in the initial cell clone used to develop the Master Cell Bank should be provided as described in Q5B and Q5D.
- Cell banking system, characterization and testing.
  Information on the cell banking system; quality control activities and cell line stability during production and storage (including procedures used to generate the Master and Working Cell Bank(s)) should be provided as described in Q5B and Q5D.

Reference ICH Guidelines: Q5A, Q5B, Q5C, and Q5D

S2.4 Controls of Critical Steps and intermediates

Critical steps: tests and acceptance criteria with justification, including experimental data, performed at a critical steps of the manufacturing process to ensure that the process is controlled.

Intermediates: specifications and analytical method (if any), for intermediates obtained during the process.

References: ICH Guidelines Q6A, Q6B,

Addition to Biological Products: stability data that supports storage conditions.

References: ICH Guidelines Q6A, Q6B, Biological Products: Stability data supporting storage conditions.

References: ICH Guidelines Q5C.

S2.5 Process validation and/or evaluation

Process validation and/or evaluation studies for sterilization and aseptic processes should be included.

Biological Products:

Sufficient validation information and validation evaluation to prove that the manufacturing process (including the reprocessing steps) is in accordance with the purpose and for the selection of appropriate critical process control (operational parameters and during the manufacturing process/in-process test) and its limitations for critical manufacturing steps (e.g., cell culture, harvesting, purification, and modification).

Information should include a description of the study plan as well as the results of the analysis and conclusions of the study. Validation of analytical methods and determination of levels should be compared, as part of the justification of the selection of critical process controls and their limitations.

Studies of the removal or inactivation of viral contaminants in the manufacturing process should be submitted.
References: ICH Guidelines Q5A, Q5D, Q6B.

S2.6 Manufacturing Process Development

New Chemical Entity:

Description and discussion of significant changes to the manufacturing process and manufacture site for Active Pharmaceutical Ingredients used in nonclinical trial batches, clinical trial batches, pilot batches, and if any, manufacture scale batches.

References: ICH Guidelines: Q3A

Biological Products:

History of the development of the manufacturing process as described in point S2.2. Description of changes made to the manufacture of Active Pharmaceutical Ingredient batches used as support for Registration (e.g., nonclinical and clinical trials), including changes in critical processes or equipment. The reasons for the changes should be explained including relevant information on the manufacture of Active Pharmaceutical Ingredient batches during development, such as batch numbers, batch size of manufacture and use (e.g. stability, nonclinical comparing materials) associated with the change.

Significant changes should be assessed by evaluating the potential to the quality impact of Active Pharmaceutical Ingredients (and/or intermediate compounds, if any). For significant changes in the manufacturing process, there must be data from the analysis test compared to the associated Active Pharmaceutical Ingredients. Discussion should include justification of test selection and evaluation of test results.

Clinical and nonclinical trials in other modules may be included to complete the evaluation of the effect of manufacturing process changes on Active Pharmaceutical Ingredients and Related Drugs.

References: ICH Guidelines Q6B.

S3 Characterization

S3.1 Elucidation of the structure and Characteristic

New Chemical Entity:

Confirmation of structures based on synthesis routes and spectrum analysis. Information on the potential occurrence of isomerism, stereochemical identification, or potential for the formation of polymorphs should be included.

References: ICH Guidelines Q6A.

Biological Products:

A detailed description of primary, secondary, and higher order structures, as well as information on biological activity, purity, and immunochemical properties (if relevant).

References: ICH Guidelines Q6B.

Generic Drugs, Major Variations, Minor Variations:

Pharmacopoeia requirements or other information from the manufacturer.

S3.2 Impurities

Information on impurities should be stated.

References: ICH Guidelines Q3A, Q3C, Q5C, Q6A, and Q6B.

Generic Drugs:

Pharmacopoeial requirements or other information from the manufacturer.

S4 Specifications and Testing Methods for Active Pharmaceutical Ingredients

S4.1 Specifications

Detailed information on specifications, tests, and acceptance criteria for Active Pharmaceutical Ingredients need to be included.

References: ICH Guidelines, New Drugs: Q6A.

Biological Products:

Sources, including animal species, types of microorganisms, etc. should be specified.

References: ICH Guidelines Q6B.

Generic Drugs, Major Variations, Minor Variations:

Active Pharmaceutical Ingredient Specifications according to Pharmacopoeia. Specifications for Active Pharmaceutical Ingredients that do not refer to Pharmacopoeia must be stated whether based on Certificate of Analysis (CoA) from the manufacturer or based on testing by the Applicant.

S4.2 Analytical procedures

The analytical procedures used for testing for Active Pharmaceutical Ingredients must be detailed to enable

reproducible testing by another laboratory.

References: ICH Guidelines, New Drugs: Q2A; Biological Products: Q6B.

Generic Drugs, Major Variations, Minor Variations:

Pharmacopeia Requirements or other information from the manufacturer.

S4.3 Validation of Analytical Procedures

Analytical validation information including experimental data on the analytical methods used for testing the Active Pharmaceutical Ingredients needs to be included.

Validation parameters that must be considered are selectivity, precision (intermediate precision repetition and reproducibility), accuracy, linearity, range, quantitation limit, detection limit, robustness, and system suitability test.

References: ICH Guidelines, New Drugs: Q2A and Q2B; Biological Products: Q6B.

Generic Drugs, Major Variations, Minor Variations:

Required only for non-Pharmacopoeial methods.

References: ASEAN Guideline for Validation of Analytical Procedure.

S4.4 Batch Analysis

A description of the batch analysis and analysis results need to be included. References: ICH Guidelines, New Drugs: Q3A, Q3C and Q6A; Biological Products: Q6B.

S4.5 Specification justification

The justification for the determination of the Active Pharmaceutical Ingredient specification needs to be stated.

References: ICH Guidelines, New Drugs: Q6A; Biological Products: Q6B.

S5 Reference Standards

Information on the quality of reference substances or materials used for testing of Active Pharmaceutical Ingredients needs to be stated.
References: ICH Guidelines, New Drugs: Q6A; Biological Products: Q6B.

Generic Drugs, Major Variations, Minor Variations:

Pharmacopeia Requirements or other information from the manufacturer.

S6 Specification and Testing of Container Closure System

New Drugs and Biological Products:

In order to include a description of the packaging system, including the identity of the primary packaging components and their specifications. Specifications for each of these components should include description and identification (critical measurements and

drawings where appropriate). For non-Pharmacopoeial methods with appropriate validation.

For non-functional secondary packaging components (which are not in direct contact with the product), a brief description is sufficient, while for functional secondary packaging components, additional information is required for these components.

Things that need to be considered in the selection of packaging such as packaging materials, ability to protect Active Pharmaceutical Ingredients against moisture and light, compatibility between packaging materials and Active Pharmaceutical Ingredients include interactions between Active Pharmaceutical Ingredients and packaging, leaching and/or safety of packaging components.

S7 Stability

Stability Summary and Conclusions

It is necessary to provide a summary of the studies conducted, the study protocols and results. The summary shall include the study results, for example the results of forced degradation and stress condition, including the conclusions of storage conditions and the date of retest or shelf life.

References: ICH Guidelines Q1A (R2), Q1B, and Q5C.

Post-approval Stability Protocols and Stability Commitments

Post approval stability testing protocols and stability commitments.

References: ICH Guidelines Q1A (R2) and Q5C.

Stability data

The results of the stability testing (for example, the results of the forced degradation study and stress conditions) outlined in the form of tables, charts, or narratives, by including information on the analytical procedures used and the validation of these procedures according to the specified format.

References: ICH Guidelines Q1A (R2), Q1B, Q2A, Q2B, and Q5C.

<u>Generic Drugs, Major Variations, Minor Variations:</u>

Stability data from the manufacturer or appropriate information.

P DRUGS

P1 Description and Formula

Description and composition of drugs must be stated, such as:

- Dosage form;
- Complete composition, quantity of each raw material in one production batch (including overage, if any), function of each raw material, and quality reference used (for example Pharmacopoeial monograph or manufacturer's specifications);
- Description of the solvents used for reconstitution; and
- Types of packaging used for Drugs and reconstituted solvents, if required.

References: ICH Guidelines, New Drugs: Q6A; Biological Products: Q6B.

P2 Product Development

P2.1 Informationon Development Studies

Drugs with New Chemical Entity and Biological Products:
Product Development Division provides information and data on the results of development studies conducted to ensure that the dosage form, formulation, manufacturing process, container closure system, microbiological attributes, and methods of administration are in accordance with the registered Drug intended use. Such studies differ from routine testing carried out according to Drug specifications. This section should also identify and describe the formulation and process attributes (clinical parameters) that can affect batch reproducibility, product performance/efficacy, and Drug quality. Supporting data and specific study results or information from published literature can be included as an appendix. Additional supporting data can be used as a relevant reference for nonclinical sections.

References: ICH Guidelines, New Drugs: Q6A; Biological Products: Q6B.

P2.2 Component of Drug Product

P2.2.1 Active Pharmaceutical Ingredients

Drugs with <u>New Chemical Entity</u> and Biological Products:

The compatibility of the Active Pharmaceutical Ingredients with Excipients should be explained. In addition, the physicochemical characteristics (e.g. moisture content, solubility, particle size distribution, polymorphs or solid form) of the Active Pharmaceutical Ingredients which can affect the quality of the Drugs should be described in this section. It is the same for combination preparations.

Compatibility of Active Pharmaceutical Ingredient Drugs with Excipients and physicochemical characteristics of Active Pharmaceutical Ingredients that can affect the quality of Drugs such as moisture content, solubility, particle size distribution, polymorphs, or solid form should be described in this section. It is the same for combination preparations.

<u>Generic Drugs, Major Variations, Minor Variations:</u>

Information according to literature data.

P2.2.2 Excipients

Selection of Excipients as listed in point P1, concentrations and characteristics that affect the appearance of Drugs, should be explained according to their respective functions.

<u>Generic Drugs, Major Variations, Minor Variations:</u>

Information according to literature data.

P2.3 Finished product

P2.3.1 Formulation Development

Summary of information on the development of The Drug Formula should consider how to administer Drugs according to their intended use. The difference between clinical formulations and formulations (e.g. Composition) as mentioned in point P1 and P2 should

be explained. The results of comparable (if required) in vitro (e.g. dissolution tests) andin vivo (e.g. bioequivalence) comparable studies should be described.

P2.3.2 Overages

Overages in the formulation listed in point P1 should be described.

P2.3.3 Physicochemical and Biological Properties

It is necessary to list all relevant drug parameters such as pH, ionic bonding strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, flow properties, biological activities or potential and immunological activities.

P2.4 Manufacturing Process Development

The selection and optimization of the manufacturing process listed in point P3.2 especially at the critical step should be explained. The method of sterilization should be explained and given its justification if necessary.

Differences between the manufacturing processes used to produce pivotal clinical batches and the processes mentioned in point P3.2 that can affect the efficacy of thefinished product needs to be included.

Generic Drugs: refers to P3.2.

P2.5 Container Closure System

The suitability of the container closure system used for storage, transportation (shipping), and use of Drugs shall be explained. Discussion should consider (e.g selection of packaging materials, protection against the influence of moisture and light, compatibility between packaging materials and drugs including sorption to container, leaching, safety of material and of construction, and accuracy of the dosage of the devices used as part of the finished product.

P2.6 Microbiological Attributes

Microbiological attributes of the preparations need to be listed including the rationale for not performing microbial limit tests on non-sterile preparations, selection and testing of the effectiveness of preservatives in Drugs containing preservatives, if necessary.

For sterile preparations, the integrity of the container closure system into prevent microbial contamination should be included.

P2.7 Compatibility

Compatibility of finished product with solvents for reconstitution or compatibility of finished product with packaging/medical devices used, indicated by the occurrence of sediment in the solution, interaction of finished product with injection vessels, and finished product stability information are included to support information for labelling

Generic Drugs, Major Variations, Minor Variations:

Literature data can be used.

P3 Manufacturing Procedures

P3.1 Drug Manufacturers

Must include the name, address, and information of the person in charge of each production facility, including the Contract Giver or other production facilities involved in the manufacturing and testing process.

P3.2 Batch Formula

The formula must include the name/quantity of Active Pharmaceutical Ingredients and Excipients used including materials lost during the manufacturing process.

- Quantity of materials (g, kg, Liters, etc.).
- Overage: supporting data and overage justification must be included.
- The amount per batch and the total unit of dosage should be mentioned.
- Description of all steps involved in the manufacture of dosage form.

References: ICH Guidelines, Biological Products: Q6B.

P3.3 Manufacturing Process and Process Control.

The flowchart of the manufacturing process should be included by describing each step of the manufacturing process and showing at which step the materials are used. Supervision is carried out at a critical step on intermediate products and Finished Products.

- The full description of the manufacturing process should include in detail all the essentials at each step of the manufacturing process.
- For sterile preparations, the description includes the preparation and sterilization of components (e.g., containers, closure, etc.).

P3.4 Control of Critical Steps and Intermediates

Critical steps: Testing and acceptance criteria (with justification, including experimental data) performed at a critical step of the manufacturing process to ensure that the process is controlled.

Intermediates: Information on quality and control of intermediates during the manufacturing process.

References: ICH Guidelines Q2A, Q2B, Q6A, and Q6B.

P3.5 Process and/or Report Validation

Description, documentation, and results of validation studies from critical steps or determination of critical assays used in the manufacturing process should be submitted (For example, validation of sterilization processes or aseptic or filling processes).

References: ICH Guidelines, New Drugs: Q6A; Biological Products: Q6B.

Generic Drugs, Major Variations, Minor Variations:

ASEAN Guideline on process validation

P4 Specifications and Testing Methods for Excipients

P4.1 Spesifications

Excipient Specifications.

References: ICH Guidelines, New Drugs: Q6A; Biological Products: Q6B. Generic Drugs, Major Variations, Minor Variations:

According to the requirements of Pharmacopeia or other information from the manufacturer.

P4.2 Analytical Procedures

The analytical procedures used for Excipient testing is listed if necessary

References: ICH Guidelines, New Drugs: Q2A;

Biological Products: Q6B.

Generic Drugs, Major Variations, Minor Variations:

According to the requirements of Pharmacopeia or other information from the manufacturer.

P4.3 Excipients of animals and/or human origin

For Excipients of animal and/or human origin, there must be information on adventitious agents (e.g., sources, specifications, descriptions of testing performed, viral safety data).

References: ICH Guidelines, New Drugs: Q5A, Q5D; Biological Products: Q6B.

Generic Drugs, Major Variations, Minor Variations:

According to the requirements of Pharmacopeia or other information from the manufacturer.

P4.4 Novel Excipients

Detailed information on manufacture, characterization, and control which can be used to support nonclinical or clinical safety data.

P5 Specification and Testing Methods for Finished Products

P5.1 Specifications

specifications for finished product should be provided.

References: ICH Guidelines, New Drugs: Q6A; Biological Products: Q6B.

P5.2 Analytical Procedures

The analytical procedures used for Drug testing should be provided.

References: ICH Guidelines, New Drugs: Q2A; Biological Products: Q6B.

P5.3 Analytical Method Validation Report

Analytical validation information including experimental data for the analytical methods used for testing Finished product needs to be included.

References: ICH Guidelines, New Drugs: Q2A and Q2B; Biological Products: Q6B.

Generic Drugs, Major Variations, Minor Variations:

Required for Non-pharmacopoeial method only. However, verification for the applicability of pharmacopeia method used is required.

References: ASEAN Guideline for validation of analytical procedure.

P5.4 Batch Analysis

The description of the batch and the results of the

batch analysis need to be included.

Biological Products:

Descriptions (including batch size, origin and usage) and test results of all relevant batches (e.g. non-clinic, pilots for clinical trials, scale-up, and if there are batches of production scales) used to establish specifications and evaluate consistency in the manufacturing process need to be included.

References: ICH Guidelines, New Drugs: Q3A, Q3C and Q6A; Biological Products: Q6B; Generic Drugs: refer to P3.4, P3.2.

Generic Drugs and Major Variations:

A summary of the batch analysis table with the corresponding charts needs to be included.

P5.5 Characterization of Impurities

Characterization of impurities should be provided in this section, if the information has not been provided in point S3.2.

References: ICH Guidelines, New Drugs: Q3B and Q6A; Biological Products: Q6B.

Generic Drugs, Major Variations, Minor Variations:

Pharmacopeia Requirements or other information from the manufacturer.

P5.6 Justification of Specification

Justification of the determination of Finished Product specifications should be provided.

References: ICH Guidelines, New Drugs: Q3B and Q6A; Biological Products: Q6B.

Generic Drugs, Major Variations, Minor Variations:

Pharmacopeia Requirements or other information from the manufacturer.

P6 Reference Standards

Information on the quality of reference standards used for Finished product testing should be provided.

References: ICH Guidelines, New Drugs: Q6A; Biological Products: Q6B. Generic Drugs, Major Variations, Minor Variations:

According to the requirements of Pharmacopeia or appropriate information from the manufacturer.

P7 Specifications and Testing Methods for Container Closure

Description of the container closure system should be provided, including the identity of the component material and the specifications of the primary and secondary packaging. These specifications should include description and identification (corresponding dimensions and drawings).

A brief description of nonfunctional secondary packaging components is included (e.g. those that neither provide additional protection nor serve to deliver the product).

For functional secondary packaging components, there should be additional information in detail.

The information stated must match in P2.

P8 Stability

Evidence is required to demonstrate that the product is stable, meets the Finished Product specifications throughout the proposed shelf life , where no significant amount of finished product decomposition occurs during this period, and demonstrate no change in the potency and effectiveness of preservatives.

Stability Summary and Conclusion

Finished Product with New Chemical Entity and Biological Products:

All criteria that follow the ICH Guidelines are acceptable except the long-term storage conditions must be at 30^{0}C, 75% RH. ability of the packaging system to provide protection against moisture should be considered.

References: ICH Guidelines Q1A (R2), Q1B, Q2A, Q2B, and Q5C. Generic Drugs, Major Variations, Minor Variations:

ASEAN Guideline on Stability Study of Drug Product.

Post approval Stability Protocols and Stability Commitment

Post approval stability protocols and stability commitment should be provided

References: ICH Guidelines, New Drugs, Biological Products: Q1A (R2) and Q5C.

Generic Drugs:

ASEAN Guideline on Stability Study of Drug Product.

Stability data

Results of stability studies should be presented in an appropriate format (e.g., tabular, graphical, narrative) including information on the analytical methods used to generate data and validation of those methods.

References:

- ASEAN Guideline on Stability Study of Drug Product.
- ASEAN Guideline on Validation of Analytical Procedure.

P9 Equivalence Study

Requirements for Generic Drugs and Major Variations:

The type of study conducted, the protocol used and the result of the studies should be presented in the study report. The type of study conducted should refer to Bioequivalence Test of the Indonesia FDA and the Guideline for Bioavailability and Bioequivalence Studies or WHO Manual for Drug Regulatory Authority.

References:

- Guidelines for Bioequivalence Test of the Indonesian FDA.
- WHO, Regulatory Support Series No 5 "Bioequivalence Studies in Humans".
- ASEAN Guideline on Bioequivalence Study.

SUBSECTION C: REFERENCES

References must be included.

CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY,

signed.

PENNY K. LUKITO

ANNEX VIII
REGULATION OF THE CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY OF THE REPUBLIC OF INDONESIA
NUMBER 24 OF 2017
ON
CRITERIA AND PROCEDURES FOR DRUG REGISTRATION

NONCLINICAL DOCUMENTS

Nonclinical documents consist of Nonclinical Overview, Nonclinical Written and Tabulated Summaries, and Nonclinical Study Reports.

The main purpose of the Nonclinical Written and Tabulated Summaries is to provide a comprehensive and factual and comprehensive-synopsis of nonclinical study data. At the time of submission of registration (e.g. new Chemical Entity) nonclinical study documents must be submitted in the form of overview, nonclinical written and tabulated summaries, while nonclinical study report is only submitted if required. Nonclinical study documents are not required for Generic Drugs. Nonclinical documents for Biosimilar Products refer to the General Guidelines for Biosimilar Product Assessment.

SUBSECTION A: NONCLINICAL OVERVIEW

The Nonclinical Overview should provide integrated information analysis. The Nonclinical Overview does not exceed thirty pages.

1. General Aspects

   The Nonclinical Overview should include anintegrated and critical assessment of the pharmacological, pharmacokinetic, and toxicological evaluations of the Drug. Where Relevant guidance on the conduct of studies exist, these should be taken in consideration, any deviation from this guidances should be discussed and justified.

   The Nonclinical Overview should include a discussion on the nonclinical testing strategy. There should be a statement that the nonclinical studies submitted are in accordance with the Good Laboratory Practice (GLP). any association between nonclinical findings and quality characteristics of Drugs, clinical trial results, or effects seen with the related product should be indicated, as appropriate.

   Except for biotechnology-derived products, an assessment of impurities and degradants present in the Drug substance and products should be included along with what is known of their potential pharmacologic and toxicologic effect. This assessment should form part of the justification for proposed impurity limits of the Drug substances and products and be appropriately cross-referenced the quality documentation. The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the nonclinical studies and the product to be marketed should be discussed. For Biotechnology-derived Products, comparability of Material used in nonclinical and clinical studies and proposed for marketing should be accessed. If a Drug product includes a novel excipient an assessment , of the information regarding its safety should be provided.

The batch quality information of the Active Pharmaceutical Ingredients used in this study should be explained. If published scientific literature is used as a substitute for a study conducted by the Applicant, it should be supported by justification of the study design and differences in guidelines.

References in the Nonclinical Overview on the study matrix in the following format (Table X.X, Report/study number).

2. Content and Format Structure

Nonclinical Overview should be displayed in the following order:

Nonclinical Overview

1. Review of nonclinical study strategies.
2. Pharmacology.
3. Pharmacokinetics.
4. Toxicology.
5. Thorough Review and Conclusion.
6. Literature List.

Studies conducted to establish the pharmacodynamic effects, workings, and potential side effects of the Drug should be evaluated, and the meaning of the results should be considered.

Evaluation of pharmacokinetic, toxicokinetic, and metabolic data should include the analysis methods used, pharmacokinetic models, and the source of relevant parameters. Cross-consideration with pharmacological or toxicological studies may be required (e.g. impact of disease conditions, changes in physiology, antibodies, and consideration of toxicokinetic data). Any data inconsistencies should be explained. Interspecies comparison in metabolism and systemic exposure in animals and humans (AUC, C_{max}, and other parameters) needs to be explained. The limitations as well as the usefulness of nonclinical studies to predict the potential side effects of Drugs in humans should be a concern.

The onset of action, severity, and duration of toxic effects, and their relation to dose and degree of reversibility (or irreversibility), as well as differences related to species or sex should be evaluated and important signs should be explained especially regarding:

- Pharmacodynamics.
- Toxic signs.
- Causes of death.
- Pathological findings.
- Genotoxic activity - chemical structure of Active Pharmaceutical Ingredient compounds, how it works, and its relationship to known genotoxic compounds.
- Carcinogenic potential is associated with the chemical structure of Active Pharmaceutical Ingredient compounds, its relationship to known carcinogens, its genotoxic potential, and exposure data.
- Carcinogenic risk in humans – If there is epidemiological data, then such data should be considered.
- Fertility, embryofetal development, pre- and postnatal toxicity.

- Studies on young animals.
- As a result of use before and during pregnancy, during lactation, and during child development.
- Local tolerance.
- Other toxicity studies and/or studies to clarify specific problems.

Evaluation of toxicology studies should be prepared logically so that all relevant data explains a particular effect and/or phenomenon.

Extrapolating data from animals to humans should take into account:

- Species of animals used.
- The number of animals used.
- Drug administration route.
- Dosage used.
- Duration of treatment or duration of study.
- Dosage of No Observed Adverse Effect Levels (NOAEL) and toxic doses in animals, and related to the maximum recommended dose in humans. Tables or images describing this information should be included.
- The effects of Active Pharmaceutical Ingredients observed in nonclinical studies, their relationship to those expected in humans.

If an alternative test animal is used, its scientific validity must be explained.

A Thorough Review and Conclusion should clearly describe the properties of Drugs, as indicated in nonclinical studies, and be a reasonable conclusion that can support the safety of the product to be used clinically. Taking into account the pharmacological, pharmacokinetic, and toxicological results, the implications of nonclinical findings for the safety of Drug use in humans should be explained (as described in the Product Information).

SUBSECTION B: NONCLINICAL WRITTEN AND TABULATED SUMMARIES

1. Nonclinical Study Summaries

1.1 Introduction

These guidelines aim to help prepare a summary of pharmacology, pharmacokinetics, and nonclinical toxicology in the appropriate format.

The order and content of the Nonclinical Study Summary section are outlined below. A good document drafter focuses on meeting regulatory requirements. If necessary, Applicants may modify the format to make it easier to understand and evaluate the results.

If necessary, age-related and sex-related effects should be explained. Findings related to stereoisomers and/or metabolites should be listed. Consistent inclusion of units in nonclinical summaries will help with the evaluation process. Table inclusion to convert units may also be required.

In the Discussion and Conclusion section, inter-study and interspecies information should be integrated, and exposure to test animals should be related to human exposure to which the maximum dose will be used.

1.2 General Description

The Order of the Information Description in each section.

If anything, in vitro studies should precede in vivo studies. If several similar studies are summarized in the Pharmacokinetics and Toxicology section, they should be sorted by species, method of administration, and then the length of administration (starting with the shortest time).

The order of species is as follows:

- Mouse.
- Rat.
- Hamster.
- Other rodents.
- Rabbit.
- Dog.
- Primates other than humans.
- Other mammals.
- Other than mammals.

The route of Drug administration is sorted as follows:

- Methods of administration for use in humans.
- Oral.
- Intravenous.
- Intramuscular.
- Intraperitoneal.
- Subcutaneous.
- Inhalation.
- Topical.
- Others.

Use of Tables and Figures

Although Nonclinical Study Summaries consist mostly of narration, some information is more effective by using tables or figures. Tables and figures can be inserted between narratives or grouped at the end of each Nonclinical Study Summary.

In the narration, the literature citation for written and tabulated summaries should be included in the following format (Table X.X. name/report/study)

Length of Nonclinical Study Summaries

Although there is no formal limit to the length of the Nonclinical Study Summary, it is recommended no more than 100 – 150 pages.

Sequence of Written and Tabulated Summaries

are Compiled in the following order:

- Introduction.
- Pharmacological summary.
- Matrix of pharmacological studies.
- Summary of pharmacokinetics.

- Matrix of pharmacokinetic studies.
- Toxicology summary.
- Matrix of toxicology studies.

2. Nonclinical Written and Tabulated Summaries

2.1 Introduction

The purpose of this section is to provide information to assessors about the Drug and its proposed clinical use. Such information should include:

- Brief information on the structure of the Drug (preferably, a diagram of the structure is also listed) and its pharmacological properties.
- Information on clinical indications, dosage, and proposed duration of use for the Drug.

2.2 Pharmacology

2.2.1 Summary

In the pharmacological summary, the data should be presented in the following order:

- A brief summary.
- Primary pharmacodynamics.
- Secondary pharmacodynamics.
- Safety pharmacology.
- Pharmacodynamics of Drug interactions.
- Discussions and conclusions.
- Tables and figures (can be listed here or in narration).

2.2.1.1 A brief summary

Important information from pharmacological studies should be summarized into two to three pages. This section should start with a brief overview of pharmacological data that should be looked into such as inclusion and/or exclusion of certain data (e.g. absence of test animal models).

2.2.1.2 Primary pharmacodynamics

Primary pharmacodynamic studies should be summarized and evaluated. If possible, it would be useful to relate the pharmacology of the Drug to existing data (e.g. selectivity, safety, potency) on other Drugs in its class.

2.2.1.3 Secondary pharmacodynamics

If any, secondary pharmacodynamic studies should be summarized by organ system and evaluated in this section.

2.2.1.4 Safety pharmacology

The safety pharmacological studies are summarized and evaluated in this section. In some cases, secondary pharmacodynamic studies can contribute to the evaluation of drug safety if the studies

predict or assess potential adverse Drug effects in humans. In such cases, these secondary pharmacodynamic studies should be considered together with the pharmacological safety studies.

2.2.1.5 Pharmacodynamics of Drug interactions

Once studies have been carried out, pharmacodynamic studies of drug interactions should be summarized.

2.2.1.6 Discussions and Conclusions

This section is to discuss pharmacological evaluation and to consider the significance of the results.

2.2.1.7 Tables and Figures

Tables and figures can be inserted between narrative summary or grouped at the end of each summary.

2.2.2 Pharmacology Study Matrix (see List of Study Matrix)

2.3. Pharmacokinetics

2.3.1 Summary

The Summary Sequence of Pharmacokinetics is as follows:

- A brief summary.
- Analysis Methods.
- Absorption.
- Distribution.
- Metabolism.
- Excretion.
- Pharmacokinetic of Drug interactions.
- Other pharmacokinetic studies.
- Discussions and conclusions.
- Tables and charts (can be listed here or in narration).

2.3.1.1. A Brief Summary

Important findings from pharmacokinetic studies should be briefly summarized in two or three pages. This section should begin with an overview of the scope of pharmacokinetic evaluation, with emphasis, for example, on whether the species and strains studied are the same as those used for pharmacological and toxicological evaluations, and whether the formulations used are the same or identical.

2.3.1.2. Analysis Methods

This section shall contain a brief summary of the analysis methods for biological samples, including the detection and quantification limits of an analytical procedure. If possible, data validation for analysis methods and the stability of biological samples are discussed

in this section. The potential impact of different analysis methods on the interpretation of the results should be discussed in the relevant sections below.

2.3.1.3. Absorption.

The following data should be summarized in this section:

- Absorption (rabsorption rate and speed, in vivo and in situ studies).
- Kinetic parameters, bioequivalence and/or bioavailability serum / plasma / blood pharmacokinetic studies).

2.3.1.4 Distribution

The following data should be summarized in this section:

- Tissue distribution studies.
- Protein binding and distribution in blood cells.
- Transfer studies into the placenta.

2.3.1.5 Metabolism (Interspecies Comparison)

The following data should be summarized in this section:

- The chemical structure and quantities of metabolites in biological samples.
- Possible metabolic pathways.
- Presystemic metabolism (early gastro intestinal /hepatic first-pass effect).
- In vitro metabolism was included in the P450 study.
- Enzyme induction and inhibition.

2.3.1.6 Excretion

The following data should be summarized in this section:

- Route and extent of excretion.
- Excretion in milk.

2.3.1.7 Pharmacokinetic of Drug Interactions.

Once studies have been carried out, the pharmacokinetic studies of non-clinical Drug interactions (in vitro and/or in vivo) should be briefly summarized in this section.

2.3.1.8 Other Pharmacokinetic Studies.

If studies have been carried out on non-clinical disease models (e.g. animals with renal impairment), they should be summarized in this section.

2.3.1.9 Discussions and Conclusions

This section is to discuss pharmacokinetic evaluation and consider the significance of the results.

2.3.1.10 Tables and Graphics

Narrative tables and charts can be included at appropriate points throughout the narrative summary. Alternatively tables and charts are included at the end of the summary.

2.3.2 Summary of the Pharmacokinetic Study Matrix in Matrix Format (see List of Study Matrix)

2.4. Toxicology

2.4.1 Summary

The order of the Toxicology Summary should be as follows:

- A brief summary.
- Single-dose toxicity.
- Repeated-dose toxicity.
- Genotoxicity.
- Carcinogenicity.
- Reproductive and developmental toxicity.
- Studies on young animals.
- Local tolerance.
- Other toxicity studies.
- Discussions and Conclusions.
- Tables and Charts (can be listed here or in narration).

2.4.1.1. A Brief Summary

Important findings from a toxicological study should be briefly summarized in a few pages (generally no more than six pages). In this section, the number of toxicological evaluations can be indicated using a table containing a list of the main toxicological studies (results do not have to be presented as in this table), for example:

Toxicology Program

Type and length of study	Administration methods	Species	Given compound *
Single-dose toxicity	po and iv	Mouse and rat	Parent Drug compound
Single-dose toxicity	po and iv	Rat and mouse	Metabolite X
Repeated-dose toxicity			
1 month	Po	Rats and dogs	Parent Drug compound
6 months	po	Rat	Parent Drug compound
9 months	po	Dog	Parent Drug compound
etc.			

* This column should be included only if the metabolite is studied.

The scope of the toxicological evaluation should be described in terms of its proposed clinical utility. Comments on the GLP status of the study should be provided.

2.4.1.2. Single-Dose Toxicity

Single-dose data should be summarized by species and administration methods. In some cases, it may be helpful to present the data in tabular form.

2.4.1.3. Repeated-Dose Toxicity (including supporting toxicokinetic evaluation)

Studies should be summarized by species, administration methods, and duration of administration, providing brief details of methodology and emphasis on important findings (e.g. nature and severity of target organ toxicity, relationship between dose (exposure) and/or response, and NOAEL). Studies other than the pivotal study, can be summarized in not too detail (the pivotal study is a definitive GLP study according to the ICH M3 guidelines).

2.4.1.4. Genotoxicity

The studies should be summarized in the following order:

- In vitro nonmammal cell system.
- In vitro mammalian cell system.
- In vivo mammalian systems (including supporting toxicokinetic evaluation).
- Other systems.

2.4.1.5. Carcinogenicity (including supporting toxicokinetic evaluation)

It should be explained why the study was selected and what was the basis for selecting a high dose. Each study should be summarized in the following order:

- Long-term studies (by species), including studies to determine the dose range that is not appropriate when included in the toxicity or pharmacokinetics section of repeated-doses.
- Short or medium term studies (including studies that determine the dose range that is not appropriate when included in the toxicity or pharmacokinetics section of repeated-doses).
- Other studies.

2.4.1.6. Reproductive and Developmental Toxicity (including dose range determination and supporting toxicokinetic evaluation)

The study should be summarized by providing a brief description of the methodology and emphasizing the key findings in the following order:

- Fertility and early embryonic development.
- Embryonic-fetal development.
- Prenatal and Postnatal Development.
- Studies in which offspring (young animals) are given the Drug and/or are further evaluated if such studies have been conducted.

If a modified study design is used, the subtitles must also be modified.

2.4.1.7. Local Tolerance.

Once a local tolerance study has been carried out, it should be summarized by species, administration methods, and duration of administration, providing a brief description of the methodology and emphasizing key findings.

2.4.1.8. Other Toxicity Studies (If any)

If other toxicity studies have been carried out, they should be summarized. Where appropriate, a rationale for conducting the study should be provided.

- Antigenisity.
- Immunotoxicity.
- Mechanistic studies (if not included elsewhere).
- Dependency.
- Study of metabolites.
- Study of impurities.
- Other studies.

2.4.1.9. Discussions and Conclusions

This section is to discuss the toxicological assessment and the significance of the results. It is recommended to use tables or figures to summarize this information.

2.4.1.10. Tables and Figures

Narrative tables and figures can be included at appropriate points throughout the narrative summary. Alternatively, tables and figures can be included at the end of the summary.

2.4.2. Summary of the Toxicology Study Matrix (seeList of Study Matrix)

3. Nonclinical Written and Tabulated Summaries

It is recommended that the summary table for nonclinical information in Common Technical Document (CTD) is created in a format that complies with these guidelines. Applicants may modify the format, if necessary, to provide the best possible presentation of the information and to assist in understanding the evaluation of results.

These guidelines are not intended to indicate what studies are required, but only to provide advice on how to tabulate the results of studies that have been conducted. If necessary, Applicants can add or remove some parts of the format. One study matrix format can contain the results of multiple studies. Alternatively, it can also list data from a single study in several study matrix formats.

The format proposed for the table in the nonclinical written and tabulated summaries is given in the List of study matrix. The study matrix list contains a standard format (templates) for use in creating tables. The default format contains notes that are italicized to provide guidance on its creation (information that is italicized should be deleted when the tables

are created). However, it remains the Applicant's responsibility to decide on the best way of presenting the data for each product. It should be noted that the written and tabulated summary review together with the summary is the overview of nonclinical information. The presentation of data using the standard format and the examples provided must still ensure the availability of sufficient information for the assessor and must provide a brief overview of the related information.

If studies on young animals have been carried out, a matrix should be made using a standard format appropriate for the type of study.

The table creation for the Nonclinical Written and Tabulated Summaries should follow the order of the Nonclinical Study Summary.

SUBSECTION C: NON-CLINICAL STUDY REPORT

Full report of non-clinical studies is not required unless deemed necessary[1]. This guideline provides an agreed format for the arrangement of non-clinical reports in the Registration Document Part III for registration to be submitted to the Indonesian FDA. These guidelines are not intended to indicate what studies are required, but only indicate an appropriate format for the non-clinical data that has been obtained.

A suitable placement for each individual test animal data is in the study report or as an annex to the study report.

1. Table of Contents of Non-clinical Study Reports

   The table of contents should list all Non-clinical Study Reports and include the location of each study report in the Registration Document part III. The table of contents for the Non-clinical Study Report must include all numerical items contained in the Registration Document part III to identify all the essential components of a Drug registration (e.g., 2.3.5.1 Fertility and early embryonic development) and continue until the summary of the study report. So, each study report must be identified in the table of contents.

   Illustration of Part of Table of Contents of Non-clinical Study Report

   1.1. Repeated-Dose Toxicity

   Aa-aaa study : 30 days of repeated-dose toxicity study with Drug X in rats.

   Bb-bbb study : 6 months of repeated-dose toxicity study with Drug X in rats.

   Cc-ccc study : 30 days of repeated-dose toxicity study with Drug X in dogs.

   Dd-ddd study : 6 months of repeated-dose toxicity study with Drug X in dogs.

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[1] In other ASEAN member states, non-clinical study reports may not be required for registration of new Chemical Entity (NCE), biotechnology products, or other major variations if the originator product has been registered and approved for market in the reference countries.

1.2. Genotoxicity

1.2.1. In vitro
Ee-eee study: Ames Test with Drug X; etc.

2. Clinical Study

Study reports should be presented in the following order:

2.1 Pharmacology

2.1.1 Primary pharmacodynamics.
2.1.2 Secondary pharmacodynamics.
2.1.3 Safety pharmacology.
2.1.4 Pharmacodynamics of Drug interactions.

2.2 Pharmacokinetics

2.2.1 Analysis and validation method reports (if the reports are separate).
2.2.2 Absorption.
2.2.3 Distribution.
2.2.4 Metabolism (comparison between species).
2.2.5 Excretion.
2.2.6 Pharmacokinetic of Drug interactions.
2.2.7 Other pharmacokinetic studies.

2.3 Toxicology

2.3.1 Single dose toxicity (by species, administration methods).
2.3.2 Repeated-dose toxicity (based on species, administration methods, duration of administration, including supporting toxicokinetic evaluation).
2.3.3 Genotoxicity
2.3.3.1 In vitro.
2.3.3.2 In vivo (including supporting toxicokinetic evaluation).
2.3.4 Carcinogenicity (including supporting toxicokinetic evaluation)
2.3.4.1 Long-term studies (by species, including studies to determine the dose range that cannot be included in the toxicity or pharmacokinetics of repeated-doses).
2.3.4.2 Short or medium term studies (including studies that determine the dose range that cannot be included in the toxicity or pharmacokinetics of repeated-doses).
2.3.4.3 Other studies.
2.3.5 Reproductive and developmental toxicity (including studies to determine the dose range and adjunctive toxicokinetic evaluation. When a modified study design is used, the following subtitles should also be modified)
2.3.5.1 Fertility and early embryonic development.
2.3.5.2 Embryonic-fetal development.
2.3.5.3 Prenatal and postnatal development, including maternal function.
2.3.5.4 Studies in which offspring (young animals) are given the Drug and/or are further evaluated if such studies have been conducted.
2.3.6 Local Tolerance.
2.3.7 Other Toxicity Studies (if any)

2.3.7.1 Antigenisity.
2.3.7.2 Immunotoxicity.
2.3.7.3 Mechanistic studies (if not included elsewhere).
2.3.7.4 Dependency.
2.3.7.5 Metabolites.
2.3.7.6 Impurities.
2.3.7.7 Other studies.

SUBSECTION D: REFERENCES

The references used are determined in accordance with the Vancouver Declaration, 1979 "Uniform Requirements for Manuscripts Submitted to Biomedical Journals", or the system used in "Chemical Abstracts". Copies of the important references mentioned in the non-clinical review must be included in this section. All references that are not yet given must be available upon request.

MATRIX: STANDARD FORMAT OF NONCLINICAL WRITTEN AND TABULATED SUMMARIES

2.2.2 Pharmacology
2.2.2.1 Pharmacology: a Overview
2.2.2.2 Primary pharmacodynamics*
2.2.2.3 Secondary pharmacodynamics*
2.2.2.4 Safety pharmacology
2.2.2.5 Pharmacodynamics of Drug interactions*

2.3.2 Pharmacokinetics
2.3.2.1 Pharmacokinetics: a Overview
2.3.2.2 Analysis methods and validation reports *
2.3.2.3 Pharmacokinetics: absorption after a single dose
2.3.2.4 Pharmacokinetics: absorption after repeated-doses
2.3.2.5 Pharmacokinetics: organ distribution
2.3.2.6 Pharmacokinetics: plasma protein binding
2.3.2.7 Pharmacokinetics: study in pregnant or nursing animals
2.3.2.8 Pharmacokinetics: other distribution study
2.3.2.9 Pharmacokinetics: metabolism In Vivo
2.3.2.10 Pharmacokinetics: metabolism In Vitro
2.3.2.11 Pharmacokinetics: possible metabolic pathways
2.3.2.12 Pharmacokinetics: induction/inhibition of drug-metabolizing enzymes
2.3.2.13 Pharmacokinetics: excretion
2.3.2.14 Pharmacokinetics: excretion into bile
2.3.2.15 Pharmacokinetics: drug interactions
2.3.2.16 Pharmacokinetics: others

2.4.2 Toxicology
2.4.2.1 Toxicology: a Overview
2.4.2.2 Toxicokinetics: a Overview of toxicokinetic studies
2.4.2.3 Toxicokinetics: a Overview of toxicokinetic studies
2.4.2.4 Toxicology: Drug Substance
2.4.2.5 Single-dose toxicity
2.4.2.6 Repeated-dose toxicity: a nonpivotal study
2.4.2.7 Repeated-dose toxicity: a nonpivotal study
2.4.2.8 Genotoxicity: in vitro
2.4.2.9 Genotoxicity: in vivo
2.4.2.10 Carcinogenicity.
2.4.2.11 Reproductive and developmental toxicity: a nonpivotal study
2.4.2.12 Reproductive and developmental toxicity: fertility and early embryonic development until implantation (pivotal)
2.4.2.13 Reproductive and developmental toxicity: effect on embryofetal development (pivotal)
2.4.2.14 Reproductive and developmental toxicity: effects on pre and postnatal development, including maternal (pivotal) function
2.4.2.15 Studies on young animals[a]
2.4.2.16 Local tolerance.
2.4.2.17 Other toxicity studies.

* : Study matrix summary is optional. Preferably in the form of narrative tables and figures with a Non-clinical Study Summary.
a : If studies on young animals have been carried out, it is necessary to create a matrix using a standard format appropriate to the type of study and is placed in Section 2.4.2.15.

The Common Technical Dossier - Nonclinical Study Data

2.2.2.1 Pharmacology Overview Test Drugs: *(1)*

Type of study	Test system	Method of administration	Test Facility	Study Number *(4)*	Location *(3)* Vol.	Pg
Primary pharmacodynamics *(2)*						
Secondary pharmacodynamics						
Safety pharmacology						
Pharmacodynamics of Drug interactions						

Note:
(1) International Nonproprietary Name (INN)
(2) There should be one line for each pharmacological report, in the same order as the CTD. Reports that include the GLP Compliance Statement should be identified in footnotes.
(3) The location of the Technical Report in the CTD should be indicated.
(4) Or No. Reports (on all tables)

2.2.2.4 Safety Pharmacology *(1)* Test Drugs: *(2)*

Organ Systems evaluated	Species/Strain	Method Administration	Dose[a] (mg/kg)	Gender and No. per group	Noteworthy Findings	Compliance to GLP	No. Studies (3)

Note: (1) All safety pharmacological studies should be summarized
(2) International Nonproprietary Name (INN)
(3) Or No. Reports (on all tables)
a - Single dose unless otherwise stated

2.3.2.1 Pharmacokinetics Review Test Drugs: *(1)*

Type of study	Test System	Method of administration	Test Facility	Studies Number	Location *(3)* Vol.	Pg
Absorption *(2)*						
Distribution						
Metabolism						
Excretory						
Pharmacokinetics of drug interactions						
Others						

Note: (1) International Nonproprietary Name (INN)

(2) There should be one line for each pharmacological report, in the same order as the CTD. Reports that contains the GLP Compliance Statement should be identified in footnotes.

(3) The location of the Technical Report in the CTD should be indicated.

2.3.2.3 Pharmacokinetics: Absorption after a single dose

Test drug: *(1)*

Location in CTD: Volume. Page
No study.

Species					
Gender (M/F)/number of animals *(4)*					
Feeding conditions					
Vehicle/formulations					
Method of administration					
Dose (mg/kg)					
Sample (e.g. blood, plasma, serum)					
Analyte					
Assay *(2)*					
Pharmacokinetic parameters					

Additional information *(3)*
Note*:*
(1) International Nonproprietary Name (INN)
(2) For example: HPLC, LSC with labeled compounds ^{14}C
(3) For example, brief narrative of results, differences in species, differences in sex, relevance to dose, or special comments.
(4) One column for each study conducted. By comparison, information on the maximum recommended dose in humans should be included.

2.3.2.4. Pharmacokinetics : Absorption after repeated dosing

Test Drug:

(Data can be tabulated as in 2.3.2.3 format (if applicable))

Format A

2.3.2.5 Pharmacokinetics: Organ distribution

Test Drug :
Location in

CTD: Vol. Page

No study.

Species:
Gender (M/F) Number of animals:
Feeding conditions:
Vehicle/Formulation:
Administration methods
Dose (mg/kg)
Radionuclides:
Specific activities:

Sampling Period:	Concentration (unit)					
	T (1)	T (2)	T (3)	T (4	T (5)	T ½
Tissue/organ						

Additional Information:

Alternative Format B:

2.3.2.5 Pharmacokinetics: Organ distribution

Test Drug:
Location in

CTD: Vol. Page

No study.

Species:
Gender (M/F) Number of animals:
Feeding conditions
Vehicle/formulations
Administration methods
Dose (mg/kg)
Radionuclides:
Specific activities:
Analyte/Assignment (unit)
Sampling time:

	Ct		Last Sampling Time		
Tissue/organ	Concentration	T/P [1)]	Concentration	T/P [1)]	time

AUC	t ½

Additional Information:

[1)](Tissue)/(Plasma)

2.3.2.6. Pharmacokinetics : Plasma Protein Bonds

Test Drug

Study system:
Targets, systems, and testing methods:

Species	Concentration tested	% bound	Location in CTD: No. Study	Volume	Pages

Additional Information:

2.3.2.7. Pharmacokinetics : Pharmacokinetics: studies in pregnant or lactating animals *(1)*

Test Drug: *(2)*

Location in CTD: Vol. Study page No:

Transfer via Placenta
Species:
Gestational age/number of animals:
Vehicle/Formulation:
Administration methods
Dose (mg/kg)
Analyte:
Assay: time (hour) _____ _____ _____ ____ _____
Concentration/amount (% of dose)
Dam: *(3)*
Fetus *(3)*

Additional information:

Additional Information:

Location in CTD: Vol. Page No.Study

Excretion into breast milk
Species:
Date of lactation/number of animals:
Feeding conditions:
Vehicle/Formulation:
Dose (mg/kg)
Analyte:
Assay: _____ _____ _____ ____ _____
time (hour)
Concentration:
Breast Milk:
Plasma
Breast Milk/plasma:
Neonates:

Additional Information:

Notes to Table 2.3.2.7

(1) Although data are obtained from reproductive toxicology studies, the results should be included in this table
(2) International Nonproprietary Name (INN)
(3) Sample of a tissue taken should be described (e.g plasma foe dams, fetal levels)

2.3.2.8 Pharmacokinetics. Other Distribution Studies

Test Drug :

2.3.2.9 Pharmacokinetics. Metabolism in vivo Test Drug:

Gender(M/F) Number of animals:
Feeding conditions:
Vehicle/Formulation:
Administration methods:
Dose (mg/kg)
Radionuclides:
Specific activities:

				% Compounds in Sample				Location in CTD	
Species	Sample	Time or Sampling Period	% Dose in Sample	Parent Compound	M1	M2	Study No	Vol	Pages
	Plasma								
	Urine								
	Bile								
	Feces								
	Plasma								
	Urine								
	Bile								
	Feces								
	Plasma								
	Urine								
	Bile								
	Feces								

Additional Information:

Note: Human data should be included for ~~a~~ comparison (if available)

2.3.2.10 Pharmacokinetics. Metabolism in vitro	Test Drug:			
	Location in CTD: page No:	Vol.	Study	
Study system:				
Time				
Concentration				
Compounds				
Parent compound				
M-1				
M-2				

Additional Information:

Note: Human data should be included for a comparison (if available)

2.3.2.11 Pharmacokinetics. Possible Metabolic Pathways Test Drug:

(Illustrate possible metabolic map indicating species in which metabolic reactions occur).

2.3.2.12 Pharmacokinetics. Induction/Inhibition of Drug Metabolic Enzymes

Test Drug:
Location in CTD: Vol. page
Study No:

Note: Non-clinical studies only

Study type:

Method:

Tabulated results:

Additional Information:

2.3.2.13 Pharmacokinetics: Excretion				Test Drug*(1)*								
Species												
Gender (M/F) / Number of animals:	*(3)*											
Feeding conditions												
Vehicle/formulations												
Administration method												
Dose (mg/kg)												
Analyte												
Assay												
excretion route *(4)*	Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total
Time												
0 - T hour												
No study Locations in CTD												

Additional information: *(2)*

Note:
(1) International Nonproprietary Name (INN)
(2) For example, brief textual results, species differences, gender differences, dose dependency, or special comments.
(3) There should be one column for each study conducted. For comparison, representative information on humans at the maximum recommended dose should be included. Can be combined with the absorption table (if appropriate)
(4) Other routes (e.g biliary, respiratory) should be added, (if performed).

2.3.2.14 Pharmacokinetics. Excretion into bile Test Drug:

(Data can be tabulated as in 2.3.2.13 format (if requested)).

2.3.2.15 Pharmacokinetics. Drug Interaction	Test Drug: Location in CTD: Vol. Page Study No;

Study type:

Method:

Tabulated results:

Additional Information:

2.3.2.16 Pharmacokinetics. Other studies	Test Drug: Location in CTD: Vol. Page Study No.;

Study type:

Method:

Tabulated results:

Additional Information:

2.4.2.1 Toxicology Overview drug testings: *(1)*

Study type	Species and Strains	Administration methods	Duration of drug administration:	Dose (mg/kg[a])	GLP compliance:	Testing facilities	Study Number	Location Vol. Page.
Single-dose toxicity	*(2)*							*(3)*
Repeated-Dose Toxicity								
Genotoxicity								
Carcinogenicity								
Reproductive and Developmental Toxicity.								
Local Tolerance.								
Other toxicity studies.								

Note: *(1) International Nonproprietary Name (INN).*
(2) There should be one line for each pharmacological report, in the same order as the CTD.
(3) Must include the location of the Technical Report in CTD
a- Unless otherwise noted. For repeated-dose toxicity, the highest NOAEL is underlined.

2.4.2.2 Toxicokinetics: Overview of Toxicokinetics Studies Test Drug: *(1)*

Study type	System Test	Administration Methods	Dose (mg/kg)	GLP Compliance:	Number Study	Location Vol.	Page
(2)						*(3)*	

Note: (1) International Nonproprietary Name (INN).
(2) There should be one line for each toxicokinetic report, in the same order as the CTD (subsection C, Toxicology
(3) Must include the location of the Technical Report in CTD

2.4.2.3 Toxicokinetics	Overview of Toxicokinetic Studies	Test Drug: *(1)*
	(2)	

Notes: (1) International Nonproprietary Name (INN).
(2) A one- to three-page summary (tables and/or figures) of steady state toxicokinetic data should be prepared in a format that facilitates comparisons across species, including humans.

2.4.2.4 Toxicology

No. Batch	Purity (%)	Drug Substance Specified Impurities*(1)*	Study Number	Test Drug*(1)* Type of Study
PROPOSED SPECIFICATIONS:				
(2)				*(3)*

Note:
(1) International Nonproprietary Name (INN).
(2) All batches used in toxicological studies should be listed in approximate chronological order.
(3) The Toxicology studies in which each batch was used should be identified.

2.4.2.5 Single-Dose Toxicity *(1)* Test Drug: *(2)*

Species/ Strain	Administration (Vehicle/ Formulation)	Method	Dose (mg/kg)	Gender and No per Group	Observed Maximum Nonlethal dose (mg/kg)	Approximate Lethal Dose(mg/kg)	Noteworthy Findings	Study Number

Note:
(1) All single dose toxicity studies should be summarized in the same order as CTD. Footnotes should be used to indicate special characteristics, such as unusual duration, infusion rate, or age of the test subject.
(2) International Nonproprietary Name (INN).

2.4.2.6. Repeated Dose Toxicity — Nonpivotal Studies *(1)* — Articles tested: *(2)*

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing:	Dose (mg/kg)	Gender and No. per group	NOAEL[a] (mg/kg)	Noteworthy Findings	Study Number

Note: (1) All repeated-dose toxicity studies (including toxicity determining dosing studies) not mentioned in the ICH Guidance M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (November 1997), should be summarized in the same order as CTD. Footnotes should be used to indicate special characteristics, for example, the unusual age of the subject.

(2) International Nonproprietary Name (INN).

a - NOAEL dosage.

2.4.2.7 *(1)* Repeated Dose Toxicity *(2)* Report Title Test Drug: *(3)*

Species/Strains Duration of drug dosing: No. Study; Location

Initial age: Duration of post-dose: CTD: Vol. Page.

Date of the first dose: Administration methods

Vehicle/Formulation: Compliance to GLP:

Special characteristics:

NOAEL

Daily Dose (mg/kg)	0 (Control)								
Number of Tested Animals	M:	F:	M:	F:		M:	F:	M:	F:
Toxicokinetics: AUC () *(4)*	*(5)*								

Noteworthy Findings

Death or sacrificed									
body weight (%a)									
Food Consumption (%a)	*(5)*								
Water Consumption ()	*(5)*								
Clinical Observations									
Ophthalmoscopy									
Electrocardiograpy									

Noteworthy findings

- important + Mild ++ Moderate +++ Severe *(6)*

** -

(7) *- p <0.05 ** - p <0.01

at the end of dosing period: For controls, group means are shown. For treated groups, percent differences from the controls are shown.

a - Statistical significance is based on actual data (not percent difference)

(To be continued)

2.4.2.7 *(1)*Repeated-Dose Toxicity No. Study; Continued

Daily dose (mg/kg)	0 (Control)							
Number Animals:	M:	F:	M:	F:	M:	F:	M:	F:
Hematology:								
Serum Chemistry:								
Urinalysis:								
Organ Weight[a](%):								
Gross pathology:								
Histopathology:								
Additional examination								
Postdose Evaluation:								
Number Evaluated *(8) (9)*								

\- no noteworthy findings.
*

(7) - $p<0.05$ ** - $p<0.01$

a - Absolute and relative weights differed from the controls in the directions indicated. Number indicates percent difference for absolute organ weights.

Notes to Table 2.4.2.7

(1) The tables are numbered consecutively (for example, 2.4.2.7A, 2.4.2.7B, 2.4.2.7C).

(2) There should be one table for each repeated dose toxicity study mentioned in the ICH Guidance M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (November 1997), as well as for any other repeated dose toxicity studies that are considered pivotal.

(3) International Nonproprietary Name (INN).

(4) steady-state AUC, Cmax, Css, or other toxicokinetic information supporting the study. If the information is obtained from a separate study, the study number should be provided in a footnote.

(5) ONLY IMPORTANT FINDINGS SHOULD BE SHOWN. If there are additional parameters (other than the default format) indicating important changes, add them to the table. In general, data on the end of dosing can be shown; however, if there are additional important findings in the beginning of an observation, these data should be included. Footnotes should be used where additional information on tests or study results are required.

(6) Or another scale (if necessary).

(7) Please include statistical analysis methods.

(8) All parameters indicating drug-related changes should be listed. This section should be omitted if the study does not carry out a post-dose evaluation.

(9) If necessary, information on the testing animal necropsied earlier should be presented separately.

Report Title

2.4.2.8 (1) Genotoxicity: In Vitro

Test Drug: *(2)*

Test for Induction:

No. of Independent Assays:

Study Number.
Location in CTD:

Strain:

No. of Replicate Cultures:
No. of Cells/Analysed Cultures:

Vol. Page.

Metabolic System:
Vehicle: For the drug testing: For Positive Control:

GLP compliance:

Treatment:

Treatment Date:

Cytotoxic Effects:
Genotoxic Effects:

Activation Metabolic	Drugs Test	Concentration or Dose L (*(3)*)				
Without Activation		*(4)*				
With Activation						

Note:

*(*1) The tables are numbered consecutively (for example, 2.4.2.8A, 2.4.2.8B). Results of replicate assays should be shown on subsequent pages.

(2) International Nonproprietary Name (INN).

(3) Units must be inserted.

(4) If precipitation is observed, this should be indicated in a footnote.

(5) Methods of statistical analyses should be indicated.

(5) * - $p<0.05$ ** - $p<0.01$

2.4.2.9 (1) Genotoxicity: In Vivo	Report Title:		Test Drug *(2)*	
Test for Induction:		Treatment Schedule:	No Study.	
			Location in CTD:	
Species/Strains		Sampling Period:	Vol.	Page.
Age:		Methode of Administration:		
Evaluated cells:		Vehicle/Formulation:	GLP compliance:	
Number analyzed cells/animal:			Drug Administration Date:	
Special characteristics:				
Toxic/Cytotoxic Effects:				
Genotoxic Effects:				
Evidence of Exposure:				

drug testings	Dose (mg/kg)	Number of Animals			

Note: (1) The tables are numbered consecutively (for example, 2.4.2.9A, 2.4.2.9B).
(2) International Nonproprietary Name (INN).
(3) Methods of statistical analyses should be indicated.

(3) * - p<0.05 ** - p<0.01

2.4.2.10 (1) Carcinogenicity | Report Title | Test Drug: *(2)*

Species/Strains | Duration of dosing: | No. Study;

Study-start age: | Post-dose length: | Location in CTD: Vol. Page.

Date of the first dose: | Administration methods:

Vehicle/Formulation: | Compliance to GLP:

Basis for High-Dose Selection: *(3)*

Special characteristics:

Daily dose (mg/kg)	0 (Control)							
Gender	M:	F:	M:	F:	M:	F:	M:	F:
Toxicokinetics: AUC (*4*)								
Number of Animals								
At the beginning of:								
Dead/Sacrificed:								
Terminal Sacrifice:								
Survival (%):	*(5)*							
Body Weight (‰a):								
Food Consumption (‰a):								

(6) * - p<0.05 ** - p<0.01

a – at the 6th month. For controls group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not percent difference).

(To be continued)

2.4.2.10 *(1)* Carcinogenicity Study No. (advanced)

Daily dose (mg/kg)	(Control))		0 (Control)							
Evaluated number	M:	F:	M:	F:	M:	F:	M:	F:	M:	F:
Number of Animals										
With neoplastic lesion:										
(7)										
Important Findings										
Pathology *gross*										
Histopathology -Nonneoplastic Lesions										

- no noteworthy findings.

* - p<0.05 ** - p<0.01

Notes to Table 2.4.2.10

(1) Tables are sequentially numbered (for example, 2.4.2.10A, 2.4.2.10B). There should be one table for each carcinogenicity study.

(2) International Nonproprietary Name (INN).

(3) From the ICH SIC Guidelines Dose Selection for Carcinogenicity Studies of Pharmaceuticals (March 1995).

(4) steady-state AUC, Cmax, Css, or other toxicokinetic information supporting the study. If the information is obtained from a separate study, the study number should be provided in a footnote.

(5) If additional parameters show drug-related changes, they should be added to the table. Footnotes should be used to provide additional information on tests and results (if necessary).

(6) Statistical analysis method should be mentioned.

(7) Drug-related lesions should be listed first. Then other lesions are listed alphabetically according to organ and/or tissue.

2.4.2.11 Reproductive and developmental toxicity — Nonpivotal studies *(1)* — Test Drug*(2)*

Species/ Strain	Method of Administration (Vehicle/Formulation)	Dosing Period Dose:	Dose (mg/kg)	Numbers Per group	Noteworth Findings	Number Study

Note: (1) All reproduction toxicity studies (including all relevant range-finding studies), other than the definitive GLP studies specified by M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals, November 1997, should be summarized in. However, investigative studies should be summarized using a more detailed temp.

(2) International Nonproprietary Name (INN).

2.4.2.12 *(1)* Reproductive and developmental toxicity- Fertility and Early Embryonic Development up to implantation *(3)*

Report Title: Test Drug:

Study Designs: Duration of dosing: M: No. Study

Species/Strains Mating Day: *(8)* F:

Initial age: Day of C-Section:

Date of the first dose: Administration methods

Special characteristics: Vehicle/Formulation:

NOAEL:

F_0 Male:

F_0 Female:

F_1 Litters:

Daily dose (mg/kg)	0 (Control)
Male Toxicokinetics: AUC (*4*)	
Number of animals evaluated	
Number of animals died or sacrificed for	
Clinical observation	
Necropsy observation of	
Body weight (%a)	
Food consumption (%a)	
Mean No. Days Prior to Mating	
Number of Males that Mated	
Number of Fertiles Males	

(5)

\- No noteworthy findings + Mild ++ Moderate +++ Severe *(6)*

(7) *- p<0.05 ** - p<;0.01

a - After 4 weeks of dosing. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences). (Continued)

2.4.2.12 (1) Reproductive and developmental toxicity — No. Studies (Continued)

Daily dose (mg/kg)		0 (Control)
Female	Toxicokinetics: AUC (*4*)	
	No. Evaluated	
	No. Died or Sacrificed Moribund	
	Clinical observation	
	Necropsy observations	
	Pre-mating Weight (‰a)	
	Gestation Body Weight (‰a)	
	Pre-mating Food Consumption (‰a)	
	Food Consumption During Pregnancy (‰an)	
	Mean Number of Estrus Cycles/14 days	
	Mean Number of Days Prior to mating	
	Number of Positive Sperm in Female	
	Number of Pregnant Females	
	Number of Aborted or with Total Resopsies Litter	
	Mean Number *Corpora Lutea*	
	Mean Number of Implantations	
	Mean % Preimplantation Loss	
	Mean No. Live *Conceptuses*	
	Mean Number resorption	
	Number of dead *conceptus*	
	Mean % Postimplantation loss	

\- There are no noteworthy findings. + Mild ++ Moderate +++ Severe *(6)*

*(7)** - p <0.05 ** - p <0.01

a - At the end of the mating or pregnant period. For the control group, group mean estimation is indicated. For test group, percent differences from the control group are indicated. Statistical significance is based on actual data (not percent difference).

Notes for tables 2.4.2.12, 2.4.2.13 and 2.4.2.14

(1) If there are multiple studies of this type, the tables should be numbered consecutively (eg 2.4.2.12A, 2.4.2.12B, 2.4.2.13A, 2.4.2.13B).

(2) International Nonproprietary Name (INN).

(3) If a modified study design is used, tables should be modified accordingly

(4) steady-state AUC, Cmax, or other toxicokinetic information supporting the study. If the information is obtained from a separate study, the study number should be provided in a footnote.

(5) THE PRESENTATION OF THE RESULTS CAN BE VIEWED ON THIS STANDARD FORMAT. DATA PRESENTATION MUST BE FLEXIBLE AND APPROPRIATE BASED ON OPTIMUM STATISTICAL ANALYSIS AND STUDY DESIGN. If additional parameters show drug-related changes, they should be added to the table. Footnotes should be used to provide additional information on tests and results (if necessary).

(6) Or other scale as appropriate.

(7) Methods of statistical analysis should be indicated.

(8) Day of mating should be indicated (e.g., Day 0 or Day 1).

2.4.2.13 (*1*)	Reproductive toxicity and Development - Effects on Fetal Embryo Development *(3)*	Report Title:	drug testing (*2*)

Study Designs	Duration of Dosing: Mating Day: *(8)*	No Study.
Species/Strain: Initial Aged Date of the first dose: Special characteristics: NOAEL Fo Females: F1 Litters:	Day of C-section Day: Vehicle/Formulation:	Location in CTD: Vol. Page. GLP compliance:

Daily dose (mg/kg) 0 (Control)

Dams/Does: Toxicokinetics: AUC (*4*)

Number of pregnant animals
Number of animals died or sacrificed Moribund *(5)*
Number of Aborted or total adoptions Litter
Clinical observation
Necropsy observation
Body weight (%a)
Food consumption (%a)
Mean Number *Corpora Lutea*
Mean Number of Implants
Mean % of preimplantation losses

\- no noteworthy findings + Mild ++ Moderate +++ Severe*(6)* G = Gestation day

*(7)** - p <0.05 ** - p <0.01

a - At the end of the Drug administration period. For the control group, group mean estimation is indicated. For test group, percent differences from the control group are indicated. Statistical significance is based on actual data (not percent difference) (continued)

2.4.2.13	*(1)* Reproductive and developmental toxicity	No. Study;	(To be continued)

Daily dose (mg/kg)	0 (Control)
Litters: The number of Litter evaluated	
No. Live Fetuses	
Mean of resorption	
Number of Litter with Dead Fetuses	
Mean % Postimplantation Loss	
Fetal Body Weight (g)	
Fetal Sex Ratio	
Fetal Anomalies:	
Gross External	
Visceral Anomalies	
Skeletal Anomalies	
Total Affected Fetuses (Litters)	

- no noteworthy findings

*- p <; 0.05 ** - p < 0.01

2.4.2.14 *(1)*Reproductive and developmental toxicity - Effects in Pre and Post-natal Development, Including Maternal Function *(3)*	Report Title:	Test Drug*(2)*
Study Designs	Duration of Dosing: Day of Mating: *(8)*	No. Study
Species/Strains:	methods of Administration:	Location in CTD: Vol. Page.
Initial Age	Vehicle/Formulations:	
Date of the first dose:	Litters Culled/not Culled:	GLP Compliance:
Special characteristics:		
NOAEL		
F0 Female:		
F1 Male:		
F1 Female:		
Daily Dose (mg/kg)	0 (Control)	
Fo Females: Toxicokinetics: AUC (*4*)		
Number of Pregnant Animals		
No. Died or Sacrified Moribund		
No. Aborted or with Total Res. Litter		
Clinical observation		
Necropsy observations		
Gestation Body Weight (%[a])	*(5)*	
Lactation Body Weight (%[a])		
Gestation Food Consumption (%[a])		
Lactation Food Consumption (%[a])		
Mean duration of gestation (days)		
Abnormal Parturition		

\- There are no important findings + Mild ++ Moderate +++ Severe (*6*) G = Pregnancy Days L = Lactation Days

*(7)** - p <0.05 ** - p <0.01

a - At the end of pregnancy or lactation. For the control group, group mean estimation is indicated. For test group, percent differences from the control group are indicated. Statistical significance is based on actual data (not percent difference)

(continued)

2.4.2.14 *(1)* Reproductive and developmental toxicity No. Study
Continued

Daily Dose (mg/kg)		0 (Control)
F1 Litter:		
Preweaning	The number Litter evaluated	
	Mean No. of Implantations	
	Mean Number Pups/Litter	
	No. of Litters with Stillborn Pups	
	Postnatal Survival to Day 4	
	Postnatal Survival to Weaning	
	Number of Total Litter Losses	
	Change in Pup Body Weights[a] (g)	
	Pup Sex Ratios	
	Pup Clinical Signs	
	Pup Necropsy Observations	
F1 Male:	No. Evaluated Postweaning Per Litter	
Postweaning	No, Died or Sacrificed Moribund	
	Clinical observations	
	Necropsy observations	
	Body Weight Change[b](g)	
	Food consumption (%[c])	
	Preputial Separation	
	Motor Activity	
	Sensory Functions	
	Learning and Memory	
	Mean No. days Prior to Mating	
	No. of males that mated	
	No. of fertile males	

\- No noteworthy findings + Mild ++ Moderate +++ Severe (*6*)
(7) * - p <0.05 ** - p <0.01
a - From birth to weaning
b - From weaning to mating
c - At the end of the period after weaning. For the control group, group mean estimation is indicated. For test group, percent differences from the control group are indicated. Statistical significance is based on actual data (not percent difference) (continued)

2.4.2.14 *(1)*Reproductive and developmental toxicity — No. Studies (Continued)

Daily Dose (mg/kg)		0 (Control)
F1 Female:	No. evaluated Post weaning	
Postweaning	No. Died or Sacrificed Moribund	
	Clinical Observations	
	Necropsy observations	
	Premating Body Weigth Change[a] (g)	
	Gestation Body Weight Change (g)	
	Premating Food Consumption (%[b])	
	Gestation Food Consumption (%[b])	
	Mean Age of Vaginal Patency(Days)	
	Sensory Function	
	Motor Activity	
	Learning and Memory	
	Mean No. Days Prior to Mating	
	No. Females Sperm-Positive Number	
	No. of Pregnant Females	
	Mean No. *Corpora Lutea*	
	Mean No. of Implatations	
	Mean % of Preimplantation Losses	
F2 Litter:	Mean No. Live Conceptuses/Litter	
	Mean No. Resorption	
	No. of Litter with Dead Conceptuses	
	No. dead Conceptuses	
	Mean % Postimplantation Loss Fetal Body	
	Weights (g)	
	Fetal Sex Ratio (% males)	
	Fetal Anomalies	

\- no noteworthy findings + Mild ++ Moderate +++ Severe*(6)*

*(7)** - p <0.05 ** - p <0.01

a - Since weaning period until mating.

b - At the end of the period or pregnancy. For the control group, group mean estimation is indicated. For test group, percent differences from the control group are indicated. Statistical significance is based on actual data (not percent difference). To be continued

2.4.2.14 *(1)* Reproductive and developmental toxicity — No. Studies (Continued)

Daily Dose (mg/kg)		0 (Control)
F1 Females:	No. Died or Sacrificed Moribund	
	Clinical Observations	
	Necropsy Observations	
	Premating Body Weigth Changea (g)	
	Gestation Body Weight Change (g)	
	Premating Food Consumption (%[b])	
	Gestation Food Consumption (%[ab])	
	Mean Age of Vaginal Patency (days)	
	Sensory Function	*Note: Alternate Format*
	Motor Activity	*For natural parturition*
	Learning and Memory	
	Mean No. Days Prior to Mating	
	No. of Females Sperm-Positive	
	No. of Pregnant Females	
	Mean Duration of Gestation	
	Abnormal Parturition	
F1 Females:	No. Litters Evaluated	
	Mean No. of Implantations	
	Mean No. Pups/Litter	
	Mean No. Liveborn Pups/Litter	
	Mean No. Stillborn Pups/Litter	
	Postnatal Survival to Day 4	
	Postnatal Survival to Weaning	
	Change in Pup Body Weightsa (g)	
	Pup Sex Ratios	
	Pup Clinical Signs	
	Pup Necropsy Observations	

\- No noteworthy findings + Mild ++ Moderate +++ Severe (*6*)
(7) *- p <0.05 ** - p <0.01

a - From birth to mating.

b - At the end of the period before marriage or pregnancy. For control, the group mean value was used. For the drug group, percent difference value from the controls were used. Statistical significance is based on actual data (not percent difference value).

2.4.2.16 Local Tolerance *(1)* drug testings: *(2)*

Species Strain	Methode Administration	Dose (mg/kg)	gender; and No. per Group	Notheworthy findings	Study Number

Note: *(1)* All local tolerance studies should be concise.
(2) International Nonproprietary Name (INN).

2.3.2.17 Local Toxicity Study
(1) drug testing: (*2*)

Species/ Strain	Method Administration	Duration of Dosing	Dose (mg/kg)	Gender and No. per Groups	Noteworthy Findings	Study Number

Note: *(1)*All local toxicity studies should be concise.
(1) International Nonproprietary Name (INN).

CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY,
signed.

PENNY K. LUKITO

ANNEX IX
REGULATION OF THE CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY OF THE REPUBLIC OF INDONESIA
NUMBER 24 OF 2017
ON
CRITERIA AND GOVERNANCE OF DRUG REGISTRATION

CLINICAL DOCUMENTS

The clinical document consists of a Clinical Overview, a Clinical Summary, a Tabular Listing of All Clinical Studies, and Clinical Study Reports.

SUBSECTION A: CLINICAL OVERVIEW

This Clinical Overview aims to provide critical analysis of clinical data in the Common Technical Dossier (CTD).

Clinical Overview refers to Registration data contained in comprehensive Clinical Study Summaries, individual Clinical Study Reports and other relevant reports; principally presenting the conclusions and implications of the data, and not simply a recapitulation. In particular, the Clinical Study Summary provides a detailed factual summary of the clinical information in the CTD, and the Clinical Study Review provides a brief discussion and interpretation of the findings along with other relevant information (for example, relevant animal data or product quality issues that may have clinical implications).

The Clinical Overview is primarly intended for use by The Indonesian Food and Drug Authority in the review of the registrations in the clinical section. The overview also serves as a reference for overall clinical findings for assessors involved in the review of other sections of the Registration process. The Clinical Overview should present the strengths and limitations of the development program and study results, analyse the benefits and risks of the Medicinal products in its intended use, and describe how the study results support critical parts of the Drug information.

In order to achieve these objectives, a Clinical Overview must:

- Describe and explain the overall approach to the clinical development of a Medicinal product, including study design decisions.
- Assess the quality of study design and performance, including statements regarding compliance with Good Clinical Practice.
- Provide a brief overview of clinical findings, including limitations that are important to know (e.g., lack of comparisons with relevant active comparators, or absence of information regarding some subject populations, regarding associated endpoints, or on their use in combination therapy).
- Provide an evaluation of benefits and risks based on the conclusions of relevant clinical studies, including interpretation of how the efficacy and safety findings support the proposed dose and target indication, as well as an evaluation of how drug information and other approaches will optimize benefits and manage risks.
- Discuss specific safety or efficacy issues encountered during development,

and how these issues are evaluated and resolved.
- Explore unresolved issues, explain why these issues should not be considered as an obstacle to provide approval, and outline plans for addressing them.
- Explain the basis of important aspects or unusual aspects of Drug information.

The Clinical Study Overview is generally a short document (around thirty pages), but the length depends on the complexity of the submission. It is recommended to use graphs and tables in the text content to summarize and ease understanding, but it does not mean that the material presented in full elsewhere is to be repeated in the Clinical Study Overview. It is advisable to adapt the contents of the Clinical Study Overview with more detailed information in the Clinical Study Summary or Clinical Study Report.

Table of CONTENTS OF CLINICAL OVERVIEW

DETAILED DISCUSSION OF CONTENTS OF THE CLINICAL OVERVIEW SECTION

1. Drug Development Rationale
   The discussion of the rationale for the development of the drug product must:
   - Identify the pharmacological class of the drug product.
   - Describe the particular pathophysiological/clinical condition that the drug product is intended to treat, prevent, or diagnose (the targeted indication).
   - Briefly summarise the scientific background that supported the investigation of the drug product for the indication(s) that was (were) studied.
   - Briefly describe the clinical development programme of the medicinal product, including ongoing and planned clinical studies and the basis for the decision to submit the Registration at this point in the programme.
   - Describe the conformity or non-conformity with current standard regarding the design, implementation and analysis of the studies that refer to published literature. Regulatory guidelines shall be identified (at least from the area where this ClinicalOverview is proposed), accompanied by their discussion and application.
2. Overview of Biopharmaceutics

   This section describes critical analyzes regarding bioavailability that may affect the efficacy and/or safety of the formulations to be marketed (e.g. dosage form/strength proportionality, differences between the formulations to be marketed and those used in clinical trials, and the effect of food on exposure).

3. Overview of Clinical Pharmacology

   This section describes critical analysis of the pharmacokinetic (PK),

pharmacodynamic (PD), and related *in vitro* data by considering all relevant data and suppor the conclusions drawn. If there is an unusual result and a potential problems, it should be explained.

This section explains:

- Pharmacokinetics (PK), for example the comparison of PK in healthy subjects, sick subjects, and specific populations; PK is related to intrinsic factors (e.g. age, sex, race, kidney, and liver disorders) and to extrinsic factors (e.g. smoking, concomitant drugs, diet); rate and magnitude of absorption, distribution, including plasma protein binding; specific metabolic pathways, including the possible influence of genetic polymorphisms and the formation of active and inactive metabolites, excretion, time-dependent pharmacokinetic changes, stereo-chemical issues; clinically relevant PK interactions with Drugs or other substances.
- Pharmacodynamics (PD), e.g. information on mechanisms of action, such as receptor binding; action onset and/or offset; relationship between expected and unexpected pharmacodynamics effects and plasma dose or concentration (e.g. PK/PD relationship); PD support to the proposed dose and dosing interval; clinically relevant interactions of PD with medicinal products or other substances, as well as responses due to genetic differences.
- Interpretation of the results and implications of immunogenicity studies, clinical microbiological studies or specific PD studies for similar drug classes.

4. Overview of Efficacy

This section describes a critical analysis of clinical data relating to drug efficacy according to the target population. This analysis must consider all relevant data, both positive and negative, and must explain why and how it supports the proposed indications. Studies deemed relevant for efficacy evaluation must be identified, and the reasons why sufficient and well-compared studies are considered irrelevant must be identified. Studies that are terminated prematurely must be noted and their impact must be considered.

The following matters must be considered:

- An overview of the relevant subject population, including demographic features, stage of disease, any other potentially important covariates, any major subject populations excluded from important studies, and participation of children and the elderly (ICH E11 and E7). There should be a discussion of the differences between the population studied and the population that will receive the drug after it has been marketed.
- Implications of study design, including subject selection, study duration, and selection of endpoints and comparison groups. Particular attention should be paid to endpoints with limited study outcomes. The use of a surrogate endpoint must be justified. The validation of each scale used should be discussed.
- In non-inferiority studies used to demonstrate efficacy, the evidence provided should support the determination that the study has a sensitivity in determining level and justifying the selection of a non-inferiority margin (ICH E10).
- Statistical methods and problems that could affect the interpretation of study results (e.g. important modifications to the study design,

including endpoint assessments and planned analysis as specified in the original protocol, support for any unplanned analysis, procedures for dealing with missing data, and correction for multiple endpoints).

- Similarities and differences in results between various studies, or within different subgroups of subjects within the studies, and their effect on the interpretation of efficacy data.
- Observed associations between efficacy, dose and dose regimen for each indication, both in the population as a whole and in different subject subgroups (ICH E4).
- In products intended for long-term use, evidence of efficacy relating to long-term maintenance of efficacy and long-term dosage determination. The development of tolerance must be considered.
- Data suggesting that treatment outcomes can be improved through monitoring plasma concentrations (if applicable), and documentation for the optimal range of plasma concentrations.
- Clinical relevance of the magnitude of the observed effect.
- The nature and magnitude of the expected clinical benefit and the justification for using a surrogate endpoint.
- Efficacy in special populations. If efficacy is claimed by insufficient clinical data in the population, this should be supported by extrapolated efficacy data from the general population.

5. Safety Review

This section describes a summary of critical analysis of safety data, records the results that can support and provides justification for the proposed drug information.

A critical security analysis should consider:

- The undesirable effect characteristics of the pharmacological class. The approach taken to monitor the same effects.
- Specific approaches for monitoring certain undesirable effects (e.g. on the eye, QT prolongation).
- Relevant animal toxicology and product quality information. Findings that influence or may influence the evaluation of safety in clinical use.
- The nature of the subject population and the extent of exposure, both for test and control drugs. Limited safety databases, for example related to the inclusion/exclusion criteria and demographics of the subjects studied and the implications of limitations related to the prediction of product safety in the market.
- Undesirable effects, which are common and not serious. The discussion should be brief, focusing on events with a relatively high frequency, incidents more frequent than those with placebo and events known to occur in active comparators or other drugs from the same class of therapy. The events that are more or less common or problematic (considering the duration and degree of observed events) with the test drug compared to active comparators should be given special attention.
- Serious adverse events (*Kejadian Tidak Diinginkan yang Serius*, KTDS). This section should discuss the number and frequency of serious adverse events (KTDS), including death, and other significant adverse events (e.g. events leading to discontinuation or dose modification), and should discuss the results obtained by test drugs

versus comparison drugs. Any conclusions regarding the causal relationship with the Drug should be noted. Laboratory test findings that reflect possible serious medical effects should be considered.

- Similarities and differences in results between studies, and their influence on the interpretation of safety data.
- Differences in rates of adverse events within population subgroups, as determined by demographic factors, body weight, concomitant disease, concurrent therapy, or polymorphic metabolism.
- Relationship between adverse events and dose, dosage regimen, and duration of treatment.
- Long term safety (E1a).
- Methods for preventing, reducing, or managing adverse events.
- Reaction due to overdose, potential for dependence, rebound phenomena and abuse, or lack of data on this issue.
- Worldwide marketing experience. The following points should be discussed briefly:
  i. Extensive experience around the world,
  ii. Any new or different security issues identified,
  iii. Regulatory follow-up related to safety.

2. Conclusion of Benefits and Risks

This section describes all the conclusions obtained in the previous sections regarding biopharmaceutical, clinical pharmacology, efficacy and safety of the Drug, and to provide an overall assessment of the benefits and risks of their use in clinical practice. In addition, the implications of any deviation from regulatory advice or guidelines and any data limitations should be discussed. This assessment includes important aspects of the information of the proposed Drug and also considers the risks and benefits of the drug when compared to available or no treatment alternatives in diseases for which no treatment is a medically acceptable option. If there is a risk to an individual other than the recipient of the Drug, this risk should be explained (for example, the risk of developing drug-resistant strains of bacteria with widespread use of antibiotics for minor illnesses).

The benefit and risk analysis is generally brief, but must explain the following important points:

- Drug efficacy for each proposed indication.
- Meaningful safety findings and actions that enhance the safety.
- Dosage-response and dose-toxicity relationships, optimal dosage ranges and dosage regimens.
- Efficacy and safety in subpopulations, for example determined by age, sex, ethnic group, organ function, disease severity, and genetic polymorphisms.
- Data on children in different age groups, if any, and plans for child development programs.
- Risks to the subject in case of known or potential interactions, including drug-drug and food-drug interactions, and recommendations for use of drugs.
- Potential effects of the Drug, which may affect the ability to drive or operate heavy equipment.

Examples of issues and concerns that may require a more detailed discussion of benefits and risks include:

- Drugs are proposed for the treatment of nonfatal diseases but have the potential to cause serious toxicity, such as signs of carcinogenicity, teratogenicity, potential *proarhythmias* (influence on the QT interval), or signs of hepatotoxicity.
- The proposed use is based on a surrogate endpoint and there is a well-documented important toxicity.
- Safe and/or effective use of drugs is difficult to choose or requires a management approach that requires specialist expertise of a doctor or subject education.

SUBSECTION B: CLINICAL STUDY SUMMARY

The documents in this section are not required for Minor Variation Registration.

Clinical Study Summary aims to present a detailed summary of clinical information on CTD. This includes information contained in the Clinical Study Reports, information from meta-analysis or inter-study analysis whose full reports have been included in the Clinical Study Reports and post-market data for the Drugs that have been marketed in other countries.

The comparison and analysis of results between studies described in this document focuses on factual observations. In contrast, the CTD Clinical Study Review document provides a critical analysis of the clinical study program and its results, including the discussion and interpretation of clinical findings.

The length of the Clinical Study Summary varies depending on the information provided, but it is expected that the Clinical Study Summary is ranging between 50 - 400 pages (excluding attached tables).

CONTENTS OF CLINICAL STUDY SUMMARY

1. SUMMARY OF BIOPHARMACEUTICAL AND RELEVANT ANALYSIS METHOD
   - 1.1 Background and overview.
   - 1.2 Summary of result of individual study.
   - 1.3 Comparison and analysis of results from various studies.

   Appendix 1.

2. SUMMARY OF CLINICAL PHARMACOLOGY STUDY
   - 2.1 Background and overview.
   - 2.2 Summary of result of individual study.
   - 2.3 Comparison and analysis of results from various studies.
   - 2.4 Special study.

   Example 1: Immunogenicity.
   Example 2: Clinical microbiology.
   Appendix 2.

3. SUMMARY OF CLINICAL EFFICACY
   - 3.1 Background and overview of clinical efficacy.
   - 3.2 Summary of result of individual study.
   - 3.3 Comparison and analysis of results from various studies.
   - 3.4 Analysis of clinical information relevant to the recommended dosing.
   - 3.5 Persistence of efficacy and/or tolerance effect.

   Appendix 3.

4. SUMMARY OF CLINICAL SAFETY
   - 4.1 Exposure to Drugs.
   - 4.2 Undesirable Effects.
   - 4.3 Clinical laboratory Evaluation.
   - 4.4 Vital signs, physical findings and other observations related to safety.
   - 4.5 Safety in special groups and situations.
   - 4.6 Post-Marketing Data.

   Appendix 4.

5. SYNOPSYS OF INDIVIDUAL STUDY

DETAILED GUIDELINES FOR CLINICAL STUDY SUMMARY

1. SUMMARY OF BIOPHARMACEUTICAL AND RELEVANT ANALYSIS METHOD

1.1 Background and Overview

This section provides a comprehensive overview of the formulation development process, dosage form performance *in vitro* and *in vivo*, general approaches and rationale for the development of bioavailability (BA) profiles, bioequivalence (BE), and *in vitro* dissolution.

Guidelines and literature that serve as references in planning and conducting the studies should be mentioned. This subsection should also provide an overview of the analytical methods used, with an emphasis on the performance characteristics of the assay validation (e.g. linearity range, sensitivity, specificity), and quality control (e.g. accuracy and precision). This subsection should not provide detailed information on individual studies.

1.2 Summary of result of individual study

A matrix containing all biopharmaceutical studies is presented along with narrative descriptions of the results of individual studies, which provides important *in vitro* and *in vivo* data and information relevant to BA and BE (please refer to Appendix 1 to this Section IV). The narrative description should be concise, and describe critical designs and outcomes. The same study can be described at the same time by emphasizing the results of individual studies and the differences between them. This narrative can be summarized from the synopsis of ICH E3. References or electronic links to the full report of each study should be included in the narrative.

1.3 Comparison and Analysis of Inter-Study Results

This section provides a summary of all *in vitro* dissolution studies, BA, and BA studies comparative to Active Pharmaceutical Ingredient or Drug, with particular attention to differences in outcomes between studies. This review summarizes the findings in text and tables (please refer to Appendix 1 to this Section IV) and should consider the following:

- Effect of formulation and changes in the drug manufacturing process on *in vitro* dissolution and BA, as well as conclusions on BE. If a Drug containing a complex substance (e.g. protein) undergoes a change in formulation and manufacturing process, a pharmacokinetic (PK) study can be performed, which compares the Drug before and after the change to ensure that PK

characteristics have not changed as a result of the change. Although these studies are considered BE studies, generally not only assessing the release of Active Pharmaceutical Ingredients from drugs, they should still be reported. It should also be noted that PK studies alone are not sufficient to guarantee the similarities between the Drugs. In some circumstances, pharmacodynamics (PD) studies, clinical studies or antigenicity data may be required. The results of the study (if required) must be included in the appropriate document section.

- Evidence on the effect of food on BA and conclusions on BE with respect to type of food or timing of meals (if appropriate).
- Evidence on the correlation between *in vitro* dissolution and BA, including the effect of pH on dissolution, and conclusions regarding dissolution specifications.
- Comparative bioavailability, including BE conclusions for various dosage form strengths.
- Comparative bioavailability between clinical study formulations (for clinical studies providing evidence of efficacy) with the formulations to be marketed.
- Source and magnitude of observed intra and inter-subject variability for each formulation in the comparative BA study.

Appendix 1.

Tables and figures are placed within the text in the appropriate subsections, so that the document is easy to read. Long tables can be presented in the appendix at the end of the Subsection.

Table 1.1 and Table 1.2 provide examples of tabular formats for providing information and results related to bioavailability and *in vitro* dissolution studies. These examples provide the results and identify the type and design of the study. The table also lists the results of the BE study and includes the mean (test/reference) ratios for Cmax and AUC as well as a 90% confidence interval, or the most recent recommended metric for assessing BE.

This table is not intended as a standard format, but only to illustrate the type of information that must be considered by Applicants in designing tables for biopharmaceutical studies. Applicants should also decide whether the information and study results are best presented in the form of tables, text or figures. If results are best presented in the form of text and images, then tables may only be used to list the studies conducted.

Please refer to Matrix: Standard Format of Clinical Study Summary Matrix

2. SUMMARY OF CLINICAL PHARMACOLOGY STUDY

2.1 Background and Overview

This section provides an overall overview of clinical pharmacological studies. These studies include clinical studies conducted to evaluate human pharmacokinetics (PK), pharmacodynamics (PD), and *in vitro* studies conducted with human cells, tissues, or PK (human biomaterials) process-related material. For vaccine products, it should describe immune response data that support dose selection, dosing schedule, and final product formulation. Where appropriate, the relevant data summarized in Sections 1, 3 and 4 Subsection C can also

be used as reference in order to obtain a comprehensive picture of the approaches and reasons for the development of pharmacokinetics, pharmacodynamics, PK/PD and human biomaterials. This chapter should not include detailed individual study information.

This chapter begins with a brief overview of the human biomaterial studies conducted and aims to assist in the interpretation of PK and PD data. Studies of permeability (e.g. intestinal absorption, blood-brain barrier pathways), protein binding, hepatic metabolism, and metabolic-based drug interactions are particularly relevant, and should be followed by a brief review of clinical studies conducted to characterize PK and PD of the drug, including the relationship of PK/PD in healthy subjects and sick subjects. Important aspects of the study design and data analysis should be noted, such as the selection of the single or repeated doses used, the study population, the selection of PD endpoints, and whether traditional or population approaches are used to collect and analyze data in assessing PK or PD.

2.2 Summary of result of individual study

A matrix containing all clinical pharmacological studies is presented along with narrative descriptions of the results of individual studies providing important *in vitro* and *in vivo* data and information relevant to PK, PD and PK/PD relationships (please refer to Appendix 2 in this Section IV). Narrative descriptions should be concise and describe critical designs and outcomes. The same study can be described at the same time by emphasizing the results of individual studies and the differences between them. References or electronic links to the full report of each study should be included in the narrative.

A summary of level response (PK/PD) or dose response studies with pharmacodynamics endpoints is provided in this section. In some cases, however, if a well-controlled PD dose response or level response (PK/PD) study provides evidence of efficacy or safety, the study should be included in Section 3 or 4 and sufficiently referenced here.

2.3 Comparison and Analysis of Result of Various Studies

This section uses results from all human biomaterials studies and PK, PD and PK/PD studies to describe the characteristics of PK, PD and PK/PD drug relationships. The discussion includes results related to intra- and inter-individual variability, which affects pharmacokinetic relationships.

This section (using text and tables) includes all data from various studies relating to the following:

- *In vitro* Drug metabolism and Drug-Drug interactions studies and a study of its clinical implications.
- Human PK studies, including best estimates of standardized parameters and sources of variability. Focus on evidence supporting dosage and dose individualization in target populations and specific populations, such as children or the elderly, or subjects with impaired liver or kidney function.
- Comparison between single-dose and repeated-dose PKs.
- Population PK analysis, such as results based on a sparse sample

between studies that account for inter-individual variation in PK or PD of the Active Pharmaceutical Ingredient of the drug.

- Dose-response or level-response relationships. This discussion should focus on the evidence supporting the selection of doses and the dose intervals studied in important clinical studies. In addition, information supporting dosage instructions on the proposed Label should be discussed in Section 3.4.
- Major inconsistencies in the human biomaterials database, PK or PD.

2.4 Special Studies

This section includes studies with specific data relevant to a particular Drug. For immunogenicity studies and other studies where data may be correlated with PK, PD, safety, and/or efficacy studies, an explanation of the correlation should be summarized. Potential effects on PK, PD, safety and/or efficacy should be considered in other appropriate sections in the Clinical Study Summary, with cross-reference to this section. Clinical studies that address specific safety issues should not be reported here, but reported in Section 4.

Example 1: Immunogenicity
For protein products and other products for which specific immunological reactions have been measured, data regarding immunogenicity are summarized in this section. For vaccines or other products intended to enhance a specific immune reaction, immunogenicity data are described in the Efficacy Subsection, Summary of Clinical Efficacy. The level determination method used is briefly described and information about performance is summarized (e.g. sensitivity, specificity, reliability and validity).

Data on incidence, titer, onset time, and duration of antibody response are summarized for each type of antibody level determination used (e.g. IgG by ELISA, neutralization). The relationship between antibody formation to disease, concomitant treatment, dose, duration, regimen, and formulation should be explained and summarized. For drugs intended for chronic and ongoing treatment, data on the impact of interrupting treatment on antigenicity should be analyzed and summarized.

It is important to summarize analysis of potentially clinically relevant immunogenicity correlations, for example to determine the extent to which certain types of antibodies or in certain titers are correlated with changes in PK, changes in PD, loss of efficacy, loss of adverse events profile, or development of adverse events. Particular attention should be paid to events that may be immunologically mediated (e.g. serum sickness) and events that may result from the binding of an endogenous substance that cross-reacts by antibodies to the provided Drug.

Example 2: Clinical Microbiology
For antimicrobial or antiviral, *in vitro* studies describing the characteristics of the activity spectrum are an important part of a study program relevant to clinical efficacy. Clinical efficacy studies that include exposure characterization of clinical isolates as part of efficacy determination are included in Section 3. However, studies that evaluate findings such as *in vitro* exposure patterns of bacterial strains originating from other countries can be described here.

Appendix 2.
Tables and figures should be inserted into the text at the appropriate section if it makes reading the document easier. A long table is presented in the appendix at the end.

Table 2.1 is provided as an example of a tabular format for reporting information and results relating to pharmacokinetic studies of Drug-Drug interactions. Similar tables can be prepared for PK/PD studies, dose-response studies, impact studies on human biomaterials, and population PK studies. This table is not intended as a standard format, but only to illustrate the type of information that must be considered by sponsors in designing their own tables. Applicants should also decide whether the information and results of clinical pharmacological studies are best presented in tables, text, or figures for clarity. If results are best presented in text and figures, the table may only list the studies conducted.

In designing the table, for the various types of clinical pharmacology studies as listed below, Applicants should consider to include the following information. This example is for illustration only, the sponsor must decide which information needs to be presented.

- Metabolic studies using human biomaterials: biomaterials used (e.g. microsomes, hepatocytes), probe drugs, enzymatic pathways and % contribution, and relevant kinetic parameters (e.g. Vmax, Km).
- *In vitro* studies of Drug-Drug interactions using human biomaterials: studies of other Drugs that inhibit the New Drug, inhibited metabolites, affected enzymatic pathways, ranges of inhibitor levels used, values of IC50 and Ki, and proposed mechanisms of inhibition should be described. For the study of New Drugs that inhibit Other Drugs, the Drugs and metabolites that are inhibited should be described, along with the aforementioned information.
- Study of Population PK: studied covariates, number and type of subjects, summary of statistical parameters and final estimates of mean (± standard deviation) for PK parameters.

Please refer to Matrix: Standard Format of Clinical Study Summary Matrix.

3. SUMMARY OF CLINICAL EFFICACY

If a Drug is effective for more than one indication, it should be presented separately for each indication in Section 3, although closely related indications may be presented together. If more than one Section 3 is proposed, the Section shall be marked 3A, 3B, 3C and so on.

3.1 Background and Clinical Efficacy Overview

This section describes comparative studies and other studies related to the proposed indications. The results of the safety-related studies are discussed in Section 4.

This section begins with a brief overview of the design of the comparative studies conducted to evaluate efficacy. These studies include dose-response, comparative efficacy, long-term efficacy and efficacy studies in population subsets. The study design should be described, such as randomization, blinding, choice of comparison treatment, choice of subject population, unusual design features such as crossover, or randomized withdrawal design, use of run-in periods, other enrichment methods, study duration, and analysis plan of study results. Although this section focuses on clinical investigations,

nonclinical data and clinical pharmacological data can also be referenced as necessary to provide a comprehensive summary of the human experience with respect to efficacy. This section should not include detailed individual study information.

3.2 Summary of Result of Individual Study

A matrix containing all studies related to drug efficacy is presented along with narrative descriptions of important studies (please refer to Appendix 3 in this Section IV). The narrative description should be concise, and describe critical designs and outcomes. The same study can be described together by noting the results of individual studies and the differences between the studies. For studies that also contribute to a safety analysis, the study narrative should include information about the study subject's exposure to the test or comparison drug, and how safety data are collected. This narrative can be summarized from the synopsis of ICH E3. References or electronic links to the full report of each study should be included in the narrative.

3.3 Comparison and Analysis of Results from Various Studies

Text, figures and tables are used as required (please refer to Appendix 3 in Section IV), Section 3.3 summarizes all Drug efficacy characterization data, including analysis of all data. Major inconsistencies in the data regarding efficacy are stated and parts requiring in-depth exploration are identified.

This section describes two types of analysis: comparison of the results of individual studies, and analysis of data combined from different studies. A more complete details of the analysis is presented in a separate section, which is outlined in the Clinical Study Report.

This section is adapted to the important evidence in Section 2, such as the data that supports the dosage and how to use Drugs on the Label. These data include recommended dosage and dose intervals, evidence related to dose individualization, and the need for dose modification for specific groups (e.g. pediatric or elderly subjects, or subjects with liver or kidney disorders), and data relevant to the relationships of dose-response or level-response (PK/PD).

3.3.1 Study Population

Subject demographic and baseline characteristics of various efficacy studies are described. The following should be explained:

- Disease characteristics (e.g. severity, duration) and previous treatment in study subjects, and study inclusion/exclusion criteria.
- Differences in baseline characteristics of different study populations or study groups.
- Differences between the population included in the efficacy analysis and the overall subject population that are expected to receive the Drug when it is marketed should also be noted.
- Assessment of the number of subjects dropping out of the study, time of withdrawal (specific study days or visits during the study period or follow-up), and reasons for discontinuation.

A tabular presentation that combines and compares the populations from different studies will be useful.

3.3.2 Comparison of Efficacy Results from All Studies

The results of all studies designed to evaluate drug efficacy must be summarized and compared, including studies that are inconclusive or give negative results. Important differences in study design such as endpoint, comparison group, study duration, subject population statistical methods, and dose must be identified.

Comparison of results from various studies focuses on the primary endpoints described previously. However, if the primary endpoint involves different variables or time points in different efficacy studies, it is necessary to explain the inter-study comparisons of the important data elements obtained from across the studies. If results are considered important over time, they can be displayed in a figure depicting changes over time for each study.

Confidence intervals (CI) for the effect of the treatment are given to aid interpretation. If the placebo and drug tests show a different change from the baseline, the baseline value and the magnitude of the effect on the treatment group, including placebo and active comparison (if used), must be made in table or text that describes a figure. If the objective of the active comparison test is to demonstrate equivalence or non-inferiority, the difference in outcome ratio between the treatments should be provided in Confidence Intervals (CI). Results should be evaluated using pre-defined criteria to determine equivalence or non-inferiority. The rationale for the criteria and support for determining that the study has assay sensitivity should be explained (please refer to ICH E10).

Important differences in results between studies of similar designs should be discussed. Comparisons of factors between studies that may have contributed to the differences in the results of various studies are described.

If a clinical study is meta-analysis, it should be clear whether this analysis is carried out according to a predetermined protocol or a post hoc exercise.

Differences in study design or population, or in measures of efficacy between studies should be explained in order to make an assessment of the relevance and validity of the results and conclusions (please refer to ICH E9). A detailed description of the methodology and results of the meta-analysis should be provided in a separate report (Clinical Study Report).

3.3.3 Comparison of Results in Subpopulation

The results of individual studies or a review of efficacy analysis in specific populations are summarized in this section. The purpose of these comparisons is to show whether the effect of the claimed treatment is observed consistently across all relevant subpopulations, especially those for particular reason of concern. This comparison may highlight a large variety of

properties, which subsequently requires further investigation and discussion. However, such analysis is limited (ICH E9), and it is important to note that the aim of such analysis is not to provide a basis for a particular claim or to fix evidence of efficacy in situations where the overall results are not as expected.

Given the limited sample size in individual studies, analysis of multiple studies should be carried out to evaluate the effect of demographic factors (age, sex, and race) on efficacy. Special factors can arise from general things (such as the elderly) or from special issues related to the pharmacology of Drugs or that arise at the beginning of the Drug development. Efficacy in the pediatric population should be routinely analyzed in proposed indications for children. If the data analysis is too broad, a detailed efficacy analysis shall be carried out and placed in the Clinical Study Report with the results of the analysis described in this section.

3.4 Analysis of Clinical Information Relevant to the Recommended Dosing

This section provides an integrated summary and analysis of all data relating to dose-response effectiveness or blood level response relationships (including blood dose-level relationships), thus contributing to the choice of dose and choice of dose interval. Relevant data from nonclinical studies can be referenced, and relevant data from pharmacokinetic studies, other clinical pharmacological studies, and clinical studies with or without comparison are summarized to illustrate the dose-response or blood level response relationships. For pharmacokinetic and pharmacodynamics studies whose data are summarized in Section 2.2, it would be more appropriate to use these data in this summary in accordance with the summary in Section 2.2, without repetition.

Although interpretations of how these data support dosing recommendations are included in the Clinical Study Overview document, individual study results and cross-study analysis that will be used to support dosing recommendations (including recommended initial and maximum dosing, dosing titration methods, and other guidelines regarding individualization of dosage) should be summarized here. Any identified deviations from dose-response or blood level response relationships due to pharmacokinetic nonlinearities, delayed effects, tolerance, enzyme induction, and so on, should be described.

Any differences in dose-response relationships that result from age of the subject, sex, race, disease, or other factors should be explained. Any differences in pharmacokinetic or pharmacodynamics responses are also discussed and adjusted for Section 2. How they are seen, even if no differences are found, should be explained (e.g. specific studies in the subpopulation, analysis of efficacy results by subgroup, or test drug level determination).

3.5. Persistence of Efficacy and/or Tolerance Effect

Persistence or efficacy information from time to time should be summarized. The number of subjects for which long-term efficacy data are available, and the length of exposure, should be described. Any

evidence of tolerance (loss of effect over time) should be recorded. It may be useful to examine the relationship between changing dose over time and long-term efficacy.

Controlled studies designed to gather long-term efficacy data should be a major focus, and these studies should be clearly distinguished other studies that are more loosely defined, such as open extension studies. This difference also applies to studies specifically designed to evaluate the effects of tolerance and withdrawal. Data on withdrawal or rebound effects related to product safety are presented in the safety section (see Section 4).

In long-term efficacy tests, the effect of early discontinuation of therapy or switching to other therapies on outcome assessment should be considered. This issue is also useful for short-term test and should be mentioned when discussing study results, if necessary.

Appendix 3
Tables and figures should be included in the text of the appropriate Chapters if this makes reading the document easier. A long table can be presented in the appendix at the end of the chapter.

The table should list all studies related to efficacy evaluation (including discontinued or unfinished studies, studies that failed to demonstrate effectiveness for some reason, studies available as publications only, studies reported in the full report (ICH E3), and studies that are described in a brief report), and should present the most important results of the study. It should be noted that unplanned interim analysis in ongoing studies are usually unnecessary. If Section 3 is more than one for a Drug registration with more than one indication, usually each section has its own appendix to the table.

Illustrative tables for antihypertensive Drugs are presented as examples, but these examples are not always relevant for every drug registration. In general, Drug registration will require tables and/or figures developed specifically for a particular Drug class and the study conducted.

Table 3.1 Overview of the clinical efficacy and safety studies.
Table 3.2 Results of the efficacy study
Please refer to Matrix: Standard Format of Clinical Study Summary Matrix

4. SUMMARY OF CLINICAL SAFETY

This section provides a summary of the data relevant to safety in the intended subject population, by combining all results of individual clinical study reports as well as other relevant reports, such as an integrated analysis of safety data that is routinely submitted to several countries.

The display of safety-related data can be considered at three levels (ICH E3)

- The extent of exposure (dose, duration, number of subjects, type of subject) should be examined to determine the extent to which safety can be assessed from the database.
- Common adverse events and changes in laboratory tests are identified, classified, and summarized.
- adverse events (defined in ICH E2A) and other significant adverse events (defined in ICH E3) should be identified and summarized. The

frequency of these occurrences should be checked throughout the study, especially for Drugs used chronically.

The drug safety profile described based on the analysis of all clinical safety data must be described in detail, clearly and objectively, using tables and figures.

4.1. Exposure to Drugs

4.1.1 Comprehensive Safety Evaluation Plan and Safety Study Narrative

Comprehensive safety evaluation plan should be briefly described, including special considerations and observations of nonclinical data, the effects of the relevant pharmacological classes, and the source of the safety data (controlled tests, open studies, etc.). A matrix of all clinical studies presenting the safety data breakdown should be included (please refer to Appendix 4 in this Section IV). In addition to studies evaluating efficacy and safety, and non-comparable studies providing safety information, this section also includes studies that consider specific safety concerns, for example studies to compare rates of adverse events for two therapies, to assess safety in a specific demographic subset, to evaluate withdrawal or rebound phenomena, or to evaluate certain adverse events (e.g. sedation, sexual function, influence on driving ability, absence of unwanted classroom effects). Studies of indications that have not been proposed and current ongoing studies are also included if they contribute to the safety analysis.

A narrative description of the study should be provided, except for a description of the study narrative that contributes to both the efficacy and safety data included in Section 3.2 and adjusted to this section. The narratives should be sufficiently detailed to enable the assessor to understand the study subjects' exposure to the test or comparison drug, and to understand how the safety data are collected (including the methods used and the extent of monitoring of the safety of subjects involved in individual studies). If several studies are not analyzed separately but are categorized for safety analysis, these matters should be noted, and a single narrative description can be provided.

4.1.2 Overall Extent of Exposure

Proper tables (see example in appendix 4 of Section IV) and texts should be produced to summarize the exposure levels for the Drug at all stages of clinical study development. The table shows the number of subjects exposed in various study types and at various doses, routes, and durations. If several different doses and/or periods of exposure are used, these can be categorized. Therefore, for each dose or dose range, the duration of exposure can be summarized according to the number of subjects exposed to a specific time period, such as 1 day or less, 2 days to 1 week, 1 week to 1 month, 1 month to 6 months, 6 months to 1 year, more than 1 year (ICH E3). In Drug registration, it is also important to identify diagnostic subgroups and/or groups receiving concurrently specific therapies that are considered relevant to the safety

assessment.

Each subject can obtain a dose as needed, in the form of the maximum dose, the dose with the longest exposure, and/or the average daily dose. In some cases, a cumulative dose may be considered. Dosage can be provided as an actual daily dose or on mg/kg or mg/m2 basis, as required. Where available, drug level data (e.g. drug level at the time of adverse events, maximum plasma level, and area under the/AUC curve) can help to relate individual subjects to adverse events or changes in laboratory variables.

It is assumed that all subjects involved and received at least one dose of treatment are included in the safety analysis. If not, it must be explained.

4.1.3 Demographics and Other Characteristics of the Study Population

The summary table should provide an overview of the demographic characteristics (Table 4.2) of the population exposed to the Drug during the development process. The choice of age range to be used should consider the discussions in ICH E7 [Study Supporting Special Populations: Geriatrics] and ICH E11 [Clinical Study of Medicine in a Pediatric Population]. If the relative exposure of the demographic group in the controlled studies differs from the overall exposure, a separate table should be provided.

The table must show the relevant characteristics of the study population and the number of subjects with specific characteristics. These characteristics may include:

- Disease severity.
- Hospitalisation.
- Impaired renal function.
- Concomitant illness.
- Concomitant use of particular medications.
- Geographical location.

If these characteristics are distributed differently in the comparative study versus the overall database, tables should be created for the two groups.

The text contained in the table should mention any imbalance (if any) between the drug and placebo and/or the comparison regarding any of the demographic characteristics above, especially if it could result in differences in safety outcomes.

If a specific subject is excluded from the study (due to concomitant illness, disease severity, concomitant medication), it should be mentioned.

Demographic tables for each indication should be established separately, although closely related indications can be combined together if the characteristics of the study subjects are similar so that the risks are believed to be the same.

4.2. Adverse Events (*Kejadian Tidak Diinginkan*, KTD)

4.2.1. Analysis of Adverse Events (KTD)

Data on the frequency of adverse events are described in text and tables. Texts listed in Section 4.2.1 as appropriate and tables not included in the text are placed in Appendix 4.

All adverse events or adverse events that worsened after starting the treatment ("signs and symptoms arising from the treatment," adverse events that are not seen at baseline and worsened even though they exist at baseline) should be summarized in a table listing each event, the number of subjects experiencing the event and the frequency of occurrence in subjects receiving the studied drug, with the control drug and placebo. The table can also present the results of each dose and can be modified to show, among other things, the adverse event rate based on severity, onset of therapy or assessment of causality.

If most of the relevant safety data come from a limited number of studies (e.g. one or two studies), or if the subject populations involved in those studies are very different, a study-based presentation of the data is more appropriate. If relevant exposure data are not included in a limited study, categorizing the studies and combining the results to increase the accuracy of estimates and sensitivity to differences should be considered.

Combining safety data from various studies should be carried out with care because in some cases, interpretation can be difficult and the aggregation can obscure real differences. In cases where discrepancies are evident, it may be more appropriate to present study-based data. The following matters should be considered:

- It is most appropriate to combine data for studies with similar designs, e.g. similar in dose, duration, methods for determining adverse events, and in population.
- If adverse events clearly differ across the various collected individual studies, the combined estimate is less informative.
- Studies with unusual adverse events should be presented separately.
- The depth of the analysis depends on the seriousness of the adverse event and the strength of the evidence that it is caused by the Drugs. Differences in the level of Drug association, serious events or events that led to discontinuation or a change in dose require more in-depth investigation, whereas other adverse events do not need complicated analysis.
- Examination of subjects with extreme laboratory abnormalities ("outliers") is useful in identifying a subgroup of individuals at risk for a particular adverse event.

The study groups that can be used in a combined safety analysis are as follows:

- All comparison studies or subset of comparison studies, such as placebo comparison studies, positive trials, certain positive trials, or studies of a specific indication (conducted in different populations). These groupings can provide the best information on the more common

adverse events and can differentiate drug-related events from spontaneous events. Figures in the comparison and treatment groups should be compared.

- All studies, excluding short-term studies in healthy subjects. This grouping is useful for evaluating rarer events.
- All studies using a specific dosage regimen or route, or other concurrent therapies.
- Studies in which adverse event reports are disclosed via a checklist or in person, or studies where the incident is voluntary.
- Combined studies by region/country.

The discussion of the first two groups is useful, while the other groups will vary depending on the drugs discussed, and influenced by the examination of the results of individual studies. In the method used, it should be noted that each number is only a rough estimation, as is the case with a single study.

If data from several studies will be combined, it should be explained the reasons for choosing the method for combination. Combining the event numerator and denominator for the study can be carried out. Another method for aggregating the results of the entire study is by calculating the data based on study sizes or variants.

If the rates of adverse events in the clinical study differ greatly, these differences should be noted and the reasons should be discussed (e.g. differences in study populations, dose administration, or in the methods of collecting adverse events data).

Adverse events should be described as described in individual study reports (ICH E3). In combining data from multiple studies, use standardized terms to describe the event and collect synonyms under a single term. This can be done with dictionaries of international standards and their terminology. Studies in which adverse events lead to changes in therapy (discontinuation of drug use, change in dose, and need for additional therapy) can help assess the clinical aspects of these adverse events. This figure can be added to the adverse events table, or can be presented in a separate table. The number of all drug discontinuations from each study is useful and it is also important to include adverse events that lead to discontinuation in a separate table.

4.2.1.1 Common Adverse Events

A matrix presenting the adverse event rates (please refer to Appendix 4 in this Section IV) is used to compare the numbers in the test and comparison groups. Combining the event severity category and causality category can be useful for this analysis. The causality category is reported and its data presentation should include the total number of adverse events (whether considered or not related to treatment) because the evaluation of causality is subjective and can ignore treatment-related adverse

events. The comparison of the adverse event rates between the test group and the comparison group in the individual study is summarized in this section. Inputting the numbers in the table for the selected study (please refer to table 4.4 example, in Appendix 4) is often useful.

In-depth examination of the more common adverse events that are likely to be Drug-related can also be useful (e.g. events that show dose-response and/or differences in rates between the Drug and placebo) for their association with relevant factors, including:

- dosage;
- dose mg/kg or mg/m2;
- dosage regimen;
- duration of treatment;
- total dose;
- demographic characteristics such as age, gender, race;
- concurrent use of other drugs;
- other baseline features such as renal status;
- efficacy results;
- Drug levels, if available.

A summary of the results of examining the time of onset and duration for Drug-related events is also useful.

Rigorous statistical evaluation of the possible association between adverse events and each of the above factors is often unnecessary. Initial presentation and examination of the data can show that there is no evidence of a significant relationship with demographics or other baseline figures so that no further analysis of these factors is necessary. The analysis does not need to be presented in a report. If the safety analysis is too broad to be presented in detail in the report, it should be presented as a separate report in the Clinical Study Report, and summarized in this section.

In some circumstances, life tables or similar analysis may be more informative than reporting unprocessed adverse events data.

4.2.1.2 Deaths

The table in Appendix 4 to Section IV should list all fatalities occurred during the study (including those occurred after discontinuation of treatment, for example within thirty days or as specified in the study protocol, including any other fatalities occurred later that may be caused by the process during study period). Excluded from this list are fatalities associated with the disease as per the protocol and not associated with the studied Drug, either in studies with high mortality conditions such as advanced cancer or in studies where fatality is the primary endpoint of the study

(however, it is assumed that such fatalities will still be reported in individual E3 ICH study reports). These fatalities still need to be studied to discover unexpected patterns between study stages, and then analyzed if there are unexplained differences. Fatality should be studied on an individual basis and analyzed by numbers in individual studies and in combination studies, taking into account both total mortality and cause-specific deaths. The relationship with the factors listed in section 4.2.1.1 must also be considered. Fatalities in a population of subjects whose cause is predictable (e.g. from cardiac arrest and sudden death in the angina population) is considered uninformative, but a single death due to arrhythmias associated with prolonged QT interval, aplastic anemia, or liver disease can be informative. Particular care must be taken before an unusual death from concomitant disease occurs.

4.2.1.3 Other Serious Adverse Events

A summary of all KTDS (other than fatalities but including KTDS that are considered death-related) should be reported. KTD occurring after drug discontinuation should be reported. Reporting should include major laboratory abnormalities, vital signs, and physical examination abnormalities deemed to be KTDS according to the ICH E2A definition. The results of the KTDS analysis in various studies should be reported. The frequency of KTDS must be examined especially for drugs that are used chronically. The possible relationship with the factors listed in Section 4.2.1.1 should also be considered.

4.2.1.4 Other Significant Adverse Events

Other hematologic and laboratory abnormalities (other than those that meet the definition of serious) and any events that lead to essential intervention (untimely discontinuation of the test drug, dose reduction, or concurrent adjunct therapy) other than those reported as KTDS, should be reported.

An event leading to an untimely discontinuation of the test Drug represents an important safety issue and should receive particular attention in the analysis of Drug safety for two reasons. First, for an unexpected event (based on pharmacological activity), the need to stop (or change) treatment indicates the severity of the event and its perceived importance for both the subject and the doctor.

Second, discontinuation can represent a Drug-related event, but not necessarily related to the Drug. KTD that leads to treatment interruption should be considered a potentially Drug-related event even if the event is initially not seen, and even if it is thought to represent an inter-current

illness. The reasons for untimely discontinuation should be discussed and the numbers compared between studies, with the placebo group and/or with active comparative tests. In addition, study data should be examined for possible associations with the factors listed in Section 4.2.1.1.

4.2.1.5 Analysis of Adverse Events (KTD) Based on Organ Systems or Syndromes

Assessment of causality and risk factors for death, KTDS and KTD with other meanings are often difficult to do because they are uncommon. Categorizing these events, including those that are less important to the pathophysiology involved, can be important in understanding the safety profile. For example, the relationship between treating sudden death may become clearer when viewed in the context of syncope cases, palpitations, and asymptomatic arrhythmias.

Therefore, summarizing KTD based on organ systems would be beneficial, so that these events could be considered as Drug-related events, including laboratory abnormalities. The presentation of KTD based on this organ system must be placed in Section 4.2.1.5 (4.2.1.5.1; 4.2.1.5.2; and others), and given a title according to the organ system discussed. The list of organ systems should be stated and the basis for categorizing events should be determined appropriately to present data on Drug KTD. If multiple KTDs present as syndromes (e.g. influenza syndrome, cytokine-releasing syndrome), the sponsor may develop some of Section 4.2.1.5 specifically for the syndrome, not for the organ system.

The same data and summary should not be repeated in more than one subsection in Chapter 4.2.1. However, the presentation summary can be placed in one section and adjusted with other sections.

4.2.2 Narrative

Narrative should only be made for certain events that are considered important for the summary assessment of the Drug. The location of individual narratives about the subject's death, other KTDS, and KTD that have other meanings in the application for Registration that is considered important due to its clinical aspects (as described in individual study reports in ICH E3) should be referred to here for the convenience of the assessor. These narratives should form part of the individual study reports. If there is no individual study report (e.g. if many open studies are combined in the safety analysis and not individually described), narratives can be placed in Clinical Study Reports, Chapter 5.3.

4.3. Clinical Laboratory Data Evaluation

This section describes the relationship between changes in laboratory results and drug use. Obvious laboratory abnormalities that lead to important interventions are reported in Sections 4.2.1.3 or 4.2.1.4. If such data are also presented in this section, duplication of the report should be made clear to the assessor. Evaluation is determined from the results of available laboratory tests, but a description of the analysis should be provided in this section. For each analysis, a comparison between the test and comparative groups should be made. In addition, the range of normal laboratory values should be included in each analysis (ICH E3). Where possible, laboratory values are presented in international standard units.

A brief overview of the major changes in laboratory values in clinical studies should be provided. Laboratory data include hematology, clinical chemistry, urinalysis and other data as appropriate. Each parameter at each time during the study (e.g. at each visit) should be described at the following three levels:

- Central Tendency, namely the average (mean) and median values of the group,
- Range of values and the number of subjects with an abnormal value or with an abnormal value of a certain size (e.g. 2 times the normal upper limit, 5 times the upper limit; the choice must be explained). When the data are combined from multiple study centers with differences in normal laboratory values, the methodology of incorporation should be described. The analysis of changes in individual subjects by test group can be demonstrated by various approaches (e.g. slide tables, see examples in ICH E3),
- Individual clinically important abnormalities, including those leading to treatment discontinuation. The significance of changes in laboratory values and their possible relationship to treatment should be assessed (e.g. by analyzing these figures in relation to dose, in relation to drug levels, absence of follow-up therapy, positive de-challenge, positive re-challenge, and nature of concurrent therapy). Possible linkages with other factors listed in Section 4.2.1.1 should also be considered.

4.4. Vital Signs, Physical Findings, and Other Observations regarding Safety

The way in which cross-study observations and comparisons of vital signs (e.g. heart rate, blood pressure, temperature, respiratory rate), body weight and other data (e.g. electrocardiogram, X-rays) relating to safety are presented should be the same as the way laboratory variables are presented. If there is evidence of the effect of the drug, dose-response relationships, drug-response relationships or relationships with individual variables (e.g. disease, demographics, concomitant therapy), it should be identified and the clinical relevance of these observations should be explained. Particular attention should be paid to changes that are not evaluated as efficacy variables and to changes perceived as KTD. Particular attention should also be paid to studies designed to evaluate specific safety concerns, for example studies on QT interval prolongation.

4.5. Safety in Special Groups and Situations

4.5.1 Subject Group

This section summarizes the safety data related to

individualization of therapy or subject management based on demographics, age, sex, height, weight, lean body mass, genetic polymorphisms, body composition, other diseases, and organ dysfunction. In proposed indications for children, safety in the pediatric population should be routinely analyzed. The impact analysis on safety results is presented in another section but is summarized here, along with kinetic or other relevant information, for example on subjects with kidney or liver disease, the medical environment, use of other drugs (please refer to 4.5.2, Drug interactions), tobacco, alcohol, and food habits. For example, if interactions with alcohol are indicated by metabolic profiles, study results, post-marketing experience, or by information about similar drugs, that information should be presented here. If a large number of subjects with comorbid conditions such as hypertension, heart disease, or diabetes are included in the study, an analysis is conducted to assess whether these comorbid conditions affect the safety of the studied Drug. Adjustments to the table or description of KTD should be made when the analysis of these subgroups has been carried out.

4.5.2 Drug Interactions

Studies on the potential for drug-food interactions or Drug-drug interactions are summarized in the Summary Section of Clinical Pharmacology Studies in ACTD. The impact on the safety of these interactions is summarized here, based on pharmacokinetics, pharmacodynamics, or clinical observation. Any observed changes in the adverse events profile, changes in blood levels of the Drug that are considered to be associated with risk, or changes in the effect of the Drug associated with other therapies are presented here.

4.5.3 Use on Pregnancy and Lactation

Information on the safety of using the Drug in pregnancy or breastfeeding during clinical development or from other sources is summarized here.

4.5.4 Overdose

Clinical information regarding overdose, including signs/symptoms, laboratory findings and therapeutic/treatment and antidote measurements (if available) is summarized and discussed. Information on the efficacy of specific antidotes and dialysis is provided where available.

4.5.5 Drug Abuse

Studies/information related to the investigation of potential dependence on New Chemical Entity in animals and humans are summarized and adjusted to the Nonclinical Summary. Vulnerable subject populations should be identified.

4.5.6 Withdrawal and Rebound

Information or study results regarding rebound are summarized. Events that arise, or get worse after discontinuation of the drug (withdrawal) in an active or double

blind study should be checked to see if it is due to discontinuation of the drug. Particular emphasis is given to studies evaluating withdrawals and/or rebounds.

Data on tolerance are summarized in Section 3.5 of the Summary of Clinical Efficacy.

4.5.7 Effect on Ability to Drive Vehicles, Operate Machines or Impairment of Mental Ability

Safety data related to sensory disturbances, coordination, or other factors that will reduce the ability to drive, operate machinery or impair mental abilities are summarized here, including KTD reported in safety monitoring (e.g. drowsiness) and specific studies on the effect of drugs on ability to drive, operate machinery or impairment of mental abilities.

4.6 Post-Marketing Data

If a Drug has been marketed, all available post-market data (published and unpublished, including current periodic safety reports if available) should be summarized. The most recent periodic safety reports are included in the Clinical Study Reports. The estimated number of exposed subjects is categorized by indication, dose, route, duration of treatment, and geographic location. The methodology used to estimate the number of subjects exposed should be described. Estimated demographic details from any source should be provided where available.

A matrix of serious events reported after the Drug has been marketed is presented, including the presence of the potential for serious Drug interactions.

Any post-marketing findings in the subgroups are described.

Appendix 4

Matrix is presented to summarize the important results of all studies related to safety evaluation and in particular to support Drug Labeling.

Tables and figures are inserted in the text at the appropriate section if this makes reading the document easier. Tables can be presented in the appendix at the end of the section.

A Clinical Study Summary requires tables and figures to be created to describe a particular Drug, Drug class, and clinical indication.

Please refer to Section 4.2.1, 4.2.2.3, and 4.3 of this guidelines for additional discussion of the contents of Section 4 tables.

Table 4.1 Study Subject Drug Exposure by Mean Dailiy Dose and Duration of Exposure.

Table 4.2 Demographic profiles of Patients in Controlled Trials.

Table 4.3 Incidence of Adverse Events (KTD) in Pooled Placebo and Active Controlled Trials

Table 4.4 Incidence of Adverse Events (KTD) in the largest trials.

Table 4.5 Patient Withdrawals by Study: Controlled Trials

Table 4.6 Listing of Deaths.

Please refer to Matrix: Standard Format of Clinical Study Summary matrix.

5. SYNOPSIS OF INDIVIDUAL STUDIES

Based on the ICH E3 Guidelines (Structure and Contents of Clinical Study Reports), a clinical study synopsis is included in each Clinical Study Report.

This section should include a table entitled Clinical Study Matrix, described in the Clinical Study Report guidelines, followed by all study synopses arranged in the same order as in the Clinical Study Reports.

One synopsis is prepared for each study used in all countries. Length of synopsis is usually up to three pages long, but synopsis for more complex studies can be longer, for example ten pages. In individual synopsis, tables and figures are used as necessary to add clarity.

SUBSECTION C: CLINICAL STUDY MATRIX

A matrix of all clinical studies and related information should be available. The matrix should include the type of information for each study identified in Table 1 of this Section. Other information may be included in this table if deemed necessary. The order of the study matrix follows the order described in Subsection D: Clinical Study Reports.

Table 1. Matrix of Overall Clinical Study

	Study Identity	Study Report Location	Study Objectives	Study Design and Type of Comparison	Test Product: Dosage Regimen, Route of Administration	Amount of Subjects	Healthy Subjects or Subject Diagnosis	Duration of Treatment	Study Status: Type of Report
BA	001	Vol 3, Chp. 1.1, P. 183	BA IV absolute vs Tablets	Cross Study	Tablet, 50mg, single dose, oral, 10 mg IV	20	Healthy Subject	Single Dose	Finish; Summary
BE	002	Vol 4, Chp. 1.2, P. 254	Comparing Drug Formulation in clinical study and those to be marketed.	Cross Study	Formulation of 2 tablets, 50 mg, oral	32	Healthy Subject	Single Dose	Finish; Summary
PK	1010	Vol 6, Chp. 3.3, P. 29	Determining PK	Cross Study	Tablet, 50mg, single dose, oral	50	Renal Insufficiency	Single Dose	Finish; Complete
PD	020	Vol 6, Chp. 4.2, P. 147	Bridging Study between regions/ countries	Random, with Placebo Comparison	Tablet, 50mg, repeated dose, oral, every 8 hours	24 (12 Drugs, 12 Placebo)	Subject with Primary hypertension	2 weeks	On-Going; Temporary Report
Efficacy	035	Vol 10, Chp. 5.1, P. 1286	Long term efficacy & safety; Analysis of PK Population	Random, with Active Comparison	Tablet, 50mg, oral, every 8 hours	300 (152 test Drug, 148 active comparator)	Subject with Primary hypertension	48 weeks	Finish; Complete

SUBSECTION D: CLINICAL STUDY REPORTS

INTRODUCTION

This subsection describes the preparation of Clinical Study Reports, other clinical data, and references in general technical documents (Common Technical Dossier/CTD) for registration of Drugs used by humans. Indonesia requires a special Study Report for clinical evaluation.

COMPOSITION OF CLINICAL STUDY REPORTSAND RELATED INFORMATION

1. LIST OF CONTENTS OF CLINICAL STUDY REPORTS

2. CLINICAL STUDY REPORTS

   2.1. Biopharmaceutical Study Report
      2.1.1. Bioavailability study report (BA).
      2.1.2. Comparative bioavailability (BA) and bioequivalence (BE) study report.
      2.1.3. *In vitro-in vivo* correlation study report.
      2.1.4. Bioanalytical and analytical methods for human study report.

   2.2. Reports of Pharmacokinetic Studies Using Human Biomaterials
      2.2.1. Plasma protein binding study report.
      2.2.2. Hepatic metabolism and drug interactions study report.
      2.2.3. Report of Study using other human biomaterials.

   2.3. Human Pharmacokinetic (PK) Study Report
      2.3.1. Healthy Subject PK and Initial Tolerability Study Reports.
      2.3.2. Patient PK and Initiaal Tolerability Study Reports.
      2.3.3. Population PK Study Reports.

   2.4. Human Pharmacodynamics (PD) Study Report
      2.4.1. PD and PK/PD on healthy subject Study Report.
      2.4.2. PD and PK/PD on subject Study Report.

   2.5. Efficacy and Safety Study Report
      2.5.1. Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication.
      2.5.2. Study Reports of Uncontrolloed Clinical Studies.
      2.5.3. Data analysis reports from more than one study, including integrated formal analysis, meta-analysis, and bridging analysis.
      2.5.4. Other clinical study reports.

3. Post-Marketing Experience Report

4. Case Report Forms and Individual Patient Listings

GUIDELINES FOR PREPARING CLINICAL STUDY REPORTS
AND RELATED INFORMATION

These guidelines provide recommendations for the structure of the Clinical Study Reports and related information to simplify the preparation and review of documents and ensure their completeness. The placement of the report is determined by the main objective of the study. Each study report will only appear in one section. If there are several objectives, the study should be adjusted to other sections.

An explanation such as "none" or "no study conducted" is provided when no report or information is available for a Section or Subsection.

1. LIST OF CONTENTS OF STUDY REPORT

List of Contents for the Study Report must be available.
List of Contents for Subsection D includes all chapters listed in the CTD manual down to the smallest subsection to identify all the essential components of a proposed Registration (for example, 5.1.1 Placebo Controlled Trials).

Illustration of part of List of Contents Subsection E

5. Indication Z - Efficacy and Safety Study Report

5.1 Indication Z – Study Report of Controlled Clinical Studies Pertinent to the Claimed Indication

5.1.1 Indication Z - Placebo Comparative Study
Study xx-xxx: A double-blind, placebo-comparative study of Drug A for Indication Z
Study yy-yyy: Double-blind study .....

5.1.2 Indication Z - Active Comparative Study
Study *zz-zzz*: A double-blind, comparative study of Drug A vs Drug C for indication Z

5. Indication Q - Efficacy and Safety Study Report

5.1 Indication Q – Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

2. CLINICAL STUDY REPORT

2.1. Biopharmaceutical Study Report

Bioavailability (BA) studies assess the speed and extent of release of the Active Pharmaceutical Ingredient from the Drug. Comparative BA or Bioequivalence (BE) studies may use kinetic, dynamic, clinical, or *in vitro* dissolution endpoints, and can be either a single dose or a repeated dose. If the main purpose of the study is to assess Drug kinetics and also includes BA information, the study report is submitted in Section 1, and is referred to in Sections 1.1 and/or 1.2.

2.1.1. BA Study Report
In this Section should include:
1) Studies comparing the release and systemic availability of the Active Pharmaceutical Ingredient from the oral solid dosage form with the systemic availability of the

Active Pharmaceutical Ingredient administered intravenously or as a liquid oral dosage form,
2) Study of dosage form proportionality, and
3) Study of the effects of food.

2.1.2. BA and BE Comparative Study Report

The studies in this section compare the amount and extent of release of the Active Pharmaceutical Ingredient from similar Drugs (for example, tablet with tablet, tablet with capsule). A BA or BE comparative study may include comparisons between:
1) Drugs used in clinical studies that support the effectiveness and drugs to be marketed,
2) Drugs used in clinical studies that support their effectiveness and Drugs used in batch stability, and
3) Similar drugs from different manufacturers.

2.1.3. *In Vitro-In Vivo* Correlation Study Report

In vitro dissolution studies that provide BA information, including those used to correlate *in vitro* with *in vivo* data, are presented in Section 1.3.

In vitro dissolution test reports used for batch quality control and/or batch release are presented in the Quality Department of the CTD.

2.1.4. Report on Bioanalytical and Analytical Methods for Human Studies

Bioanalytical and/or analytical methods for biopharmaceutical studies or *in vitro* dissolution are usually presented in Individual Study Reports. If a method is used in multiple studies, that method and its validation are included in Section 1.4 and referenced in the appropriate Individual Study Reports.

2.2. Reports of Pharmacokinetic Studies Using Human Biomaterials

Human biomaterials is a term used for proteins, cells, tissues and other materials of human origin, which are used in *in vitro* or *ex vivo* manner to assess the kinetic properties of the Active Pharmaceutical Ingredient. Examples include human cell colony cultures, which are used to assess permeability through biological membranes and transport processes, and human albumin, which is used to assess plasma protein binding. The most important thing is the use of human biomaterials such as hepatocytes and/or liver microsomes to study metabolic pathways and assess Drug-Drug interactions with these pathways.

Studies using biomaterials to address other properties (e.g. sterility or pharmacodynamics) should not be presented in a Sub-Section of Clinical Study Reports, but in the Nonclinical Studies Section (Section III).

2.2.1. Plasma Protein Binding Study Report

An *ex vivo* protein binding study report is presented here. Protein binding data from blood and/or plasma kinetic studies are presented in Section 3.

2.2.2. Reports of the Study of Hepatic Metabolism and Drug Interactions
Study report of Hepatic metabolism and drug interactions with Hepatic tissue is presented here.

2.2.3. Studies Using Other Human Biomaterials
Study report using other biomaterials is presented here.

2.3. Study Reports of Human Pharmacokinetic (PK)

The kinetic assessment of the drug in a healthy subject and/or patient is considered important for designing dosing strategies and dose titration stages, to anticipate the effects of concomitant use with other drugs, and to interpret observed pharmacodynamics differences. This assessment should provide a description of how the body handles the Drug over time, with a focus on maximum plasma levels (peak exposure), areas under the curve (total exposure), clearance, and accumulation of the parent drug and its metabolites, particularly those with pharmacological activity.

PK studies whose reports are included in Sections 3.1 and 3.2 are generally designed to (1) measure drug and metabolite levels in plasma over time, (2) measure Drug and metabolite levels in urine or feces if needed, and/or (3) measure Drug binding and metabolites against protein or red blood cells.

In some conditions, PK studies may include measuring the distribution of the Drug to tissues, organs, or body fluids (e.g. synovial or cerebrospinal fluid), and the results of these distribution studies are included in Sections 3.1 and 3.2. This study provides the kinetic characteristics of the drug and information on absorption, distribution, metabolism, and excretion of drugs and active metabolites in healthy subjects and/or patients. The study of mass balance and changes in dose-related kinetics (e.g. determination of dose proportionality) or time (e.g. due to enzyme induction or antibody formation) are great importance and should be presented in Sections 3.1 and/or 3.2. In addition to describing the mean kinetic in healthy subjects and patients, kinetics also describe the range of individual variability.

2.3.1. Reports of PK Studies on Healthy Subjects and Initial Tolerability
Reports of PK studies and initial tolerability in healthy subjects are presented in this chapter.

2.3.2. Reports of PK Studies on Subjects and initial Tolerability
Reports of PK studies and initial tolerability in subjects are presented in this chapter.

2.3.3. Reports of PK Studies on Population
Reports of PK studies on a population based on a sparse sample obtained from clinical studies including efficacy and safety studies are presented in this chapter.

2.4. Human Pharmacodynamics (PD) Study Report

A study report with the main objective of determining the effect of Drug PD in humans is presented in this chapter. Meanwhile, study reports whose main purpose is to determine efficacy or to collect safety data are presented in Chapter 5.

This section includes reports of (1) studies of known or suspected pharmacological properties associated with the desired clinical effect (biomarkers), (2) short-term studies of major clinical effects, and (1) studies of PD on other characteristics not associated with the desired clinical effect. Since the quantitative relationship between this pharmacological effect on dose and/or Drug concentration and metabolites in plasma is usually important, PD information is often collected in dose-response studies or together with drug level information in PK studies (level-response or PK/PD studies). The relationships between the effects of PK and PD that is not obtained in well comparative studies is often evaluated using appropriate models and used as a basis for designing further dose-response studies or, in some cases, for interpreting the effects of differences in levels in population subsets.

Dosage finding studies, PD and/or PK-PD can be conducted on healthy subjects and/or subjects, and can also be included in studies evaluating the safety and efficacy of a clinical indication. Reports of studies of dosage findings, PD and/or PK/PD conducted on healthy subjects are presented in Chapter 4.1, while reports on studies conducted on subjects are presented in Chapter 4.2.

In some cases, short-term PD information, dose finding, and/or PK-PD found in pharmacodynamics studies of the subject will contribute data to the efficacy assessment, because these information indicate an influence on acceptable surrogate markers (e.g. blood pressure) or at the endpoint of clinical benefit (e.g. pain relief). PD studies may also contain important clinical safety information. When these studies become part of the evidence for efficacy or safety, they are considered clinical efficacy and safety studies that should be included in Chapter 5, not in Chapter 4.

2.4.1. PD and PK/PD on Healthy Subjects Study Report
PD and/or PK/PD Studies that have non-therapeutic goals on healthy subjects are presented in this chapter

2.4.2. PD and PK/PD on Subject Study Report
PD and/or PK/PD studies on the subject should be presented in this chapter.

2.5. Efficacy and Safety Study Report

This chapter includes reports on all clinical studies of the efficacy and/or safety of the Drugs conducted by the sponsor, including all studies that have been completed or are in progress for proposed or not proposed indications. The study report must be presented in detail according to the study and its role in Drug registration. ICH E3 describes the contents of a complete report for studies that provide evidence of efficacy and safety. Brief reports can be produced for multiple studies (please refer to ICH E3 and guidelines in each country).

In Chapter 5, the studies are organized by design (comparative, non-comparative) and in comparative studies, according to the type of comparison. Within each chapter, the studies are further classified, sorted according to completeness and summary of the study (ICH E3), with studies whose full reports are presented first. Published reports with limited data or no further data are presented last in this chapter.

If the application for registration includes multiple indications for therapy, a report is prepared in a separate Chapter 5 for each indication. In that case, if the clinical efficacy study is relevant to only one of the proposed indications, the study is included in Chapter 5 as appropriate. Whereas if a clinical efficacy study is relevant with some indications, the study report is included in the appropriate Chapter 5 and referred to as necessary in other Chapters 5, for example, Chapter 5A, Chapter 5B.

2.5.1. Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

The controlled clinical study Reports are sorted by type of comparison:

- Placebo control (may include other comparison groups, such as active comparison or other doses).
- No-treatment control.
- Dose-Response (without placebo).
- Active control (without placebo).
- External control (Historical), regardless of Comparator.

In each type of control, studies should be structured by duration of treatment if relevant to an assessment of Drug effect. Studies of indications other than those proposed, but supporting efficacy for the proposed indications, are included in Chapter 5.1.

If a pharmacodynamics study contributes to evidence of efficacy, it is included in Chapter 5.1. Placebo-comparative studies, whether conducted at baseline or at the end, are presented in Chapter 5.1. Comparative safety studies, including studies in conditions not for registration, are also reported in Chapter 5.1.

2.5.2. Study Reports of Uncontrolled Clinical Studies

Non-Comparative clinical study reports (e.g. open-label safety study reports) are presented here, including studies in conditions that are not for registration.

2.5.3. Data Analysis Reports from More Than One Study

Many clinical problems in applying for Drug registration can be overcome by analyzing data from several studies. The results of such analysis are summarized in the Clinical Study Summary document, but a detailed explanation and presentation of the results of these analysis are important for interpretation. If the details of the analysis are too broad to be reported in the summary document, they shall be presented in a separate report located in Section 5.3. Examples of reports in this section include: reports from formal meta-analysis or extensive exploratory efficacy

analysis to estimate the magnitude of the effect on all subjects and/or on specific subpopulations, and reports on integrated security analysis that assess factors such as the adequacy of a security database, estimated incidence rates, and safety-related variables such as dose, demographics, and concomitant drugs.

2.5.4. Other Clinical Study Reports:

- Interim report of analysis of studies related to claimed indications.
- Reports of controlled safety studies not reported elsewhere
- Reports of controlled or uncontrolled studies not related to the claimed indication.
- Published reports on the clinical experience of Drugs that are not included in Chapter 5.1. However, if the literature is considered important to demonstrate or prove efficacy, it is included in Chapter 5.1.
- Reports of ongoing studies.

3. POST-MARKETING EXPERIENCE REPORT

For products currently on the market, a report summarizing the marketing experience (including all meaningful safety observations) should be included in item 6.

4. CASE REPORT FORMS OF AND INDIVIDUAL PATIENT LISTINGS (AS REQUESTED)

The forms of case report and list of individual subject data described in Appendix 16.3 and 16.4 of the ICH clinical study report guidelines, are presented in this chapter, in the same order as the clinical study reports and indexed by study.

SECTION E: REFERENCES

Reference documents, including important published articles, official meeting minutes, or other regulatory guidance/advice is included here, including all references cited in the Clinical Summary and Clinical Study Reports or in individual technical reports provided in the Clinical Study Reports. Copies of referenced documents must be available upon request.

MATRIX: STANDARD FORMAT OF CLINICAL STUDY SUMMARY MATRIX

1.1 Summary of bioavailability studies.

1.2 Summary of *in vitro* dissolution studies.

2.1 Summary of Drug-Drug interactions PK Studies

3.1 Description of Clinical Efficacy and Safety Studies.

3.2 Results of efficacy studies.

4.1 Study Subject Drug Exposure by Mean Daily Dose and Duration of Exposure Intravenous formulation.

4.2 Demographic Profile of Patients in Controlled Trials.

4.3 Incidence of Adverse Events in Pooled Placebo and Active Controlled Trial Database.

4.4 Adverse event in a combined database of active and comparative trials in placebo.

4.5 Patient Withdrawals by Study: Controlled Trials.

4.6 Listing of Deaths.

Table 1.1. Summary of Bioavailability Studies

Study Ref. No.	Study Objectives	Study Designs	Treatment (Dosage, Preparation form, Route) [Product ID]	Subject (No. (M/F) Type of Age: average	Average Parameters (+/- SD)						Study Report Location
					C_{max} (mg/L)	T_{max} (hr)	AUC* (mg/Lxhr)	C_{min}** (mg/L)	$T_{1/2}$ (hr)	Others	
192 (Japan)	Relatively pilot BA that compares the absorption of a 200 mg tablet batch with a comparison batch of 200 mg.	Open, randomized, cross-over, 200 mg dose singular	200 mg Tab., p.o. [17762] 200 mg Tab., p.o. [19426]	20 (10/10) Healthy subject 27 y (20-35)	83 ± 21 80 ± 32	1 0.5	217 ± 20 223 ± 19		3.1 2.9		
195 (Japan)	BA study compared xx on fasting and eating conditions	Open, randomized, cross-over, single dose	200mg Tab, p.o. [19426]	30 (15/15) Healthy subject 32 y (26-50)	83 ± 21 120 ± 30	1 2	217 ± 20 350 ± 40				

AUC*: AUC_{TAU} or AUC_{inf}
C_{min}**: For repeated dose studies

Table 1.2. Summary of In-Vitro Dissolution Studies

Study Ref. No.	Product ID / No. Batch	Preparation form	Conditions	Number of Dosing Units	Collection time Average % of Dissolution (range)	Study Report Location
1821	979-03	25 mg Cap.	Dissolution: Equipment 2 (USP) Rotation Speed: 50 rpm Medium/temperature: 37° water	12	10 20 30 (min) 42 (32-49) 71 (58-85) 99 (96-100) (%)	

Table 2.1 Summary of Drug-Drug Interaction PK Studies

Study/Protocol # (country)	Product Identity / Batch # (NME)	Study Objectives	Study Designs	# Subject Entry/Finish (M/F)	HV/P[1] (Age: average, range)	Treatment		Pharmacokinetic Parameters Average (%CV) of Drug Substrates					The average ratio of[2] *Confidence interval*		Location
						Substrate	Drugs that interact	C_{max}	T_{max}	AUC	$T_{1/2}$	CL/kg	C_{max}	AUC	
001 (USA)	19B Batch 0034	Effect of warfarin on Drug X	Random, Cross over	(8L/4P)/ (7L/4P)	HV (34, 20-41)	Drug X 100 mg bid x 7d	Placebo	45 (18) mcg/mL	2.0 (30) hr	456 (24) mcg*hr/ mL	4.25 (30) hr	0.05 (20) mL/min/kg	1.16 1.01-1.30	1.16 1.03-1.34	
						Drug X 100 mg bid x 7d	Warfarin 10 mg qd x 7d	52 (20) mcg/mL	2.1 (35) hr	530 (27) mcg*hr/ mL	4.75 (35) hr	0.04 (22) mL/min/kg			
001 (USA)	19B Batch 0034	Effect of warfarin on Drug X	Random, Cross over	(8L/4P)/ (7L/4P)	HV (34, 20-41)	Warfarin 10 mg qd x 7d	Placebo	12 (25) mcg/mL	1.5 (30) hr	60 (37) mcg*hr/ mL	40 (35) hr	0.04 (30) mL/min/kg	1.08 0.92-1.24	1.07 0.92-1.18	
						Warfarin 10 mg qd x 7d	Drug X 100 mg bid x 7d	13 (20) mcg/mL	1.45 (27) hr	64 (39) mcg*hr/ mL	42 (37) hr	0.39 (34) mL/min/kg			
002 (UK)	19B2 Batch 0035	Effect of Cimetidine on Drug X	Cross over, Single sequence	(4L/8P) (4L/8P)	HV (30, 19-45)	Drug X 50 mg bid x 5d	Placebo	49 (18) mcg/mL	2.1 (30) hr	470 (24) mcg*hr/ mL	4.4 (30) hr	0.05 (20) mL/min/kg	1.22 1.03-1.40	1.36 1.11-1.53	
						Drug X 50 mg bid x 5d	Cimetidine 200 mg bid x 5d	60 (10) mcg/mL	2.2 (30) hr	640 (24) mcg*hr/ mL	5.2 (30) hr	0.03 (20) mL/min/kg			

[1] HV=Healthy volunteers, P=Subject

[2] Value for substrate with drug interacting/value with placebo

Table 3.1 Overview of the Study of Clinical Efficacy and Safety

ID study	Number of Study Center Location (s)	Start of Study Participation status, date Total Participation/Participation Objective	Design Control Type	Test Drug & Comparator Dosage, Routes & Regimens	Study Objectives	# of subjects according to treatment Enrolled/ completed	Duration	Sex M/F Median Age (Range)	Diagnosis Inclusion criteria	Primary Endpoint
PG-2476	1 U. Antarctica	Aug-94 Finish April 98 50 / 50	Random, double blind, parallel Placebo	PT: 30 mg po bid Pbo	Efficacy and Safety	27/24 23/21	4 weeks	27/23 38 (20-64)	Mild Hypertension Diastolic 90-100 Systolic 150-170	Change in systolic and diastolic pressure from baseline in 4 weeks.
PG-2666	4 Florida Doctors Affiliates Smith & Jones CRO	May-98 Still ongoing in May 2001 126/400	Random, open label, parallel Placebo and dose-response	PT: 100 mg po bid PT: 50 mg po bid PT: 25 mg po bid Placebo	Efficacy and Safety, Efficacy and long-term safety	34/30 30/28 34/32 28/26	4 weeks, followed by open label for 12 weeks	66/60 55 (24-68)	Mild Hypertension Systolic 150-170 Diastolic 90-100	Change in systolic and diastolic pressure from baseline in 4 weeks and 12 weeks.

Table 3.2 Efficacy Study Results

Study	Treatment	# Enrolled/ Completed	Average Systolic and Diastolic Blood Pressure			Primary Endpoint	Statistical test/p-value	Secondary endpoint	Other Comments
			Baseline	20 weeks	40 weeks	Substrate-Placebo TDD change in 40 weeks		%normal** (ITT analysis)	
PG-2678	PT: 100 mg po bid	34/30	162/96	140/85	138/84	6		88	
	PT: 50 mg po bid	30/28	165/97	146/87	146/87	4		78	
	PT: 25 mg po bid	34/32	167/96	148/88	148/88	2		50	
	PT: 10 mg po bid	26/20	162/95	153/93	153/93	-4		20	
	Placebo	28/26	166/97	160/92	159/91			30	

**Provide definition

Table 4.1 Drug Exposure to Subjects Based on Average Daily Dose and Duration of Exposure to Intravenous Formulations
N= *Cut off Date*:

Duration (Weeks)	Average Daily Dose (mg)							
	0<Dosage ≤ 5 mg	5<Dosage ≤10 mg	10<Dosage ≤20 mg	20<Dosage ≤30 mg	30<Dosage ≤50 mg	50 mg<Dosage	Total (Dosage)	Percentage
0 <Dur ≤ 1								
1 <Dur ≤ 2								
2 <Dur ≤ 4								
4 <Dur ≤ 12								
12 <Dur ≤ 24								
24 <Dur ≤ 48								
48 <Dur ≤ 96								
Dur> 96								
Total (Each Duration)								
Percentage								

Similar tables can be made for the median, for the capital, and for the maximum dose, or for the longest exposure dose. The same table can be made for combined studies and subgroups, for example on the basis of categorizing for age, sex, ethnicity factors, comorbid conditions, concomitant drug use, or a combination of these factors.
Doses may also be stated as mg/kg, mg/m2, or in plasma Drug levels if such data are available.

Table 4.2 Demographic Profiles of Subjects in Comparative Studies
Cut off Date:

	Treatment Group		
	Test Products N=	Placebo N=	Active control N=
Age (years)			
Mean ± SD	50 ± 15		
range	20-85		
Group			
<18	N (%)	N (%)	N (%)
18 - 40	N (%)	N (%)	N (%)
40 - 64	N (%)	N (%)	N (%)
65 - 75	N (%)	N (%)	N (%)
>;75	N (%)	N (%)	N (%)
Sex			
Female	N (%)	N (%)	N (%)
Male	N (%)	N (%)	N (%)
Race			
Asian	N (%)	N (%)	N (%)
Black	N (%)	N (%)	N (%)
Caucasian	N (%)	N (%)	N (%)
Others	N (%)	N (%)	N (%)
Other Factors			

Table 4.3 Adverse Events (KTD) in Database of Combined Active and Placebo Comparative Studies

Body System/KTD	Test Drug			Placebo	Active Control 1	Active Control 2	
	All doses n = 1685	10 mg n = 968	20 mg n = 717	n = 425	20 mg n = 653	50 mg	100 mg n = 546
Overall Body							
Headache	19 (1%)	7 (1%)	12 (2%)	6 (1%)	23 (4%)	1 (<1%)	3 (1%)
Etc.							
Cardiovascular							
Postural Hypotension	15 (1%)	10 (1%)	5 (1%)	2 (<1%)	7 (1%)	6 (2%)	12 (2%)
Etc.							
Gastrointestinal							
Constipation							

Table 4.4 Incidence of Adverse Events (KTD) in Individual Studies

	Incidents Reported According to Test Group							
Body System/KTD	Study 95-0403			Study 96-0011		Study 97-0007		Study 98-0102s
	Drug X 60 mg bid N=104	Drug X 30 mg bid N=102	Placebo N=100	Drug X 60 mg bid N=500	Placebo N=495	Drug X 60 mg bid N=200	Drug y 100 mg qd N=200	Drug X 60 mg bid N=800
Overall Body								
Headache	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Etc.	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Cardiovascular								
Postural Hypotension								
Etc.								
Gastrointestinal								
Constipation								

Table 4.5 Subjects who withdraw[1] from the Study: Controlled Trials

Cut off Date:

Study		Total Withdrawal				Reason for Withdrawal			Number without efficacy data post-withdrawal
		Total	Male/ Female	Age >65	Race (Describe Categorizing) / / /	KTD N (%)	Lack of efficacy N (%)	Others N (%)	N (%)
Study	Drug X	N (%)	N (%) / N (%)	N (%)	N (%)/N (%)/N (%)				
XXX	Placebo								
Study	Drug X								
AAA	Comparator A								
Study	Drug X								
BBB	Comparator B								
Study	Drug X								
CCC	Comparator C								
All Study									

Note: withdrawal data can be divided according to dosage level, if that is useful.
[1]Subjects who withdraw are those included but did not complete the study (including subjects who discontinued treatment or switched to another treatment and/or disappeared from the study)

Table 4.6 Listing of Deaths Treatment: Test Drugs Cut off Date:

Studies/ Sources[1]	Center	Subject Identity	Age (years)	Sex	Dosage (mg)	Exposure Duration (Days)	Diagnosis	Cause of death	Other Treatment	Medical Condition	Narrative Location

[1]PM=Death from post-marketing experience

This list includes all deaths that meet the inclusion rule, either arising from clinical studies or from secondary sources, such as post-marketing experiences. In electronic registration, link to narrative or other documentation regarding the incident must be available.
The footnote should describe the requirements for entering deaths into the table, for example all deaths that occurred during the period of exposure to the Drug or within a period of up to thirty days after discontinuation of the Drug and also those that occurred later but were due to adverse events that had an onset during exposure or during a thirty day of follow-up period.
Similar lists should be provided for placebo-exposed subjects and active control drugs.

CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY,
signed.

PENNY K. LUKITO

ANNEX X
REGULATION OF THE CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY OF THE REPUBLIC OF INDONESIA
NUMBER 24 OF 2017
ON
CRITERIA AND PROCEDURES FOR DRUG REGISTRATION

MINIMUM INFORMATION THAT MUST BE CONTAINED ON THE PRODUCT INFORMATION

A. SUMMARY OF PRODUCT CHARACTERISTICS/BROCHURE

1. Drug name
2. Dosage form
3. Description
4. Drug Composition (name and strength of the Active Pharmaceutical Ingredients)
5. Indications
6. Posology and route administration
7. Contraindications
8. Warnings - Precautions
9. Drug interactions
10. Pregnancy and lactation
11. Effects on ability to drive and use machines (if necessary)
12. Side effects
13. Overdose and treatment (if any)
14. Mechanism of action, and/or Pharmacodynamics and/or Pharmacokinetics
15. Non-clinical safety data (if necessary)
16. List of Excipients
17. incompatibility (if necessary)
18. Storage conditions
19. Stability/usage limits after reconstitution or after first opening (*in use stability*) (if necessary)
20. Type and size of packaging
21. Other registered dosage forms and packaging (if necessary)
22. Marketing Authorization Number
23. Applicant's Name and/MS holder in accordance with the applicable provisions
24. Applicant's Address and/or MA holder in accordance with the applicable provisions
25. Name of manufacturer
26. Address of manufacturer
27. Name of licensing industry (if necessary)

28. Address of licensing industry (if necessary)
29. Instructions for use
30. Reconstitution method (if any)
31. Date of first approval/Renewal registration (if necessary)
32. Date of Product Information change (if necessary)
33. Drug Category
34. Special precaution, for example:
    a. On medical prescription only
    b. Limited OTC drug warning sign (P.No.1- P.No.6)
    c. Box Warning
    d. Porcine origin/in contact with substance derived from porcine
    e. Alcohol content

B. PRODUCT INFORMATION FOR PATIENTS (Example) *)

1. Product name
2. Dosage form
3. Product Description
4. Composition of active pharmaceutical ingredients/what is contained in the Drug?
5. Product Strength
6. Indication/What is the medicine use for?
7. Posology and route of administration/How much and how often should you use this medicine? What should you do if you miss a dose?
8. Contraindications/when you must not use this medicine?
9. Warnings and precautions/What should be considered when using this medicine? (such as: what happens if you stop using the medicine)
10. Drug Interactions/What other medicines and foods should be avoided whilst taking this medicine?
11. Pregnancy and lactation/Can it be used by pregnant and lactating women?
12. Effects on ability to drive and use machines /Is it permitted to drive and operate machinery while taking this medicine? (if necessary)
13. Undesirable effect
14. Overdose/Signs and symptoms of overdose (if necessary)
15. Overdose treatment/What should be done if using this medicine exceeds the recommended dosage? (if necessary)
16. Storage condition/How to store this medicine?
17. Shelf life after dilution /reconstitution or shelf life after opening the container/How long can this medicine be used after the packaging is opened? (if necessary)
18. Instructions for use
19. Reconstitution method/How to dissolve this medicine? (if necessary)
20. Marketing Authorization Number
21. Applicant's Name
22. Applicant's Address

23. Date of revision (if necessary)
24. Special precaution, for example:
    a. On medical prescription only
    b. Limited OTC drug warning sign (P. No. 1 - P. No. 6)
    c. Box Warning
    d. Porcine origin/in contact with substance derived from porcine
    e. Alcohol content

Notes:
*) Product Information for Patients can be explained in the form of explanations or questions.

CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY,
signed.

PENNY K. LUKITO

ANNEX XI
REGULATION OF THE CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY
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ON
CRITERIA AND PROCEDURES FOR DRUG REGISTRATION

MINIMUM INFORMATION THAT MUST BE WRITTEN ON THE PACKAGING (LABEL)

No.	Information that must be included	Outer Packaging	*Catch Cover*/ Envelope	Label	Blister /Strip	Blister (the smallest package in OTC and Limited Free	Ampoule /Vial label
1.	Product name	√	√	√	√	√	√
2.	Dosage form	√	√	√	(-)	√	√ e)
3.	Packaging size (unit)	√	√	√	(-)	(-)	√
4.	Name and strength of the Activ Pharmaceutical ingredients	√	√	√	√	√	√
5.	Applicant's Name and Address	√	√	√	√ d)	√	√ d)
6.	Manufacturer's Name and Address	√	√	√	√ d)	√	√ f)
7.	Licensor Name and Address	√	√	√	√ d)	√	(-)
8.	Route of Administration	√	√	√	(-)	(-)	√
9.	Marketing Autorization Number	√	√	√	√	√	√
10.	Batch number	√	√	√	√	√	√
11.	Production date	√	√	(-)	(-)	√	(-)
12.	Expireddate	√	√	√	√	√	√
13.	Indications	√ a)	√	√ b)	(-)	√	(-)
14.	Posology	√ a)	√	√ b)	(-)	√	(-)
15.	Contraindications	√ b)	√	√ b)	(-)	√	(-)
16.	Undesirable effect	√ b)	√	√ b)	(-)	√	(-)
17.	Drug interactions	√ b)	√	√ b)	(-)	√	(-)
18.	Warnings - Precautions	√ b)	√	√ b)	(-)	√	(-)
19.	Special precaution, for example:						
	a. On medical prescription only "*harusdenganresepdokter*"	√	√	√	√	(-)	√ e)
	b. Limited OTC Warning signs (P. No. 1 - P. No. 6)	√	√	√	(-)	√	(-)
	c. box warning	√	√	√	(-)	√	(-)
	d. "/ in contact with substance derived from porcine "	√	√	√	(-)	(-)	√
	e. Alcohol content	√	√	√	(-)	(-)	√
20.	Storage condition (including how to store after reconstitution)	√	√	√	(-)	√	(-)
21.	Specific labels, for example:						
	a. Highest Retail Price (HET)	√	√	√	√	√	√ e)
	b. logo of drug classification(Prescription/ Limited Free/OTC Drugs)	√	√	√	√	√	(-)

	c. Generic logo (specifically for Generic Drugs)	√	√	√	√	√	√ e)
	d. Traceability identities to guarantee product validity	√ c)	√ c)	√ c)	√ c)	√ c)	√ c)

Notes:

a) : must be listed for OTC drugs and limited free drugs, for prescription drugs, can refer to Product Information for Patients.
b) : information can refer to Product Information for Patients.
c) : the application of traceable identity to guarantee product validity is regulated by a Regulation of the Agency Head.
d) : should include the name of the applicant/the name of the manufacturer/the name of the licensor.
e) : should be excluded for ampoules or vials less than 10 mL.
f) : for address, only country name.

CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY,
signed.

PENNY K. LUKITO

ANNEX XII
REGULATION OF THE CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY
NUMBER 24 OF 2017
ON
CRITERIA AND PROCEDURES FOR DRUG REGISTRATION

APPLICANT DECLARATION

I, the undersigned:

Name	: .....
Position	: .....
Telephone number	: .....
Fax number	: .....
E-mail	: .....

declare that all information contained in the registration document for the following product:

Drug name: .....
Active Pharmaceutical Ingredientscomposition and strength per unit dose: .....

Dosage form: .....
Type and size of packaging: .....
Applicant: .....
Manufacturer: .....
Registration category (to be described in detail): .....

is the latest and true. I declare that I have checked and I am responsible for:

1. The completeness of the submitted documents.
2. The validity of all information contained in the registration document.
3. The validity of documents attached to support registration.
4. Full implementation of GMP Guidelines at all production facilities involved in the production process and drug control.
5. Drug formula according to master formula and batch record.
6. The manufacturing procedure is the same as specified in the master formula and batch record.
7. The data on active pharmaceutical ingredients and excipients in the registration document corresponds to the batch of active pharmaceutical ingredients and excipients used.

8. Each batch of active pharmaceutical ingredients and excipients has been tested and meets specifications before being used in the drug production process.
9. Each batch has been tested and meets specifications before being used in the drug production process.
10. Each batch of drug has been tested and meets drug release specifications before being marketed.
11. Personnel responsible for releasing drugs to be marketed are competent personnel in accordance with the GMP Guidelines.
12. Drug testing procedures are validated/verified according to the GMP Guidelines.
13. Standard Operating procedures for handling drug recall from the market.
14. All registration documents are available for evaluation during the inspection and regulatory audit processes.
15. Clinical trials (if any) in accordance with the Guidelines for Good Clinical Practices (*Cara UjiKlinik yang Baik*, CUKB).
16. not make any changes beyond the proposed variations*).

If the statement we provided is not valid, then we are willing to be subject to cancellation of the current registration process and any applicable sanctions under prevailing provisions.

....., Date :
Duly Stamp
(Full Name)
(Position)

Notes:
*) : Specifically for Variation Registration

CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY,

signed.

PENNY K. LUKITO

ANNEX XIII
REGULATION OF THE INDONESIAN FOOD AND DRUG AUTHORITY
NUMBER 24 OF 2017
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CRITERIA AND PROCEDURES FOR DRUG REGISTRATION

PRE-REGISTRATION DOCUMENT REQUIREMENTS

A. ADMINISTRATIVE DOCUMENTS

1. Cover letter.
2. Certificates and other administrative documents in accordance with Annex 6.
3. Documents for determining the 100 (one hundred) days pathway.
   3.1. Justification that the Drug is indicated for serious and rare diseases *(Orphan Drug)*, and/or
   3.2. Justification that the Drug is indicated for the treatment of serious diseases that threaten human life (*lifesaving*), and/or easily transmitted to others, and/or there is no or lack of other treatment options that are safe and effective, and/or
   3.3. Supporting documents for public health programs.
4. Documents for determining the 120 (one hundred and twenty) days pathway.

   Supporting documents for Registration requirements that have been approved in the reference country with a well-known evaluation system:

   4.1. Information on Marketing Authorization status from other country and accompanied by valid evidence.
   4.2. Full Assessment report document is available in English from the reference country authority bodies, with the proposed indication and posology requirements similar to those approved in the reference country.

   Registration conditions with reference countries:

   4.2.1. All aspects related to Drug quality, including but not limited to source of raw materials, formula, manufacturing site, release and shelf life specifications, must be identical to those approved in the reference country.
   4.2.2. The proposed Drug is not a Drug that requires specific evaluation related to differences in disease patterns, resistance patterns and/or national program policies, such as anti-infective, antiviral (Hepatitis C; HIV), anti-malarial, Tuberculosis Drugs, Biological Products, and targeted therapy drugs.

   However, the approval of the reference country is not the main basis for granting Marketing Authorization.

   4.3. A declaration letter stating that all aspects of Drug quality are identical to those approved in the reference country, including a statement that the Drug Master File (DMF) submitted to the Indonesian FDA is identical to that submitted to the reference country, if required.

5. Documents for determining the 300 (three hundred) days pathway.

   For New Registration of New Drugs, Biological Products, or Registration of Major Variations with new indications/new posology that are not included in the 100 Days and 120 Days pathway, an evaluation will be carried out through the 300 Days pathway.

6. Drug documents related to patents (if necessary)

   6.1. Patent-related declaration letter.

   6.2. Results of patents searches from the Directorate General of Intellectual Property.

   6.3. Results of patent self assessment.

B. QUALITY DOCUMENTS

1. Quality overall summary.
2. Information on animal-derived ingredients used in the manufacturing process of Active Pharmaceutical Ingredients and Drugs.
3. DMF or equivalent document from the manufacturer of Active Pharmaceutical Ingredients for Active Pharmaceutical Ingredients (if necessary).
4. Equivalence Data (summary/protocol) or justification if it is not required for an equivalence test.

C. NON-CLINICAL DOCUMENTS (if necessary)

1. Non-clinical overview.
2. Non-clinical tabulated summary.

D. CLINICAL DOCUMENTS (if necessary)

1. Clinical overview.
2. Tabulated study synopses.

CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY,

signed.

PENNY K. LUKITO

ANNEX XIV
REGULATION OF THE CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY
NUMBER 24 OF
2017 ON
CRITERIA AND PROCEDURES FOR DRUG REGISTRATION

REQUIREMENTS OF NEW REGISTRATION DOCUMENTS

A. New Registration Category

In detail, the New Registration category consists of:

a. Category 1:
Registration of New Drugs and Biological Products, including Biosimilar Products, consists of:
1.1 New Drug Registration with new Chemical Entity, or Biological Products;
1.2 Registration of New Drugs or Biological Products with new combinations;
1.3 Registration of New Drugs or Biological Products with new dosage forms or new strengths;
1.4 Registration of New Drugs or biological products with new routes of administration;
1.5 Biosimilar Product Registration.

b. Category 2:
Registration of Generic Drugs and Branded Generic Drugs, consists of:
2.1. Registration of Generic Drugs and Branded Generic Drugs that require clinical trials;
2.2. Registration of Generic Drugs and Branded Generic Drugs that do not require clinical trials;

c. Category 3:
Registration of other preparations containing Drugs with special technology, can be in the form of transdermal patch, implant, and beads.

B. New Registration Documents Requirements

No		CATEGORY							
		1					2		3
		1.1	1.2	1.3	1.4	1.5	2.1	2.2	
SECTION I: ADMINISTRATIVE DOCUMENTS AND PRODUCT INFORMATION REQUIREMENTS									
A. ADMINISTRATIVE DOCUMENTS									
1	Cover letter.	v	v	v	v	v	v	v	v
2	Registration form	v	v	v	v	v	v	v	v
3	Applicant Declaration Letter	v	v	v	v	v	v	v	v
4	Certificates and administrative documents (according to manufacturing status: Local Production, contracts, licenses, exports or imports) in accordance with Annex 6	v	v	v	v	v	v	v	v
5	Pre-registration results	v	v	v	v	v	v	v	v
6	Receipt/proof of payment	v	v	v	v	v	v	v	v

No		CATEGORY							
		1					2		3
		1.1	1.2	1.3	1.4	1.5	2.1	2.2	
7	Patent-related documents								
	7.1. Patent-related declaration letter	v[a)]	v[a)]	v[a)]	v[a)]	v[b)]	v[b)]	v[b)]	
	7.2. Results of patent search from the Directorate General of Intellectual property	v[a)]	v[a)]	v[a)]	v[a)]	v[b)]	v[b)]	v[b)]	
	7.3. patents self-assessment	v[a)]	v[a)]	v[a)]	v[a)]	v[b)]	v[b)]	v[b)]	
8	A declaration letter from the manufacturer regarding the use of animal derived raw materials or plant-derived raw materials (including but not limited to gelatin; lactose monohydrate; magnesium stearate; materials containing fatty acids such as stearic, oleic, palmitic; glycerin and other types of hydrogenated fats ; DHA; arachidonic acid; eudragit) (if necessary) If from animals origin, accompanied by information animal origin and BSE/TSE free certificate	v	v	v	v	v	v	v	v
9	A stamped declaration letter from the manufacturer regarding the use of materials from porcine origin (if necessary)	v	v	v	v	v	v	v	v
B. PRODUCT AND LABEL INFORMATION									
1	Product Information	v	v	v	v	v	v	v	v
2	Label	v	v	v	v	v	v	v	v
3	photos or pictures of Drugs and packaging	v	v	v	v	v	v	v	v
SECTION II: QUALITY DOCUMENT REQUIREMENTS									
Subsection A. Summary of Quality Overall Summary (QOS)		v	v	v	v	v	v	v	v
Subsection B. Quality Documents									
	Active Pharmaceutical ingredients S.1. General Information								
	1.1. Nomenclature	v	v[c)]	v[c)]	v[c)]	v	v	v	v
	1.2. Chemical formula	v	v[c)]	v[c)]	v[c)]	v	v	v	v
	1.3. General characteristics	v	v[c)]	v[c)]	v[c)]	v	v	v	v
	S.2. Manufacturing process and Source of Active Pharmaceutical Ingredients								
	2.1. Manufacturer	v	v[c)]	v[c)]	v[c)]	v	v	v	v
	2.2. Description and control of the manufacturing process	v	v[c)]	v[c)]	v[c)]	v			v
	2.3. Control of Material	v	v[c)]	v[c)]	v[c)]	v			v
	2.4. Control of critical steps and intermediate	v	v[c)]	v[c)]	v[c)]	v			v
	2.5. Process validation and/or evaluation	v	v[c)]	v[c)]	v[c)]	v			v
	2.6. Manufacturing Process Development	v	v[c)]	v[c)]	v[c)]	v			v
	S.3. Characterization								
	3.1. Elucidation of structure and Characteristic	v	v[c)]	v[c)]	v[c)]	v			v
	3.2. Impurities	v	v[c)]	v[c)]	v[c)]	v			v

No		CATEGORY							
		1					2		3
		1.1	1.2	1.3	1.4	1.5	2.1	2.2	
	S.4. Specifications and Testing Methods for Active Pharmaceutical Ingredients								
	4.1. Specification	v	v[c)]	v[c)]	v[c)]	v	v	v	v
	4.2. Analytical procedure	v	v[c)]	v[c)]	v[c)]	v	v	v	v
	4.3. Validation of Analytical procedure	v	v[c)]	v[c)]	v[c)]	v	v[d)]	v[d)]	v
	4.4. Batch analysis	v	v[c)]	v[c)]	v[c)]	v	v	v	v
	4.5. specifications justification	v	v[c)]	v[c)]	v[c)]	v			v
	S.5. Reference Standard	v	v[c)]	v[c)]	v[c)]	v	v	v	v
	S.6 Specification and Testing of Container Closure System	v	v[c)]	v[c)]	v[c)]	v			
	S.7. Stability	v	v[c)]	v[c)]	v[c)]	v	v	v	v
	P. DRUGS								
	P.1. Descriptions and Formulas	v	v	v	v	v	v	v	v
	P.2. Product development								
	2.1. Information of Development studies	v	v	v	v	v	v	v	v
	2.2. Component of Drug Product	v	v	v	v	v	v	v	v
	2.3. Finished Product	v	v	v	v	v	v	v	v
	2.4. Manufacturing Process Development	v	v	v	v	v	v	v	v
	2.5. Container Closure system	v	v	v	v	v	v	v	v
	2.6. Microbiological attributes	v	v	v	v	v			v
	2.7. Compatibility	v	v	v	v	v	v	v	v
	P.3. Manufacturing Procedures								
	3.1. Drug Manufacturers	v	v	v	v	v	v	v	v
	3.2. Batch formula	v	v	v	v	v	v	v	v
	3.3. Manufacturing process and process control	v	v	v	v	v	v	v	v
	3.4. Control of critical steps and Intermediates	v	v	v	v	v	v	v	v
	3.5. Process and/or report validation	v	v	v	v	v	v	v	v
	P.4. Specifications and testing methods for Excipient								
	4.1. Specification	v	v	v	v	v	v	v	v
	4.2. Analytical procedure	v	v	v	v	v	v	v	v
	4.3. Excipients of animals and/or human origin	v	v	v	v	v	v	v	v
	4.4. Novel excipients	v	v	v	v	v	v	v	v
	P.5. specifications and testing methods for Finished Products								
	5.1. Specifications	v	v	v	v	v	v	v	v
	5.2. Analytical procedure	v	v	v	v	v	v	v	v
	5.3. analytical method validation Report	v	v	v	v	v	v	v	v
	5.4. Batch analysis	v	v	v	v	v	v	v	v
	5.5. Characterization of impurities	v	v	v	v	v	v	v	v
	5.6. Justification of specifications	v	v	v	v	v	v	v	v
	P.6. Reference Standards	v	v	v	v	v	v	v	v

No		CATEGORY							
		1					2		3
		1.1	1.2	1.3	1.4	1.5	2.1	2.2	
	P.7. Specifications and Testing Methods for Container Closure	v	v	v	v	v	v	v	v
	P.8. Stability	v	v	v	v	v	v	v	v
	P.9. EquivalenceEvidence						v		
Subsection C. References		v	v	v	v	v	v	v	v
SECTION III: NON-CLINICAL DOCUMENT REQUIREMENTS									
Subsection A. NON-CLINICAL overview		v	v	v[e)]	v	v			v[f)]
Subsection B. Summary and matrix of NON-CLINICAL study		v	v	v[e)]	v	v			v[f)]
1	Summary of NON-CLINICAL studies	v	v	v[e)]	v	v			v[f)]
2	Contents of NON-CLINICAL study summary and matrix	v	v	v[e)]	v	v			v[f)]
3	Summary of the NON-CLINICAL study matrix	v	v	v[e)]	v	v			v[f)]
Subsection C. NON-CLINICAL study reports (if necessary)		v[i)]	v [i)]	v[e)i)]	v[i)]	v[i)]			v[f)i)]
1	List of contents for NON-CLINICAL study reports	v[i)]	v[i)]	v[e)i)]	v[i)]	v[i)]			v[f)i)]
2	Study report								
	2.1. Pharmacology	v[i)]	v[i)]	v[e)i)]	v[i)]	v[h)i)]			v[f)i)]
	2.2. Pharmacokinetics	v[i)]	v[i)]	v[e)i)]	v[i)]	v[h)i)]			v[f)i)]
	2.3. Toxicology	v[i)]	v[i)]	v[e)i)]	v[i)]	v[i)]			v[f)i)]
Subsection D. References		v[i)]	v[i)]	v[i)]	v[i)]	v[i)]	v[i)]	v[i)]	v[i)]
SECTION IV: CLINICAL DOCUMENTS REQUIREMENTS									
Subsection A. Clinical overview		v	v	v	v	v	v[g)]		v
Subsection B. Summary of clinical studies							v[g)]		
1	Summary of biopharmaceutical studies and associated analytical methods	v	v	v	v	v			v
2	Summary of clinical pharmacological studies	v	v	v	v	v			v
3	Summary of clinical efficacy	v	v	v	v	v			v
4	Summary of clinical safety	v	v	v	v	v			v
5	Synopsis of individual studies	v	v	v	v	v			v
Subsection C. Clinical study matrix		v	v	v	v	v	v[g)]		v
Subsection D. Clinical study reports		v [i)]	v [i)]	v [i)]	v [i)]	v [i)]	v[g)]		v
1	List of contents for clinical study reports	v [i)]	v [i)]	v [i)]	v [i)]	v [i)]			v
2	Clinical study reports								
	2.1 Report on biopharmaceutical studies	v [i)]	v [i)]	v [i)]	v [i)]				v
	2.1.1. Bioavailability (BA) study reports								
	2.1.2. Comparative (BA) and bioequivalence (BE) studies report								
	2.1.3. in vitro-in vivo correlation study reports								
	2.1.4. bioanalytical and analytical methods for human studies Reports								
	2.2 Reports of pharmacokinetic studies using human biomaterials	v [i)]	v [i)]	v [i)]	v [i)]	v [i)]			v

No		CATEGORY							
		1					2		3
		1.1	1.2	1.3	1.4	1.5	2.1	2.2	
	2.2.1 plasma protein binding studies Reports								
	2.2.2. studies of hepatic metabolism and drug interaction studies Reports								
	2.2.3. study using other human biomaterials Reports								
	2.3 Reports of human pharmacokinetic (PK) studies	v i)	v i)	v i)	v i)	v i)			v
	2.3.1. PK studies on healthy subject PK and initial tolerability study baseline tolerability reports								
	2.3.2. Patient PK and initial tolerability study reports								
	2.3.3. Population PK study reports s								
	2.4 Reports of human pharmacodynamics (PD) studies	v i)	v i)	v i)	v i)	v i)			v
	2.4.1. Healthy subjectPD and PK/PD study reports								
	2.4.2. Patient PD and PK/PD study reports								
	2.5 Reports of efficacy and safety studies	v i)	v i)	v i)	v i)	v i)			v
	2.5.1. Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication					v			
	2.5.2. Studies Reports Uncontrolled Clinical Studies								
	2.5.3. analyses of data from more than one study reports								
	2.5.4. Other clinical study reports								
3	Post-marketing Experience Report	v i)	v i)	v i)	v i)	v i)			v
4	Case Report Forms and Individual Patient Listings (As Requested)	v i)	v i)	v i)	v i)	v i)			v
Subsection E. References		v i)	v i)	v i)	v i)	v i)	vg)		v

Notes:

va)	:	if The applicant is not the originator or does not obtain the appointment/license from the originator
vb)	:	for the first Generic Drugs or Biosimilar Products
vc)	:	if the source and manufacturing process of the Active Pharmaceutical Ingredient is different from those approved
vd)	:	for non pharmacopeial Active Pharmaceutical Ingredients
ve)	:	for new route of administration
vf)	:	is required for drug components that have never been approved
vg)	:	for generic drugs that require clinical trials
vh)	:	is required for Biosimilar Products when there are issues related to the quality and pharmacotoxicology of the Active Pharmaceutical Ingredient
vi)	:	does not apply to drug registrations with reference countries

CHAIRPERSON OF THE INDONESIAN DRUG AND FOOD AUTHORITY

signed

PENNY K. LUKITO

ANNEX XV
REGULATION OF THE INDONESIAN DRUG AND FOOD AUTHORITYNUMBER
24 OF 2017
ON
CRITERIA AND PROCEDURES FOR DRUG REGISTRATION

EXPORTED ONLY REGISTRATION
DOCUMENT REQUIREMENTS

No.		EXPORTED	
		Imported Drugs	Local Drugs
1	Cover letter	v	v
2	Registration form	v	v
3	Applicant’s statement	v	v
4	Certificates and administrative documents in accordance with Annex 6.	v	v
	4.1 Pharmaceutical Industry License	v	v
	4.2 Applicant's GMP Certificate	v	v
	4.3 GMPcertificate or other equivalent document from the manufacturer according to the registered preparation form	v	-

CHAIRPERSON OF THE INDONESIAN DRUG AND FOOD AUTHORITY,

signed

PENNY K. LUKITO

ANNEX XVI
REGULATION OF THE INDONESIAN DRUG AND FOOD AUTHORIRY
NUMBER 24 OF 2017
ON
CRITERIA AND PROCEDURES FOR DRUG REGISTRATION

TYPES OF VARIATIONS, REQUIREMENTS AND COMPLETENESS OF VARIATION REGISTRATION DOCUMENTS

A. Variation Registration Administrative Documents

Administrative documents that must be submitted at the time of submitting a Variation Registration consist of:

1. Cover letter.
2. Registration form.
3. Applicant's statement.
4. Certificates and administrative documents (according to manufacturing status: Local Production, contracts, licenses, exports or imports) in accordance with Annex 6
5. Pre-registration results (if required).
6. Receipt/proof of payment.
7. Other documents.
   - 7.1. A declaration letter regarding the fulfillment of the Variation Registration requirements (for example: a statement that the analytical method Active Pharmaceutical Ingredienthas not changed for Variation Registration of tightening the limit of the Active Pharmaceutical Ingredient specification).
   - 7.2. Marketing Authorization and all Variation Registration approval letters issued by the Indonesian Food and Drug Authority along with their attachments.
   - 7.3. Comparison table of proposed changes, including references of the changes.
   - 7.4. Justification of the proposed changes.

B. Variation Registration Technical Document

The technical documents are submitted in accordance with the proposed Variation Registration.

Specifically for vaccines, types of variations, requirements and document completeness refer to WHO guidelines. The category of variations in the WHO guidelines is different from the Registration category in Indonesia, so the Registration category is adjusted as follows:

No	Categories listed in the WHO guidelines	Registration Category in Indonesia
1	*Major*	Major Variation Registration
2	*Moderate*	Minor Variation Registration
3	*Minor*	Notification Variation Registration.

1. CATEGORY 4: MAJOR VARIATION REGISTRATION

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
A. Changes in Product Information that affect safety efficacy aspects that require clinical data			
1	Changes/addition in indication and/or posology;		A. Administrative Documents, Product Information, and Labels 1. Product Information B. Non-clinical documents (if necessary) 1. Non-clinicaloverview. 2. Non-clinical study summary and matrix C. Clinical documents 1. Clinical overview. 2. Summary of clinical studies. 3. Clinical study matrix for submission of changes or additions to indications and/or posology Tabular listing of Clinical studies for submission of changes or additions to indications and/or posology. 4. Clinical study reports (as stated in the tabular listing of clinical studies). 5. Periodic safety update report/PSUR up to the latest period. 6. Another reference Other references.
2	Changes in Product Information that affect safety aspects.		A. Administrative Documents, Product Information, and Labels 1. Product Information B. Non-clinical documents (if necessary) 1. Non-clinical overview or justification of changes/additions to Non-clinical information. 2. Summary and matrix of Non-clinical studies (in accordance with the proposed changes). C. Clinical documents 1. Clinical overview or justification of changes/additions to clinical information. 2. List of supporting documents for the proposed changes in product information. 3. Tabular listing Clinical studies for submission of changes in Product Information. 4. Clinical study report (as stated in the tabular listing of clinical studies). 5. Periodic safety report /PSUR up to the latest period (if necessary). 6. Other references (if necessary).
B. Changes in Product Information that affect safety efficacy aspects that do not require clinical data			
1	Changes in Product Information that affect safety aspects.	1. Specifically for New Drugs and Biological Products.	A. Administrative Documents, Product Information, and Labels 1. Product Information B. Clinical documents 1. Justification and/or other supporting documents in

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
			accordance with the proposed changes. 2. Periodic safety update report/PSUR (if necessary). 3. Other references.
C. Changes related to Active Pharmaceutical Ingredients and/or formulas that affect safety-efficacy aspects that require clinical data			
1	Changes related to Active Pharmaceutical Ingredients and/or Formulas that require clinical data.		A. Administrative Documents, Product Information, and Labels 1. Product Information B. Quality documents 1. Complete Active Pharmaceutical Ingredient quality document (if necessary). 2. Complete product quality documents. 3. Characterization data Characterization data that illustrates the conformation and immunogenicity of the antigen is comparable to the preparation form and/or new formula (vaccine specific). that illustrates the conformation and immunogenicity of the antigen is comparable to the preparation form and/or new formula (vaccine specific). 4. Commitment to submit long-term stability studies. C. Clinical documents 1. Clinical study overview or justification of changes/additions to clinical information. Clinical study overview or justification of changes/additions to clinical information. 2. List of supporting documents for proposed changes. List of supporting documents for proposed changes in product information 3. Tabular listing of Clinical studies for submission of changes to Product Information. Tabular listing of Clinical studies for submission of changes to Product Information. 4. Clinical study report (as stated in the tabular listing of clinical studies). Clinical study report (as stated in the tabular listing of clinical studies). 5. Periodic safety update report/PSUR up to the latest period (if necessary). 6. Other references (if necessary).
2	Replacement of Master Cell Bank (MCB)/Master Seed Lot (MSL).	1. Specific for Biological Products. 2. For manufacturing of new master cell/seed lot derived from original or pre-approved master cell/seed lot or working cell/seed lot by sub-cloning. 3. Not related to any changesin the host cell line.	A. Quality documents 1. Source, history and passage number of the new master cell /seed with documentation of all raw materials of animal or human origin used in the entire culture history. 2. Result of all identity testing, including cytogenetic characteristics that can be used to identify cells. 3. Information of characterization and testing of MCB /Working

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
			Cell Bank (WCB) and cell from end-of-production or post-production parts. 4. Result of all existing adventitious agent testing on the donor and new master cell. 5. Growth characteristics and expression if the cell substrate is used to produce recombinant proteins. Including evaluation of copy number and stability of introduced nucleic acids and quantity and quality of express protein to the passage levels that exceed anticipated production cycle times. 6. Qualification of cell bank or seed lot based on applicable standards. 7. Validated cell stability under frozen storage and storage conditions using data cell recovery or viability. 8. For viral master seed, all documents related to all manipulations of the viral phenotype, e.g. virulence attenuation or genetic reassortment or recombinant. Including the determination of nucleic acid sequences and sources of biological origin starting material. 9. Testing data of sterility, mycoplasma, adventitious virus (if necessary). 10. Comparability of approved and proposed Active Pharmaceutical Ingredients in terms of physicochemical characterization, biological activity and impurity profile. 11. Batch analysis data (in tabular format) of at least three batches of Active Pharmaceutical Ingredient derived from the proposed and approved cell/seed lot. 12. The stability study results of ofa minimum three batches produced using the proposed cells/seed lot according to the relevant stability guidelines; and a statement letter declaring to continue the stability study up to the approved shelf life, if necessary, and report to Indonesian FDA if there is test result that does not meet the requirements (with an action plan) or if requested by the Indonesian FDA 13. Commitment to submit stability study reports according to the proposed changes. B. Clinical documents 1. Clinical study overview or justification documents of changes. 2. List of documents supporting changes. 3. Clinical study matrix available

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
			for the proposed changes. 4. Clinical study report (as stated in the clinical study matrix). 5. Post Safety Update Report-/PSUR up to the latest period (if necessary). 6. Other references (if necessary).
3	Critical changes in the fermentation process (changes that have potential to impact on the quality of the Active Pharmaceutical Ingredient or Finished Product).	Specifically for recombinant products.	A. Quality documents 1. Flowchart (including process and in-process control) and a narrative description of the proposed manufacturing process. 2. Information on characterization and testing after the production of cell bank for recombinant products or antigens for non-recombinant products, if changes have an impact on increasing fermentation or sub-cultivation yields. 3. If derived from animals, information of animal origin and of Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalophaties (TSE) free-certificate should be submitted. 4. Process validation report. 5. Comparability studies before and after changes related to physicochemical properties, biological activity, purity, and contaminant . 6. Non-clinical and/or clinical studies, if quality data do not demonstrate comparability. 7. Comparison of IPC and release testing results for at least three consecutive batches of commercial-scale Active Pharmaceutical Ingredient, of pre- and post- change. 8. Comparison of long-term Active Pharmaceutical Ingredient stability test results, a minimum of three commercial-scale batches manufactured with the proposed changes (minimum three months of testing unless stated otherwise). 9. Commitment to continue long-term Active Pharmaceutical Ingredients stability studies.
4	Critical changes in the Active Pharmaceutical Ingredient purification process with the potential to impact on the process of viral clearance capacity or the Active Pharmaceutical Ingredient impurity profile.	1. Specific for Biological Products.	A. Quality documents 1. Flowchart (including process and IPC) and a narrative description of the proposed manufacturing process. 2. Process validation report. 3. Comparability studies before and after changes related to physicochemical properties, biological activity, purity, and contaminant . 4. NON-CLINICAL and/or clinical studies, if quality data do not demonstrate comparability. 5. Comparison of IPC and release testing results for at least three

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
			consecutive batches of commercial-scale Active Pharmaceutical Ingredient, of pre- and post- change. 6. Comparison of long-term stability test results, a minimum of three commercial-scale batches manufactured with the proposed changes (minimum three months of testing unless stated otherwise). 7. Commitment to continue long-term Active Pharmaceutical Ingredients stability studies. 8. Information regarding the risk of potential contamination with adventitious agents (for example, study of impact on viral clearance, risk of BSE/TSE).
D. Changes in the quality of Active Pharmaceutical Ingredients			
1	Changes to the new WCB or Working Seed Lot (WSL).	1. New cell bank or seed lot is derived from approved MCB/MSL. 2. New cell bank is in the approved passage level.	A. Administrative Documents, Product Information, and Labels 1. Revised information related to the quality and control of critical raw materials (e.g. specific pathogen-free egg and chickens) used in the new generation of proposed WCB. B. Updated quality documents 1. Qualification of cell bank or seed lot 2. Information on characterization and testing of WCB and cells from the post production passage. 3. Comparability studies of pre- and post-changes related to physicochemical properties, biological activity, purity, and contaminant. 4. Non-clinical and/or clinical studies,if the quality data does not demonstrate comparability. 5. Results of the quality control testing are in the form of quantitative data in tabular format for the proposed new cell bank. 6. Comparison of IPC testing results and release for at least three consecutive batches of commercial-scale Active Pharmaceutical Ingredient, of pre- and post- change. 7. Comparison of long-term Active Pharmaceutical Ingredient stability testing results, a minimum of three commercial-scale batches manufactured with the proposed changes (minimum three months of testing unless stated otherwise). 8. Commitment to continue long-term Active Pharmaceutical Ingredients stability studies.
2	Change and/or addition to Active Pharmaceutical Ingredient	1. Specifically for New Drugs and Drugs that require a bioequivalence test (BE test).	A. Quality documents 1. Drug Master File (DMF) from the API manufacturer 2. batch analysis of Active

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
	manufacturers or production facilities for the bulk of Active Pharmaceutical Ingredients or intermediate product .	2. Active Pharmaceutical Ingredient specifications remain unchanged 3. The specifications (passing and shelf life) of the Drug remain unchanged. 4. Drug stability tests have been carried out according to the protocol with a minimum of two pilot or production batches of Active Pharmaceutical Ingredients with a minimum of six months stability reportthat meet specifications.	Pharmaceutical Ingredient from proposed and approved manufacturers (Biological Product-specific analysis batches from a minimum of three consecutive batches of pilot/production scale). 3. Active Pharmaceutical Ingredient stability report (if necessary). 4. batch analysis of two batches of finished product (pilot/production scale)) of proposed and approvedAPI manufacturer (for Biological Product, analysis batches from a minimum of three consecutive batches of pilot/production scale). 5. stability reports of finished product and stability commitments if reports are incomplete. 6. Equivalence test data (in vitro/in vivo) (if necessary).
3	Change and/or addition manufacturing facilities of Active Pharmaceutical Ingredient or intermediates Active Pharmaceutical Ingredients.	1. Specific for Biological Products.	A. Quality documents 1. Report of process of validation of Active Pharmaceutical Ingredients. 2. Comparability studies of pre-change and post-changes related to physicochemical properties, biological activity, purity, and contaminant. 3. Non-clinical and/or clinical studies, if quality data do not demonstrate comparability. 4. Comparison of IPC testing results and release for at least three consecutive batches of commercial-scale Active Pharmaceutical Ingredient, of the pre- and post- change. 5. Comparison of long-term Active Pharmaceutical Ingredient stability testing results, a minimum of three commercial-scale batches manufactured with the proposed changes (minimum three months of testing unless stated otherwise). 6. Commitment to continue long-term Active Pharmaceutical Ingredients stability studies.
4	Changes in the process of manufacturing Active Pharmaceutical Ingredients or rawmaterials/intermediate product of Active Pharmaceutical Ingredients.	1. Not applicable for biological Product. 2. Not Applicable for Active Pharmaceutical Ingredients that requires BE testing (e.g.: pellet sustained release). 3. Not applicable for material from human/animal origin, which requires viral safety data. Active Pharmaceutical Ingredients stability tests have been carried out according to the protocol with a minimum of two pilot or production	A. Quality documents 1. Route synthesis of the Active Pharmaceutical Ingredient 2. batch analysis of Active Pharmaceutical Ingredientdata (two pilot/production scales) of the approved and proposed manufacturing processes. 3. Active Pharmaceutical Ingredient stability report of the new manufacturing process. 4. batch analysis of two batches of finished product (pilot/production scale) between Active Pharmaceutical Ingredients and the approved and proposed manufacturing

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
		batches of Active Pharmaceutical Ingredients with a minimum of six months stability report that meet specifications.	processes.
5	Introduction of reprocessing step of Active Pharmaceutical Ingredient.	1. The need for reprocessing is not due to repeated deviations from the validated process and the root cause of the reprocessing is identified.	A. Quality documents 1. Comparison of IPC test results and release for at least three consecutive batches of commercial-scale of Active Pharmaceutical Ingredient, before and after the change. 2. Comparison of the results of the Active Pharmaceutical Ingredient stability test, a minimum of three commercial scale batches manufactured with the proposed changes under long-term conditions (minimum three months of testing or stated otherwise). 3. Commitment to submit long-term stability studies of Active Pharmaceutical Ingredients. 4. Root cause analysis reprocessing, including validation data to prevent reprocessing impacting the Active Pharmaceutical Ingredients.
6	Changes and/or additions to manufacturers/ sources of raw materials of biological origin.	1. Specific for Biological Products.	A. Quality documents 1. BSE/TSE certificate (when using materials with potential BSE/TSE risk) or information and evidence that the material does not pose the potential a BSE/TSE risk. 2. Comparison of IPC testing results and release for at least three consecutive batches of commercial-scale Active Pharmaceutical Ingredient, of pre- and postchange. *3.* Information assessing the risk with respect to potential contamination with adventitious agents. 4. Information demonstrated suitability the auxiliary materials/reagents of two sources.
7	Changes in the production scale at the fermentation, viral or cellular propagation stage.	1. Specific for Biological Products. 2. There is no change in the Active Pharmaceutical Ingredient specification outside the approved limit. 3. There is no change in the Active Pharmaceutical Ingredient impurity profile outside the approved limit. 4. Changes are not result repeated events during manufacturing or due to stability issues. 5. Changes have no impact on the purification process. 6. Changes have no impact on the quality, safety or efficacy of the Finished Product.	A. Quality documents 1. Flow diagram (including process and IPC) and a narrative description of the proposed manufacturing process. 2. Information on the characterization and testing of the post production cell bank for recombinant products or antigens for non-recombinant products, if changes have an impact on increasing the number of population doubling or sub-cultivation. 3. Process validation study report. 4. Comparability studies pre- and post-changes related to physicochemical properties, biological activity, purity, and contaminant .

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
		7. There is no change in the proportionality of raw materials (there is, the change in scale is linear). 8. Scale in changes involve the use of the same bioreactor.	5. If the quality data are not sufficient to describe comparability, Non-clinical and/or clinical studies should be submitted. 6. Comparison of IPC testing results and release for at least three consecutive batches of commercial-scale Active Pharmaceutical Ingredient, of pre- and post- change.
8	Changes in the scale of the production process at the purification stage.	1. Specific for Biological Products. 2. There is no change in the principle of the antigen sterilization procedure. 3. There is no change in the antigen specification outside the approved limit 4. Changes are not due to repeated events during manufacture or due to stability issues. 5. Changes in scale is linear with respect to the proportionality of production parameters and materials.	A. Quality documents 1. Flow diagram (including process and IPC) and a narrative description of the proposed manufacturing process. 2. Process validation study report. 3. Comparability studies pre and post- changes related to physicochemical properties, biological activity, purity, and contaminant. 4. Non-clinical and/or clinical studies, if quality data do not demonstrate comparability. 5. Comparison of IPC testing results and release for at least three consecutive batches of commercial-scale Active Pharmaceutical Ingredient, of before and after the change. 6. Comparison of long-term Active Pharmaceutical Ingredient stability testing results, a minimum of three commercial-scale batches manufactured with the proposed changes (minimum three months of testing unless stated otherwise). 7. Commitment to continuelong-term Active Pharmaceutical Ingredients stability studies.
9	widening the approved in-process limit for the manufacture of Active Pharmaceutical Ingredients.	1. Specific for Biological Products.	A. Quality documents 1. Scientific and/or historical data to support the reasons/justifications for the proposed changes. 2. Information on IPC performed at critical steps of the manufacturing process and on intermediates of the proposed Active Pharmaceutical Ingredients. 3. A copy or summary of the analytical procedure, if new analytical procedures are used. 4. Validation study reports, if new analytical procedures are used. 5. IPC comparisons or specifications pre- and post-change. 6. Comparison of IPC testing results and release for at least three consecutive batches of commercial-scale Active Pharmaceutical Ingredient, of pre- and post- change. 7. justification for the new in-process testing and limits 8. Comparison of long-term Active Pharmaceutical Ingredient

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
			stability testing results, a minimum of three commercial-scale batches manufactured with the proposed changes (minimum three months of testing unless stated otherwise). 9. Commitment to continue long-term Active Pharmaceutical Ingredients stability studies. 10. Comparison of changes to Active Pharmaceutical Ingredient specifications (if necessary).
10	Deletion of in-process testing, which may have a significant effect on the overall quality of the Active Pharmaceutical Ingredient.	1. Specific for Biological Products.	A. Quality documents 1. Scientific and/or historical data to support the reasons/justifi cations for the proposed changes. 2. Information on IPC performed at critical steps of the manufacturing process and on intermediates of the proposed Active Pharmaceutical Ingredients. 3. IPC comparisons or specifications pre and post-change. 4. Comparison of IPC testing results and release for at least three consecutive batches of commercial-scale Active Pharmaceutical Ingredient, of pre and post- change.
11	Addition or replacement of an in-process testing due to safety or quality issues.	1. Specific for Biological Products.	A. Quality documents 1. Scientific and/or historical data to support the reasons/justifications for the proposed changes. 2. Information on IPC performed at critical steps of the manufacturing process and on intermediates of the proposed Active Pharmaceutical Ingredients. 3. A copy or summary of the analytical procedure, if new analytical procedures are used. 4. Validation study reports, if new analytical procedures are used. 5. IPC comparisons or specifications pre- and post-change. 6. Comparison of IPC testing results and release for at least three consecutive batches of commercial-scale Active Pharmaceutical Ingredient, of pre and post- change. 7. Comparison of changes to Active Pharmaceutical Ingredient specifications (if necessary).
12	Change in animal species/strains for Active Pharmaceutical Ingredient release testing (for example, new species/strains, animals of different ages, new supplier	1. Specific for Biological Products	A. Quality documents 1. Data demonstrating that the proposed changes in animal/strains give results that are comparable to those obtained using the approved animals/strains. 2. Relevant certificate of fitness

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
	where animal's genotype cannot be confirmed).		for used (for example veterinary certificate) .
13	Changeofspecifications of non-Pharmacopeial Active Pharmaceutical Ingredients.	1. Not including Biological Products. 2. stability tests of Active Pharmaceutical Ingredients have been carried out according to the protocol with a minimum of two batches on a pilot scale or production scale with a minimum of six months data providing results that meet specifications.	A. Quality documents 1. Specifications of the New Active Pharmaceutical Ingredients . 2. Analytical method of Active Pharmaceutical Ingredients. 3. Validation report of Active Pharmaceutical Ingredient analytical method. 4. Active Pharmaceutical Ingredient batch analysis for all methods at the new specification (two pilot/production scales). 5. Active Pharmaceutical Ingredient stability report and Active Pharmaceutical Ingredient stability commitment if the Active Pharmaceutical Ingredient stability report is incomplete.
14	widening of the specification of starting material/ intermediate, which has a significant effect on the overall quality of the Active Pharmaceutical Ingredient and/or Finished product.	1. Changes are not a consequence of prior assessment commitments to review specification limits. 2. The Change should not be the result of unexpected eventsarisingduring manufacturing process of the Active Pharmaceutical Ingredient (e,g, new impurities; changes to total contamination limit). 3. Test procedures remain unchanged, or with minor changes. 4. The test method is not the biological/immunological immunochemical method or the method that uses the biological reagent for biologically Active Pharmaceutical Ingredients (not including pharmacopeia microbiological methods). For any material, the change does not concern a genotoxic impurity. If it involves the final active substance, other than for residual solvent which must be in line with ICH /VICH limits, any new impurity control should be in linewith the Ph. Eur. or National Pharmacopoeia of a Member State.	A. Quality documents 1. Comparative table of current and proposed specifications 2. Details of any new analytical methods and validation data where relevant . 4. Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the relevant substance for all specification parameters. Where appropriate, Comparative dissolution profile data for the finished product on at least one pilot batch containing the active substance complying with the current and proposed specification 5. Justification of the new specification parameter and the limits.
15	Deletion of Active Pharmaceutical Ingredient release test parameters.	1. Specific for Biological Products.	A. Quality documents 1. Proposed Active Pharmaceutical Ingredient Specifications. 2. Scientific and/or historical data to justify the proposed changes. 3. Evidence that consistency of quality and of the production process is maintained.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
16	Widening the acceptance criteria for of the Active Pharmaceutical Ingredient release specifications.	1. Specific for Biological Products.	A. Quality documents 1. Scientific and/or historical data to justify the proposed changes. 2. Proposed Active Pharmaceutical Ingredient Specifications. 3. Evidence that consistency of quality and of the production process is maintained.
17	Change in shelf life specification of Active Pharmaceutical Ingredient	1. Specific for Biological Products 2. For any changes to the shelf life specification of Active Pharmaceutical Ingredient. 3. Drug specifications remain unchanged.	A. Quality documents 1. Scientific and/or historical data to justify the proposed changes. 2. Comparison of release and/or shelf life specifications, of approved and proposed, with marked changes. 3. Stability of Active Pharmaceutical Ingredient of at least three batches of production scale with proposed specifications and commitment to continue stability studies until the approved shelf life.
18	Changes in Excipients in the Biological Products Active Pharmaceutical Ingredients	1. For any qualitative or quantitative change of the Excipient in the Active Pharmaceutical Ingredient. 2. Changes in Excipients do not affect the analytical method of release and shelf life specification of Drugs. 3. The batch formula and Drug specifications remain unchanged.	A. Quality documents 1. Justification of change is given in the form of appropriate pharmaceutical development (including aspects of stability and preservation with antimicrobials, where appropriate). 2. Description and flowchart of the manufacturing process of Active Pharmaceutical Ingredients. 3. Specifications of approved and proposed excipient. 4. CoA of New Excipient. 5. Comparison of proposed and approved Active Pharmaceutical Ingredient specifications *6.* Information indicating comparability of approved and proposed Excipient of in terms of physicochemical characterization and impurity profile. *7.* Stability of Active Pharmaceutical Ingredients with new Excipients. *8.* For excipients at risk of TSE, if necessary: - Certificate of Suitability for Excipients. - Documented evidence demonstrating that TSE risks of Excipients have been evaluated. *9.* Specifications of release and shelf life of Drugs *10.* Comparative batch analysis data (in tabular form) of at least three batches of Drugs manufactured using Active Pharmaceutical Ingredients with approved and proposed Excipients. *11.* The results of the stability study of at least three batches of Drugs manufactured using Active Pharmaceutical

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
			Ingredients with new Excipients according to relevant stability guidelines and a declaration letter to continue the stability study until the shelf life (if necessary) and report to Indonesian FDA if there are results that do not meet requirements (with an action plan) or if requested by the Indonesian FDA
19	Changes of testing procedures in the process control, release and stability of Active Pharmaceutical Ingredients.	1. Specific for Biological Products. 2. For any changes of the testing procedure for release or stability test of the Active Pharmaceutical Ingredient. 3. Active Pharmaceutical Ingredient specifications remain unchanged	A. Quality documents 1. Description of the proposed testing method. 2. Report on the validation study of the proposed testing procedure. 3. Results of the comparative test between the approved and proposed testing procedures.
20	Changes to the Active Pharmaceutical Ingredient container closure system.	1. Specific for Biological Products. 2. For any changes, including the type of packaging, qualitative and quantitative composition, shape and dimensions of the packaging system in direct contact with the Active Pharmaceutical Ingredient. 3. For any changes that are not included in the Minor Variation category.	A. Quality documents 1. Information on construction material and design features proposed of packaging system . 2. Compatibility study report, leaching materials, leak test, etc to demonstrate the suitability of the proposed container closure system. 3. Validation reports of manufacturing process using the proposed container closure system (if necessary). *4.* Specifications of relase and shelf life of Active Pharmaceutical Ingredients. 5. The results of the stability study of at least three batches of Active Pharmaceutical Ingredients manufactured using the proposed container closure system in accordance with the relevant stability studies and a declaration letter of continuing the stability study until the shelf life, if necessary, and report to the Indonesian FDA if there are test results that do not meet the requirements (with an action plan) or when requested by Indonesian FDA
21	Inclusion of new/updated /amended to Plasma Master File (PMF).	1. Variations are made for registered blood products. 2. Changes have a potential effect on product quality and safety.	A. Administrative Documents 1. GMP certificate of plasma collection and processing facilities and/or declaration letter of compliance with GMP aspects of plasma collection and processing facilities in case of update/change of plasma source. B. Quality documents *1.* Specifications of release and shelf life of Active Pharmaceutical Ingredients. *2.* Specifications of release and shelf life of Drugs. 3. Comparative batch analysis

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
			data (in tabular form) of at least three batches manufactured of approved plasma sources and proposed plasma sources. 4. The results of the stability study of at least three batches manufactured using the new PMF source and/or a new plasma source, according to the relevant stability guidelines. 5. Reports on Adventitious Agents Safety Evaluation, if necessary. 6. . An expert statement outlining all the changes introduced with the certified VAMF and evaluating their potential impact on the finished products including product specific risk assessments. 7. For new/amended PMF, it must be enclosed by: a. New /new version of PMF; *b.* Plasma specification and batch analysis data of plasma pool; c. Annual EMA re-certification letter, and if any report of a re-certification assessment result; d. Letter of Access issued by PMF holder to the product owner; and e. Information in Section S.2.3 which includes: • Sources and pooling of plasma . • Donation characteristics. • Epidemiological data regarding blood transmissible infections. • Selection/exclusion criteria. • Plasma quality and safety. • Plasma storage and transport conditions. • Plasma specification and batch analysis data of plasma pool.
E. Changes related to the quality of Finished Product			
1	Increase of Finished product batch size by more than ten fold.	1. Not including Biological Products. 2. Formulas and specifications (release and shelf life) of finished product remain unchanged. 3. processvalidationaccordin g to the previously approved batch. 4. Changes do not affect the reproducibility and/or consistency of theFinished product. 5. Stability tests have been carried out according to the protocol with a minimum of two batches on a pilot or production scale with a minimum of six months of data providing results that meet specifications.	A. Quality documents 1. Manufacturing process and process control 2. Batch formula. 3. Flowchart of production process from start to final packaging. 4. Manufacturing Process Validation result of Finished product. 5. Finished product Specifications. 6. Analytical results of the finished product batch. 7. Comparison of batch analysis data between previous production batches (three batches of finished productat production scale) and currently proposed (minimum of two batches of Finished product at pilot scale or production scale). 8. Commitment to submit a new production scale analysis batch (if pilot scale batch analysis

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
			submitted) 9. Finished product stability report from the pilot scale or the new production scale and Finished product stability commitment if the report is incomplete.
2	Increase ofFinishedDrug product batch size up to ten fold, for sterile products.	1. Not including Biological Products. 2. Formulasand specifications (release and shelf life) offinished product remain unchanged. 3. The process validation results according to the previously approved batch. 4. Changes do not affect the reproducibility and/or consistency of theFinished product. 5. Stability tests have been carried out according to the protocol with a minimum of two batches on production scale with a minimum of six months of data providing results that meet specifications.	A. Quality documents 1. Manufacturing process and process control 2. Batch formula. 3. Flowchart of production process from start to final packaging. 4. Manufacturing Process Validation result of finished product and the sterilization validation process result. 5. Finished product Specifications. 6. Analysis results of the finished product batch. 7. Comparison of batch analysis data for at least two batches of finished product on the current and proposed production scales. 8. Finished product stability report from the current production scale and finished product stability commitment if the report is incomplete.
3	Decrease of the size of the Drug batch up to ten times, for sterile products.	1. Not including Biological Products. 2. Formulas and specifications (release and shelf life) of finished product remain unchanged. 3. The process validation results according to the previously approved batch. 4. Changes do not affect the reproducibility and/or consistency of the Finished product. 5. Changes are not due to the manufacturing process of the finished product or stability problems. 6. Stability tests have been carried out according to the protocol with a minimum of two batches on production scale with a minimum of six months of data providing results that meet specifications.	A. Quality documents 1. Manufacturing process and process control 2. Batch formula. 3. Flowchart of production process from start to final packaging. 4. Manufacturing process validation report of the finished product. 5. Finished product specifications. 6. Analysis results of the finished product batch. 7. Comparison of batch analysis data for at least two batches of finished product on the current and proposed production scales. 8. Finished product stability report from the current production scale and finished product stability commitment if the report is incomplete.
4	Scale up of manufacturing process at the formulation/filling stage.	1. Specific for Biological Products. 2. The proposed scale uses similar equipment/comparable with those already approved. Note: any change in equipment size is considered not of the same type/incomparable. 3. Other changes related to the production process	A. Quality documents 1. Description of the manufacturing process, if it is different from the approved process, and information of the critical step IPC and intermediate of the proposed Finished Products. 2. IPC testing information, as proposed. 3. Process validation study report (for example, media fill), as proposed.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
		and/or to IPC are only caused by changes in batch size (for example, the formulation, test and Standard Operating Procedure (SOP) are the same). 4. Changes cannot be done due to repeated events during production or stability issues. 5. No change in the principle of the sterilization procedures of the final product	4. Comparative release test results for at least three consecutive batches of commercial-scale finished product , before and after the change. 5. Comparativelong-term Finished-product stability test results, a minimum of three commercial-scale batches manufactured with the proposed changes (minimum three months of testing unless stated otherwise). 6. Committed to continue long-term stability studies to support complete shelf life/hold time under normal storage conditions and reporting it to Indonesian FDA if any failures occurred during the long-term stability studies. 7. Information on leachable and extractable, as proposed.
5	Change in coating weight of oral dosage forms or□change in weight of capsule shells, Gastro-resistant, modified or prolonged release□pharmaceutical	1. formula of finished product (qualitative) does not change. 2. Composition of the coating and capsule shells does not change. 3. The dissolution profile of the Finished product does not change for solid preparation forms (if applicable). 4. Specifications (release and shelf life) of the Finished product does not change except for the coating weight 5. Stability tests have been carried out according to the protocol with a minimum of two batches on a pilot or production scale with a minimum of six months of data providing results that meet specifications.	A. Quality documents 1. Batch formula. 2. batchAnalysis results of finished product . 3. Comparative finished product batch analysis data of at least two batches (pilot/production scale) of approved and proposed tablet or capsule shell coatings. 4. Finished Product stability report of two batches of pilot scale with new Formula and Finished Product stability commitment if Finished Product stability report is incomplete. 5. Equivalence study(in vitro/in vivo) (if necessary). 6. Justification for not submitting a new BE study
6	Quantitative and/or qualitative change ofExcipients.	1. Not including Biological Products. 2. Not for changes that require clinical study (efficacy and safety). 3. Stability tests have been carried out according to the protocol with a minimum of two batches on a pilot or production scale with a minimum of six months of data providing results that meet specifications.	A. Quality documents 1. Pharmaceutical development. 2. Batch formula. 3. Flowchart of manufacture process from start to final packaging. 4. manufacturing process validation Report of Finished product 5. Excipient specifications and test methods. 6. Finished product Specifications. 7. Finished product analysis procedure. 8. Analytical validation method report of finished product . 9. Batch Analysis results of Finished product 10. Comparison of finished product batch analysis data from at least two batches (pilot/production scale) of current andproposedFormulas. 11. The results of content

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
			uniformity test (forscoring or breakline). 12. Finished product stability reports and Finished product stability commitments if finished product stability reports are incomplete. 13. Equivalence study (in vitro/in vivo)(If applicable) 14. Justification for not submitting a new BE study
7	Changes in Excipients for Biological Products.	1. For any qualitative or quantitative changes to the Excipient formulation on thefinishedproduct. 2. Changes in Excipients do not affect release specification test method and f' shelf life.	A. Quality documents 1. Comparison of batch formula and formula per unit dose of approved and proposed finished product. 2. Justification of change must be given in the form of appropriate pharmaceutical development (including aspects of stability and preservation with antimicrobials, where appropriate). *3.* Information indicating comparability of Excipient between those approved and proposed in terms of physicochemical characterization and impurity profile. 4. For Excipients with TSE risk , if necessary: - Certificate of Suitability of the Excipient. - Documented evidence showing that Excipients' TSE risks have been evaluated. 5. Comparison ofreleaseandshelf life specifications of approved and proposed finished product. 6. Comparison of batch analysis data (in tabular form) of at least three batches of finished product manufactured according to the approved and proposed formulations. 7. Stability study result of at least three batches of finished product manufactured with the proposed Formula according to relevant stability guidelines and a declarationletter to continue the stability study until the shelf life, if necessary, and report to Indonesian FDAif there are results that do not meet requirements (with an action plan) or if requested by Indonesian FDA
8	Changes in theFinished Product manufacturing process that affect stability.	1. Not including Biological Products. 2. Not affecting safety and efficacy of the.product 3. processValidation/consistency of production has been carried out. 4. Formulas and specifications (release and shelf life) of Finished product remain unchanged.	A. Quality documents 1. Pharmaceutical development. 2. Manufacturing process and process control. 3. Flowchart of manufacturing process from start to final packaging. 4. Manufacturing validation Report of t finished product. 5. Batch Analysis of finished product 6. Comparative batch analysis

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
		5. Stability tests have been carried out according to the protocol with a minimum of two batches on a pilot or production scale with a minimum of six months of data providing results that meet specifications.	data in the approved manufacturingprocess (three production-scale finished product batches) and the proposed one (minimum of finished product from two production-scale batches or one production scale batch and two pilot batches). 7. Finished product stability reports of two pilot scale batches and finished product stability commitments if the stability reports are incomplete and stability commitments of one production scale batch.
9	Changes in the finished product manufacturing process at the same manufacturer	1. Biological Products Specific. 2. For any changes in the manufacturing processand/or changes in the scale of production at each step of finished product manufacturing process. 3. For any changes not included in the Minor Variation.	A. Quality documents 1. Study Reports and summary of the the proposed manufacturing process validation 2. Release and shelf lifeSpecificationsoffinished product. 3. Comparative batch analysis data (in tabular form) of at least three batches offinished product manufactured using approved and proposed processes. 4. Stability study reports of at least three batches of finished product manufactured with the proposed process according to relevant stability guidelines and a declarationletter to continue the stability study up to shelf life, if necessary, and report to the Indonesian FDA if there are test results that do not meet requirements (with an action plan) or if requested by the Indonesian FDA 5. A declarationletter stating that: a. There is no change in terms of the qualitative and quantitative impurity profile or physicochemical properties; b. Changes do not give negative changes to the reproducibility of the process; c. Changes made are not the result of adverse events during production or due to stability problems; d. Finished productspecificationsremain unchanged.
10	Replacement or additions of a manufacturingsiteforpart or all of the manufacturing process of thefinishedproduct .	1. Evaluation Results of SMF /inspection (if required) meet the requirements. 2. Satisfactory results of GMPinspection in the last two years . 3. There is no change in Formula, source of Active Pharmaceutical Ingredient materials and Excipients, production processes,finished product and packaging material specifications. 4. finished product	A. Administrative Documents, Product Information, and Labels 1. Product Information (if necessary). 2. Packaging labels (if necessary). B. Quality documents 1. Manufacturing process and process control. 2. Flowchart of manufacturing process from start to final packaging. 3. Finished Product manufacturing process validationReportin the

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
		manufacturing process validation has been carried out in accordance with the protocol of three batches of production-scale or a minimum of one finished product batch pilot-scale and validation process commitment of the first three production batches with the estimated time of delivery. (For Biological Products: Process validation reports of a minimum of three batches production scale). 5. Analytical method transfer from the current site to the proposed site meets the requirements. 6. Stability tests have been carried out according to the protocol with a minimum of two batches on a pilot or production scale with a minimum of six months of data providing results that meet specifications. (For Biological Products:Finised product stability report in the proposed site of at least three batches production scale).	proposedsite. 4. Report on analytical method transfer validation/verification results of, from the current site to the proposed site. 5. batchAnalysisof finished product . 6. Comparative batch analysis data in the current manufacturing site (three production-scale batches) and the proposed site (minimum of two production-scale batches or one production scale batch and two pilot batches). 7. Comparative dissolution profile data of finished product from the current and proposed manufacturing sites (if necessary). 8. Finished product stability reports and stability commitments if the stability reports are incomplete. (For Biological Products: Stability study reports of finished product manufacture in the current site of at least three production scale batches). 9. Equivalence study (in vitro/in vivo) (if necessary)
11	Changes to the site for Finished product primary packaging. Changes of primary packaging site of finished product	1. Not for sterile products. 2. Satisfactory Results of GMPinspection in the last two years . 3. Formula, source of Active Pharmaceutical Ingredient materials and Excipients, manufacturing process, finished product, and packaging material specifications remain unchanged 4. Finished product primary packaging process validation has been carried out in accordance with the protocol of three batches of production-scale or a minimum of one batch pilot-scale and validation process commitment of the first three production batches with the estimated time of delivery. 5. Stability tests have been carried out according to the protocol with a minimum of two batches on a pilot or production scale with a minimum of six months of data providing results that meet specifications.	A. Administrative Documents, Product Information, and Labels 1. Product Information (if necessary). 2. label (if necessary). B. Quality documents 1. Flowchart of manufacturing process from start to final packaging and information of location for each step up to the final packaging. 2. primarypackagingmanufacturing process validation in the new site. 3. batch Analysis of finished product . 4. Comparative batch analysis data in the thecurrent manufacturing site (three production-scale batches) and the proposed one (minimum of two production-scale batches or one production scale batch and two pilot batches). 5. Study of bulk holding time (if necessary). 6. Finished product stability reports and stability commitments if the stability reports are incomplete.
12	Changes of non-pharmacopeial finished product specifications.	1. Finished product analytical methodsremainunchanged. 2. Stability tests have been carried out according to the protocol with a minimum of two batches on a pilot or	A. Quality documents 1. New specifications of finished product. 2. Finished product batch analysis data for all tests of the new specifications (two

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
		production scale with a minimum of six months of data providing results that meet specifications.	pilot/production scales). 3. Finished product stability reports and stability commitments if the stability reports are incomplete.
13	Changes in shape and/or dimensions of primary packaging (for sterile preparations).	1. specifications for primary packaging materials remain unchanged. 2. The change does not concern a fundamental partof the packaging material which affects the delivery, use, safety or stability of the finished product. 3. Specifically for Finished product with final sterilization method: Finished Product manufacturing process validation has been carried out in accordance with the protocol of three batches of production-scale or a minimum of one batch pilot-scale and commitment validation process of the first three production batches with the estimated time of submission. 4. In the case of a changein the "head space" or a change in the "surface/volume ratio": • Stability tests have been carried out according to the protocol with a minimum of two batches on a pilot scale orproduction scale with at least six months of data provides results that meet specifications.	A. Administrative Documents, Product Information, and Labels *1.* Samples of primary packaging in the form of photographs or images according to the actual packaging (mock up/dummy). B. Quality documents 1. Packaging and its material testing methods. 2. Finished product manufacturing process validationReportforFinished product with final sterilization method. 3. Finished product stability reports and stability commitments if the stability reports are incomplete.
14	Changes of of release and shelf life specifications of finished product.	1. Biological Products Specific. 2. For any changes of release and shelf lifespecifications of finished product.	A. Quality documents 1. Justification of changes with scientific and/or historical data to support the proposed changes. 2. Comparative release and/or shelf life specifications of Finished product, in the current and proposed, with marked changes. 3. Finished product batch analysis for all proposed specification tests (minimum three batches). 4. For any change to the stability-indicating parameter in the specification: – appropriate stability study results of at least three batches of Finished product tested according to the proposed specifications in line with the relevant stability guidelines; and – A declarationletter stating to continue the stability study up to the approved shelf life, if necessary, and report to Indonesian FDA ifthetest

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
			results do not meet the requirements (with an action plan) and if necessary.
15	Changes in specifications on process control in the Finished product manufacturing process.	1. For any changes to specifications on process control in the Biological Product manufacturing process.	A. Quality documents 1. Justification of changes with scientific and/or historical data to support the proposed changes. 2. Comparative specifications on process controls in the current and proposed, with marked changes. 3. Batch analysis for all proposed process controls of a minimum three batches.
16	Widening of the approved in-process controllimitin the manufacturing process of finished product.	1. Biological Products Specific.	A. Quality documents 1. .Revised information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed antigen. 2. Update of Finished Product specifications, if changed. 3. A copy or summary of the analytical procedure, if new analytical procedures are used. 4. Validation study reports, if analytical procedures are used. 5. Comparative table or descriptionwhere applicable, of pre- and post- changein process test or limit.. 6. Comparative batch analysis data of at least three consecutive,commercial-scale batches of the pre- and post-change 7. Justification for the new in-process test and limit. 8. Comparative long-term Finished product stability test, a minimum of three commercial-scale batches manufactured with the proposed changes (minimum of three months testing unless otherwise justified).
17	Changes in the excipient testing procedure of .	1. Biological Products Specific. 2. For any changes to the testing procedure of Excipient 3. SpecificationsofActive Pharmaceutical Ingredients and Finished product remain unchanged.	A. Quality documents 1. Description of the proposed testing method. 2. Validation study report of the proposed testing procedure. 3. Comparative study resultof the approved -and the proposed testing procedures.. 4. Excipient Specifications.
18	Changes in the production of biological Excipients (excluding biological adjuvant).	1. Specific for Biological Products.	A. Quality documents 1. Detailed information on the source of the Excipient (e.g. animal species, country of origin) and the steps taken during the process to minimize the risk of TSE exposure. 2. Comparison of the physicochemical properties and impurity profile of the proposed and approved Excipients.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
			3. Information on manufacturing process and control of critical steps in the manufacturing process and on the intermediate the proposed Excipients. 4. Comparison of batch analysis data of at least three consecutive batches of commercial-scale Excipients, between pre- and post- change. 5. Comparison of long-term Drug stability test results, a minimum of three commercial-scale batches manufactured with the proposed changes (minimum three months of testing unless stated otherwise). 6. Commitment to continue long-term Drug stability studies. 7. Risk assessment information regarding potential contamination with adventitious agents (for example, impact on viral clearance study or BSE/TSE risks), including documentation of viral safety as required.
19	Change in manufacturers of plasma-derived Excipient.	1. Specific for Biological Products.	A. Quality documents 1. Comparison of the physicochemical properties and impurity profile of the proposed and approved Excipients. 2. Information on manufacturing process and control of critical steps in the manufacturing process and on the intermediates the proposed Excipients. 3. Comparison of batch analysis data of at least three consecutive batches of commercial-scale Excipients, between pre- and post- change. 4. Comparison of long-term Drug stability test results, a minimum of three commercial-scale batches manufactured with the proposed changes (minimum three months of testing unless stated otherwise). 5. Commitment to continue long-term Drug stability studies. *6.* Risk assessment information regarding potential contamination with adventitious agents. 7. Complete manufacturing and clinical safety data to support the use of proposed human plasma-derived Excipients.
20	Changes in testing procedures on process control in the Finished product manufacturing process.	1. Biological Products Specific. 2. For any changes in the testing procedure for the release or stability test of the Finished product. 3. Specifications of Active Pharmaceutical Ingredients and Finished product remain unchanged.	A. Quality documents 1. Description of the proposed testing method. 2. Validation study report of the proposed testing procedure. 3. Comparative testresultof the approved and proposed testing procedures.
21	Changes to Finished product testing	1. Biological Products Specific. 2. For any changes in the test	A. Quality documents *1.* Specifications of releasing and

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
	procedures for releasing/stability studies.	procedure for the passing or stability test of the Finished product. 3. Specifications for Active Pharmaceutical Ingredients and Finished product remain unchanged.	shelf life of Finished product. 2. Description of the proposed testing method. 3. Report on the validation study of the proposed testing procedure. 4. Results of the comparative test between the approved and proposed testing procedures.
22	Changes in the Finished product packaging system.	1. Biological Products and sterile preparations specific. 2. For any changes, including the type of packaging, qualitative and quantitative composition, shape and dimensions of the packaging system in direct contact with the Finished product. 3. For any changes that are not included in the Minor Variation category.	A. Quality documents 1. Information on proposed construction material and packaging system design features.. 2. Compatibility study report, leaching materials, leak test, and so forth to show the suitability of using the proposed packaging system. 3. Validation reports of production process using the proposed packaging system (if necessary). *4.* Specifications of releasing and shelf life of Finished product. 5. Comparison of long-term Finished product stability test results, a minimum of three commercial-scale batches produced with the proposed changes (minimum three months of testing unless stated otherwise). 6. Commitment to continuing long-term Finished product stability studies.
23	Changes in solvent packaging system.	1. Biological Products Specific. 2. For any changes, including the type of packaging, qualitative and quantitative composition, shape and dimensions of the packaging system in direct contact with the solvent used for reconstitution. 3. For any changes that are not included in the Minor Variation category.	A. Quality documents 1. Information on proposed construction material and packaging system design features.. 2. Compatibility study report, leaching materials, leak test, and so forth to show the suitability of using the proposed packaging system. 3. Validation reports of production process using the proposed packaging system (if necessary). *4.* Specifications of releasing and shelf life of solvents. 5. The appropriate results of stability study of at least three solvent batches produced using the proposed packaging system according to the relevant stability studies.
24	Change in package size/volume and/or change in shape or dimension of packaging for solid and liquid sterile preparations	1. Finished product with the new packaging are consistent with the posology and duration of treatment. 2. Finished product specifications remain unchanged. 3. Packaging specifications remainunchanged. 4. Stability tests have been carried out according to the protocol with a minimum of two batches	A. Product and Label Information 1. Product Information 2. Primary and secondary packaging labels. B. Quality documents 1. Justification stating that the proposed preparation volume is consistent with the approved dosage regimen. 2. Reports on process validation, sterilization, and packaging system (if necessary).

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
		on a pilot or production scale with a minimum of six months of data providing results that meet specifications.	3. Batch analysis certificate (minimum two batches of Finished product). 4. Drug stability reports and Drug stability commitments if the Drug stability data are incomplete.

2. CATEGORY 5: MINOR VARIATION REGISTRATION

No.	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
A. Changes related to Product and/or Label Information			
1.	Product Information Changes.	1. Generic Drugs Specific. 2. Product Information (proposed claim) must be in accordance with approved claim in Indonesia.	A. Product and Label Information 1. Product Information 2. Packaging labels (if necessary). 3. Supporting documents for proposed product information changes.
2.	Change in the name of Applicant/Pharmaceutical Industry/Licensor/ Importer of the Finished product.	1. The owner of the Marketing Authorization remain unchanged. 2. The location of the Applicant/Pharmaceutical Industry/Drug licensor is remain unchanged.	A. Product and Label Information 1. Certificate of Name Change 2. Product Information 3. Packaging labels.
3.	Change of a drug trade name	1. The drug name is in accordance with the applicable provisions. 2. Product Information, Labels and packaging design remain unchanged.	A. Product and Label Information 1. Product Information 2. Primary and secondary packaging labels.
4.	Large-volume packaging.	1. Product information claim remainunchanged. 2. Packaging specifications remainunchanged.	A. Product and Label Information 1. Product Information 2. Secondary packaging labels.
5.	Addition of Product Information in English/Indonesian.	1. Product Information is in accordance with the claimapproved.	A. Product and Label Information 1. Product Information 2. Packaging labels (if necessary).
6.	Tightening the claim related to safety.		A. Product and Label Information 1. Product Information B. Clinical documents 1. Justification of and/or other supporting documents in accordance with the proposed changes. 2. Post-marketing safety report/PSUR (if necessary). 3. Another reference.

B. Changes in the quality of Active Pharmaceutical Ingredients			
1.	Changes or additions to production facilities for *bulk* Active Pharmaceutical Ingredients or intermediateActive Pharmaceutical Ingredients.	1. The proposed production facility is an approved antigen production location. 2. Any changes to the production process and/or controls are considered as a category of Minor Variations *(Variasi Minor)* or Notification Variations *(VariasiNotifikasi)* 3. Facilities in the new location are under the supervision of the same quality assurance/quality control. 4. The proposed changes do not involve additional *requirements of* containment.	A. Quality documents 1. Justification that the proposed changes are included in the Minor Variation category. 2. Comparability study before and after related changes: - physicochemical characteristics, - biological activity, - Purity - contamination, and - contaminants according to the proposed changes. 3. Comparison of IPC test results and *release* for at least three consecutive batches of commercial-scale Active Pharmaceutical Ingredient, in between before and after the change. 4. Comparison of the results of the Active Pharmaceutical Ingredient stability test, a minimum of three commercial scale batches produced with the proposed changes under long-term conditions (minimum three months of testing or stated otherwise). 5. Commitment to continue long-term stability studies to support *shelf life/hold time* Completed under normal storage conditions and reported to Indonesian FDA of any failures occurred during the long-term stability studies.
2.	Minor changes in the Active Pharmaceutical Ingredient manufacturing process.	1. Biological Active Pharmaceutical Ingredients are excluded. 2. No change in qualitative and quantitative *impurity*profile/ physico-chemical properties. 3. The synthesis route remains the same (for instance: the reaction intermediate remains unchanged). 4. Specifications and stability of the Active Pharmaceutical Ingredient or product intermediate remainunchanged. 5. The manufacturing process of Active Pharmaceutical Ingredients does not use raw materials from human/animal sources requiring viral safety.	A. Quality documents 1. Characterization of Active Pharmaceutical Ingredients. 2. Description of the Active Pharmaceutical Ingredient synthesis. 3. Results of the Active Pharmaceutical Ingredient analysis. 4. Comparative data of two batches analysis for Active Pharmaceutical Ingredient (pilot/production scale) produced according to the approved and proposed Chemical Entitymanufacturing process. 5. For the sterile Active Pharmaceutical Ingredients, the report of manufacturing process production and validation should be reported (if necessary).

3.	Minor changes to the manufacturing process of Active Pharmaceutical Ingredient.	1. Biological Products Specific. 2. Applies to any minor changes in procedure and/or production scale at any stage of Active Pharmaceutical Ingredient production. 3. Regarding non-critical changes, such as in *harvesting* and/or *pooling* without changing production method, recovery, condition or production-scale storage; duplication *of fermentation strain*, adding bioreaction that is identical or similar/ *comparable*. 4. There are no principal changes to the sterilization procedure. 5. There are no changes to the specifications in regards to those have been approved. 6. There is no change in the *impurity profile of* Active Pharmaceutical Ingredientbeyond the approved limits. 7. Changes are not caused by repeated events or stability issues occurred during the manufacturing process 8. The changes had no impact on data *viral clearance* or chemical properties *inactivating agent*.	A. Quality documents 1. Justification of change. 2. Change category of justification related to the impact of antigen quality. 3. The summary of process changes is linked to the approved process in tabular form. 4. Flowchart (including process and IPC) and a narrative description of the proposed production process. 5. BSE/TSE certificate (when using materials with BSE/TSE risk) for instance *ruminant origin*, or information and evidence that the material does not have certain potential to cause a BSE/TSE risk. 6. Validate the process changes (if necessary). 7. For the changes in the manufacturing process of Active Pharmaceutical Ingredients, comparability of Active Pharmaceutical Ingredients in terms of physicochemical characterization, biological activity and profile *impurity*. 8. Comparative batch analysis data (in tabular form) of at least three batches produced using approved and proposed processes. 9. Stability studies use a minimum of three batches of Active Pharmaceutical 10. Ingredient (pilot or production scale) according to relevant stability guidelines or a commitment to carry out an appropriate stability study. If any of test results do not meet the requirements, the study should be reported to Indonesian FDA. 11. Commitment to submit drug stability study reports according to the proposed changes.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
4.	Widening the in process specification limit*of*Active Pharmaceutical Ingredients.	1. The specificationofActive Pharmaceutical Ingredientremainunchanged. 2. There is no change in the impurity profile of Active Pharmaceutical Ingredient profile beyond the approved limits. 3. Changes are not caused by repeated events or stability issues during production.	A. Quality documents 1. Control information carried out at the critical step of manufacturing process and on the intermediate of the proposed Active Pharmaceutical Ingredient. 2. Comparative data of the approved and the proposed IPC acceptance test/criteria . 3. Comparative data of IPC and *release*test results for at least three consecutive batches of commercial-scale Active Pharmaceutical Ingredient, between approved andproposed changes . *4.* Justification of new *in-process*limit and test . 5. Comparison of the results of the Active Pharmaceutical Ingredient stability test, a minimum of three commercial scale batches produced with the proposed changes under long-term conditions (minimum three months of testing unless stated otherwise). 6. Committed to continue long-term stability studies to support *shelf life/hold time* completed under normal storage conditions and reported to Indonesian FDA of any failures occurred during the long-term stability studies.
5.	Addition or Replacement equipment in Manufacturing or pdo Procedure Process of (e.g. *Finished Product tank, (e.g formulation tank, filter housing, filling line and head*, and *lyophilizer*).	1. Biological Products Specific.	A. Quality documents 1. Description of the manufacturing process, if it is different from the approved processand information on monitoring of proposed manufacturing process at critical steps and intermediate of finished product. 2. IPC testing information, as proposed. 3. Process validation study report asproposed. 4. Batch analysis data (in table) of at least three batches of pre- and post-change Finished product 5. Comparison of long-term finished product stability test results, a minimum of three commercial-scale batches manufactured with the proposed changes (minimum three months of testing unless stated otherwise). 6. Committmentto continue long-term finished product stability study. 7. Information of *leachable s*and *extractables*, as proposed. 8. Information of new equipment and comparison of similarities and differences between the approved and proposed operational principles specification.
6.	Analysis method changes of Active Pharmaceutical Ingredients (nonpharmacopeial).	1. Biological Products Excluded. 2. Active Pharmaceutical Ingredient specifications remain unchanged. 3. The specifications (release and *shelf life*) of the drug remain unchanged.	A. Quality documents 1. Analysis method of Active Pharmaceutical Ingredients. 2. Report of validation result of the approved andproposedanalytical method. 3. Report of conformity test results of approved and proposed analytical methods.
7.	IPC specification changes in the manufacturing process of	1. Changes made are not a consequence of previous assessment commitment to	A. Quality documents 1. Comparative table of approved and proposed in process test.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
	ACTIVE PHARMACEUTICAL INGREDIENT	review specification limits. 2. Changes made are not the result of unexpected events during the manufacturing process of Active Pharmaceutical Ingredients, e.g., new contamination; changes in total impurity limits. 3. Changes must be within the approved limit range. 4. The same test procedure or minor in certain changes. 5. The new testing method does not involve new non-standard techniques or newly-used standard techniques.	2. Details of non pharmacopeial analyticalmethods and new validation data, if necessary. 3. Analysis of two production batches ofActive Pharmaceutical Ingredient(three production batches for biological products, unless specified otherwise) for all specification parameters.
8.	Extensionof*retest*/storage period of Active Pharmaceutical Ingredients.	1. Changes made are not caused by unexpected event during the manufacturing process or its stabilities. 2. Changes made are not related to widening acceptance criteria of the tested parameters, removal of stability parameter or reduction of testing requency .	A. Quality documents 1. Active Pharmaceutical Ingredient stability test data. 2. Specifications of Active Pharmaceutical Ingredients.
9.	Increased batch size of Active Pharmaceutical Ingredients/*intermediate* more than ten folds.	1. Active Pharmaceutical Ingredients do not include Biological Products/immunology or sterile substances. 2. Changes made do not affect the reproducibility of the process. 3. Changes made are not caused by unexpected events during the manufacturing process or its stabilities. 4. Specifications of Active Pharmaceutical Ingredients /*intermediate* remain unchanged. 5. Analysis results of two batches minimum in accordance with the specifications should be available for the number of batches submitted. 6. Changes to the manufacturing method requiring *to scale up*, e.g., the use of	A. Quality documents *1.* Specifications of Active Pharmaceutical Ingredients /*intermediate* 2. Comparison of batch analysis data (in tabular format) Active Pharmaceutical Ingredients/*intermediate* of previous and proposed productions (minimum one batch production scale). Data from the next two production scale batches must be available and reported if they are not met the specifications.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
10.	Additional or changeof testing site of Active Pharmaceutical Ingredientincludingtesting for stability studies and process control.	1. Biological Products Specific. 2. The testing procedure remain unchanged. 3. Active Pharmaceutical Ingredient specifications remain unchanged . 4. Validation results meet the requirements. 5. Transfer of analytical method meets the requirements.	A. Quality documents 1. Summary of test validation studies at the new testing site. 2. The results of at least three batches tested in approved and proposed site. 3. Information and specifications of reference standard . 4. Specific to the changes of stability testing site , the report must be conducted in new testing site .
11.	Additionor changes in Active Pharmaceutical Ingredient storage conditions (e.g., widening or tightening of temperature range).	1. Biological Products Specific.	A. Quality documents *1.* Proposed storage conditions and *shelf life* . 2. Stability test results (in the form of complete long-term stability data for proposed *shelf life* for at least three commercial scale batches).
12.	Reduction or omission of *overage.*	1. The change represents *overage of* previously approved active ingredients. 2. The specifications (release and *shelf life*) from medications remain unchanged.	A. Quality documents 1. Justification of the proposed changes. 2. Comparison table of proposed and approved Formula. 3. Test results (*Certificate of Analysis/CoA*) of two batches of finished product. 4. Drug stability reports and Drug stability commitments if the drug stability data are incomplete.
C. Changes related to the quality of medicines			
1.	Change in the manufacturer responsible for batch release (Finished Product testing excluded).	1. Imported drugs only . 2. Valid for one *mother company.*	A. Product Information and Label 1. Product Information 2. Labels on the packaging.
2.	Changein the manufacturer responsible for batch release (Finished product testing included).	1. Biological Products Excluded. 2. Imported drugs only. *3.* Valid for one *mother company.* 4. Transfer of analytical method from the approved site to the proposed site meets the requirements.	A. Product Information and Label 1. Product Information 2. Labels on the packaging. B. Quality documents 1. Report of validation/verification results towards analytical method which is transferred from the approved site to the proposed site . 2. Batch analysis data (for at least two batches of pilot-scale drugs) at the proposed and approved testing site.
3.	Changes or additions to the finished product testing site.	1. The product owner and batch release site remainunchanged. 2. The test site has been registered. 3. Transfer of drug analytical method from the approved site to the proposed site meets the requirements. 4. Drug specifications remain unchanged.	A. Quality documents 1. Batch analysis of the finished product. 2. Drug Specifications. 3. Reference Standard 4. Batch analysis of the finished product . 5. Report of finished product analytical methodtransfer.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
4.	Increase and/or decrease in the batch size of the finished product up to ten folds, for conventional tablets and oral liquids.	1. Biological Products Excluded. 2. Changes do not affect the finished product specifications; must report any changes in the process of manufacturing and/or controlling related to batch sizes, such as equipmentsof different sizes usage. 3. The process validation results in accordance with the previousbatch that has been approved. 4. Changes do not affectreproducibility and/or consistency of the drug. 5. Changes are not influenced by the manufacturing process of the drug or its stability issues.	A. Quality documents 1. Manufacturing process and process control 2. Batch formula 3. Drug Specifications. 4. Analytical results of the finished product batch. 5. Comparative of Batch analysis data from at least two finished product batches (production scale) of approved and proposed batches. 6. Drug stability report from the new production scale and drug stability commitment if the report is incomplete.
5.	Replacemnet of one Excipient component with another the same functional characteristics.	1. Modified -release drug and sterile - dosage formare excluded. 2. Dosage form requiring clinical trials, including bioequivalence study are excluded. 3. Drug manufacturing process validation has been carried out according to the three batches protocol of production-scale drug. Or at least one batch pilot-scale drug and commitment of validation process of the first three production batches with the estimated time of submission. 4. The specifications (release and *shelf life*) of the drug remains unchanged. 5. Stability tests have been carried out according to the protocol with a minimum of two batches of pilot scale or production scale with a minimum of three months data which results meet	A. Quality documents 1. If derived from animal, the information animaloriginsand BSE/TSE free-certificate should be included. . 2. Report on the drugs manufacturing process of validation reports . 3. Comparative dissolution test report of approved and proposed formulas. 4. Drug stability reports and Drug stability commitments if the Drug stability reports are incomplete. 5. Justification for not conducting BE study.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
6.	Change of Excipient for narrow therapeutic index (NTI) Drugs or *Biopharmaceutics Classification System (BCS)* Class 4 which do not require BE study.	1. The dissolution profile of the proposed formula is comparable to the approved one. 2. Drug manufacturing process validation has been carried out in accordance with protocol of three production scale batches, or at leastonepilot-scalebatchand commitment validation process of the first three production batches with the estimated time of submission. 3. The specifications (release and*shelf life*) of the drug remain unchanged 4. Stability tests have been carried out according to the protocol with a minimum of two batches of pilot scale or production scale with a minimum of three months data which results meet specifications.	A. Quality documents 1. Comparative dissolution test data of approved and proposed formulas. 2. Report on the drug manufacturing validation process reports 3. Comparative batch analysis data of the previous production batch(two production-scale drug batches) and the currentproposed one (minimum from two production-scale batches or one production scale batch and two pilot batches). 4. Commitment to submit a new production scale batch analysis (if pilot scale batch analysissubmitted). 5. Drug stability reports and Drug stability commitments if the Drug stability reports are incomplete. 6. Justification for not conducting BE study.
7.	Changes in capsule shell manufacturer.	1. Drug specifications remain unchanged. 2. The drug formula and production process remain unchanged. 3. Stability tests have been carried out according to the protocol with a minimum of two batches on a pilot or production scale with a minimum of six months data which meet specifications. 4. Does not apply to changes of hard capsules to soft gels (soft capsules).	A. Quality documents 1. Capsule shell specifications. 2. Certificateofanalysis of capsule shell . 3. Information about gelatin resources as raw material for capsule shells. 4. BSE/TSE-Free certificate. 5. Comparative dissolution testing data ofminimalone pilot-scale batch between drugs using the proposed andapproved capsule shell (if necessary). 6. Batch Analysis results of the drug.
8.	Changes in capsule shell size.	1. Drug formula, specifications (release and *shelf life*) of drugs remain unchanged (except for certain descriptions). 2. The capsule shell material is similar to the approved capsule shell material. 3. For immediate-release capsules only.	A. Quality documents 1. Descriptions and Formulas 2. Batch Analysis results of the drug. 3. Comparative batch analysis data for minimum two production scale batches of drugs using approved and proposed capsule shells. 4. Capsule specifications. 5. The composition of the capsule shell. 6. Information about gelatin resources as raw material for capsule shells. 7. certificate of analysis Capsule shell . 8. BSE/TSE-Free certificate. 9. Comparative dissolution test data of one pilot-scale batch between drugs and the capsule shells that have been approved and submitted (if necessary).

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
9.	The shape or dimensions of the gastro resistant tablets, sustained-release tablets, and scored tablets.	1. The specifications (release andshelf life) of the drug remain unchanged. (except for its dimensions) 2. The dissolution profile of drug with new dimension is comparable to the approved drug (if required in monograph). 3. Qualitative and quantitative formulas and average weight remain unchanged.	A. Quality documents 1. Drug Specifications (including images and descriptions of approved and proposed dimensions). 2. Comparison of approved and proposed dissolution profiles (if necessary). 3. Product Information (if necessary). 4. Batch Analysis results of the drug. 5. Comparative batch analysis data for minimum two drug batches (production/pilot scale) of approved and proposed dimensions/shapes.The results of the uniformity test (for scoring or breakline tablets). 6. Justification for not conducting BE study.
10.	Shape or dimensions of immediate release tablets, capsules, suppositories or pessaries.	*1.* Not applicable for scored tablets. 2. The specifications (release and shelf life) of the drug remain unchanged. (except for its dimensions) 3. The dissolution profile of drug with new dimensional is comparable to the approved drug (if required in monograph). 4. Qualitative and quantitative formulas and average weight remain unchanged.	A. Product and Label Information 1. Product Information (if necessary). 2. Packaging labels (if necessary). B. Quality documents 1. Drug Specifications (including images and descriptions of approved and proposed dimensions). 2. Comparison of approved and proposed data dissolution profiles (if necessary). 3. Batch Analysis results of the drug. 4. Comparative batch analysis data for minimum two drug batches (production/pilot scale) of approved and proposed dimensions/shapes.
11.	Minor changes to the drug manufacturing process.	1. Biological Products Specific. 2. Valid for any minor changes in procedure and/or production scale at any step of drug production. 3. Related to non-critical process, such as: no changes in production methods, storage conditions or production scale. 4. Increase in aseptic production scale for drugs without	A. Quality documents 1. The summary of process changes related to the approved process in tabular form. 2. Justification of change. 3. Validation of the change process (if necessary). 4. Comparative batch analysis data (in tabular form) of minimum three batches produced using approved and proposed processes. 5. Stability studies of minimum three batches pilot or production scaleas per relevant stability guidelines

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
		changes in equipment, such as the number of vialsfilled. 5. There are no principal changes to the sterilization procedure. 6. There are no changes to the specifications other than have been approved. 7. Changes are not caused by repeated events occurred during the manufacturing process or stability issues.	or commitments to carry out an appropriate stability study and report to Indonesian FDA if any of test results do not meet the requirements or when requested by Indonesian FDA.
12.	Additional step of the drug-manufacturing process.	1. Biological Products Specific. 2. Changes cannot be caused by repeated events occurred during the process or stability issues.	A. Quality documents 1. Description of the production process, if it is different from the approved one and information of manufacturing process monitoring at critical step and intermediates of finished product proposed. 2. IPC testing information, as proposed. 3. Process validation study report (for example, *media fill*), as proposed. 4. Comparison of release testing results for at least three consecutive batches of commercial-scale drug, before and after the change. 5. Comparison of drug stability test results, a minimum of three commercial-scale batches manufactured with the proposed changes under long-term conditions (three months of testing or stated otherwise). 6. Information of *leachables s*and *extractable*s, as proposed.
13.	Addition or replacement of *in-process* test due to safety or quality issues.	1. Biological Products Specific. 2. Drug specifications remain unchanged.	A. Quality documents 1. Justification of changes and scientific and/or historical data to support the proposed changes. 2. Information of manufacturing process Monitoringatcritical-step and the intermediatesof the proposed antigen. 3. Analytical procedures, if new analytical procedures are used. 4. Validation study reports, if analytical procedures are used. 5. Comparative table or description, according to the change, between approved and proposed. 6. Comparison of release test results for at least three consecutive batches of commercial-scale drug, before and after the change.
14.	Solvent removal for finished product.	1. Changes proposed do not change dosage form, indications and method of administration of the drug.	A. Quality documents 1. Product Information and Label that included the proposed changes (if necessary). 2. Justification of solvent removal, including a statement indicating alternative toobtainthe solvent.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
15.	Changes in drug analytical method.	1. Biological Products Excluded. 2. The specifications (release and *shelf life*) of the drug remain unchanged.	A. Quality documents 1. Pharmaceutical Analytical Method 2. Report of validation result of new analytical method . 3. Report of conformity test results of old and new analytical methods.
16.	Changes in the drug container closure system.	1. Biological products and sterile preparations are excluded. 2. Any of changes in the packaging type that comes in direct contact with the drug. 3. Stability tests have been carried out according to the protocol with a minimum of two batches on a pilot or production scale with a minimum of three months of data providing results that meet specifications.	A. Quality documents 1. Spesificationandtesting methodsof packaging material. 2. Compatibility study report, *leak test* to show the suitability of using the proposed packaging system. *3.* Release and *shelf life* specifications. 4. Drug stability reports and stability commitments if the stability reports are incomplete.
17.	Changes in shape and/ or dimensions of primary packaging (for non-sterile preparations).	1. There is no change in the specifications for primary packaging materials. 2. It is not an essential part of the packaging material that affects the distribution, use, safety or stability of the Drug. 3. For changes to *"head space"* or changes to *"surface / volume ratio"*: • Stability tests have been carried out according to the protocol with a minimum of two batches on a pilot or production scale with a minimum of six months of data providing results that meet specifications.	A. Product and Label Information 1. Primary packaging label, including *mock up.* B. Quality documents 1. Spesification and testing methods of packaging material. . 2. Drug stability reports and stability commitments if the stability reports are incomplete.
18.	Major changes in volume of multi-dose nonparenteral preparations.	1. Product information claim remains unchanged. 2. The drug with the new packaging is consistent with the posology and duration of treatment. 3. Drug specifications remain unchanged. 4. Packaging specifications remain unchanged 5. Stability tests have been carried out according to the protocol with a minimum of two batches on a pilot or production scale with a minimum of three months of data providing results that meet specifications.	A. Product and Label Information 1. Product Information 2. Primary and secondary packaging labels. B. Quality documents 1. Justification stating that the proposed dosage volume is consistent with the approved dosage regimen. 2. Drug stability reports and stability commitments if the stability data are incomplete.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
19.	Addition of a stability testing site.	1. Shelf lifespecificationsand the drug testing methods remain unchanged.	A. Quality documents 1. Drug specifications and testing methods. 2. Reports on the analytical methods validation/verification.. 3. Drug Specifications. 4. Reference Standard 5. Stability report on-the new site.
20.	Changes in storage conditions including reconstituted products.	1. The specifications (release and *shelf life*) of the drug remain unchanged. 2. The stability test has been carried out according to the approved protocol and meets the specification requirements. 3. Changes are not influenced by the manufacturing process of the drug or because its stability issues.	A. Product and Label Information 1. Product Information 2. Labels on the packaging. B. Quality documents 1. Drug Specifications. 2. Drug stability report according to the proposed storage conditions of drug.
21.	Extension of drug shelf life: The packaging has not been opened.	1. The specifications (release and *shelf life*) of the drug remainunchanged. 2. The stability test has been carried out according to the approved protocol and meets the specification requirements. 3. Changes are not influenced by the manufacturing process of the drug or because its stability issues. 4. The shelf life period should not be more than five years.	A. Product and Label Information 1. Product Information (if necessary). B. Quality documents 1. Drug Specifications. 2. Drug stability report according to the proposed shelf life.
22.	Extension of drug shelf life: After the packaging is opened or after reconstitution.	1. The specifications (release and *shelf life*) of the drug remain unchanged. 2. The stability test has been carried out according to the approved protocol and meets the specification requirements.	A. Product and label Information 1. Product Information B. Quality documents 1. Drug Specifications. 2. Drug stability report after packaging is opened or after reconstitution according to the proposed shelf life.

3. CATEGORY 6: NOTIFICATION VARIATION OF REGISTRATION

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
A. Changes related to Product Information and/or Label			
1.	Changes or additions to logo (including company'slogo).	1. Product information claim remains unchanged. 2. Packaging specifications remain unchanged.	A. Product and Label Information 1. Images of primary and secondary packaging from all sides and samples of packaging ready to distribute (including Product Information).
2.	Additionside effects and/or contraindications claim to Product Information.		A. Product and Label Information 1. Images of primary and secondary packaging from all sides and samples of packaging ready to distribute (including Product Information). B. Clinical documents 1. Justification and/or other supporting documents in accordance with the proposed changes. 2. Periodic Safety Update Report/PSUR (if necessary). 3. Another reference.
3.	Reduction of production sites (including Active Pharmaceutical Ingredients, intermediate products or Drugs, packaging sites, batch release sites).	1. The approved production sites with the same function/designation (including Active Pharmaceutical Ingredients, intermediate products or drugs, packaging sites, batch release sites)still exist.. 2. The reduction in production sites is not caused by critical factors related to the manufacturing process.	A. Product and Label Information 1. Marketing Authorization or Variation Registration approval according to related changes.
4.	Change of Active Pharmaceutical Ingredient name.	1. Active Pharmaceutical Ingredientremains unchanged. 2. Theproposed name of the Active Pharmaceutical Ingredient must comply with *International Nonproprietary Names Modified (INNM).*	A. Administrative Documents, Product Information and Labels 1. Evidence of changing of Active Pharmaceutical Ingredient name. 2. Images of primary and secondary packaging from all sides and samples of packaging ready to distribute (including Product Information).
5.	Changes in the part of the primary package that is not in contact with drugs (such as *flip-off caps*color, *ring*coloron the ampoule, change to the needle shield (a different plastic is used).	1. It is not an essential part of the packaging material that affects the distribution, use, safety or stability of the Drug. 2. Specifications of primary packaging materials in contact with the drug remainunchanged.	A. Quality documents 1. Spesificationandtesting methods of packaging material.
6.	Removal of foreign language from Drug Label.	1. Product information claim remains unchanged.	A. Product and Label Information 1. Images of primary and secondary packaging from all sides and samples of packaging ready to distribute (including Product Information).
7.	Changes in shape and/or dimensions of secondary packaging.	1. There is no change in packaging material specifications except for shape and/or dimensions. 2. Product information claim remains unchanged.	A. Product and Label Information 1. Images of secondary packaging from all sides and samples of ready-to-distribute samples (including Product Information). B. Quality documents 1. Packaging material specifications.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
8.	Changes in packaging design.	1. Product Information and Label claims remainunchanged. 2. Only applicable to changes in text and image layout, colors, and lines. 3. Does not include image changes. 4. Does not contain promotional statement/information.	A. Product and Label Information 1. Images of primary and secondary packaging along with its samples from all sides. ready to distribute (including Product Information).
9.	Change inaddress (redactional) of Applicant/Pharmaceutical Industry/licensor.	1. The location of the Applicant/Pharmaceutical Industry/Drug licensor remainsunchanged. 2. Does not include a change in the city/regency.	A. Administrative Documents, Product Information and Labels 1. Certificate of change of address. 2. Images of primary and secondary packaging from all sides and samples of ready-to-distribute packaging (including Product Information).
10.	Changes to the batch numbering system.		A. Product and Label Information 1. Description of the new batch numbering system.
11.	Changes in Product Information and/or Labels according to government decisions.	1. Changes in Product Information and/or Labels according to government decisions.	A. Product and Label Information 1. Images of primary and secondary packaging from all sides and samples of ready-to-distribute packaging (including Product Information).
12.	Inclusion of the distributor's name.	1. Product Information and Label claims remainunchanged except for the name of the distributor.	A. Administrative Documents, Product Information and Labels 1. Pharmaceutical Wholesaler License (PBF). 2. Letter of appointment; 3. Images of primary and secondary packaging from all sides and samples of ready-to-distribute packaging (including Product Information).
B. Changes in the quality of Active Pharmaceutical Ingredients			
1.	Changes and/or additions to Active Pharmaceutical Ingredientmanufacturer.	1. New drugs, biological products and drugs requiring bioequivalence study are excluded. 2. Active Pharmaceutical Ingredient Manufacturers are listed on *new*-AeRO *database*/Web Registration of The Indonesian FDA. 3. Active Pharmaceutical Ingredient specifications remain unchanged. 4. The specifications (release and*shelf life*) of the drug remain unchanged. 5. Drugs *Shelf life* for new Active Pharmaceutical Ingredients manufacturers, for a maximum of 24 months, are unless if supported by valid data.	A. Quality documents 1. A valid current Good Manufacturing Practice (cGMP) certificate of the manufacturer. 2. Certificate of analysis of Active Pharmaceutical Ingredient. 3. Comparison of Active Pharmaceutical Ingredient batch analysis data from approved and proposed Active Pharmaceutical Ingredients manufacturer (Specific for Biological Product, - batchanalysis from a minimum of three consecutive batches of pilot/production scale). 4. Comparison of Drug batch analysis data from two drug batches (pilot/production scale) of proposed and approved Active Pharmaceutical Ingredientmanufacturers(Specific for Biological Product-batch analysis from a minimum of three consecutive batches of pilot/production scale). 5. Reports of stability test results that have been carried out and commitment to continue the stability test up toproposed*shelf life*.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
2.	Addition of tests totheActive Pharmaceutical Ingredient release specifications.	1. Changes are not caused by adverse events during manufacturing process(for example, new impurities not meeting the requirements or changes in the amount of impurity threshold). 2. Additional parameters are not intended to test new impurities.	A. Quality documents 1. Specifications of Active Pharmaceutical Ingredients. 2. Analytical method of Active Pharmaceutical Ingredients. 3. Report of analytical method validation.
3.	Change of manufacturers of *starting material/reagent/intermediate* which used in the manufacturing process of Active Pharmaceutical Ingredient or change of Active Pharmaceutical Ingredient manufacturers(including quality control testing sites).	1. Active Pharmaceutical Ingredients do not include Biological Products/immunologic or sterile substances. 2. For the specification of *starting material/reagent/intermediate*(included in the process control, analytical method of all materials) is the same as approved. 3. Preparation method and route of synthesis *intermediate* product and the Active Pharmaceutical Ingredient (including batch size) are the same as approved. 4. Particle-sized specification of the Active Pharmaceutical Ingredient and analytical method remain unchanged.	A. Quality documents 1. If the substance derives from animal, the information of animaloriginandBSE/TSE-free certificate. 2. Comparison of Active Pharmaceutical Ingredient batch analysis data of the approved and proposed manufacturers (minimum of two production-scale batches.
4.	Changes and/or additions to the name or address of producers.	1. The location of the Active Pharmaceutical Ingredient producer remains unchanged.	A. Product and Label Information 1. Supporting documents of name or address change of producers.
5.	*Update Ph. Eur. Certificate of Suitability (CEP).*	1. Biological Products Excluded 2. The specifications (release and *shelf life*) of the drug remain unchanged. *3.* Specifications for *impurity* remainunchange. 4. The manufacturing process of Active Pharmaceutical Ingredients does not use raw materials from human/animal origin that require viral safety data.	A. Quality documents 1. *new Certificate of Suitability (Ph. Eur).*
6.	Tightening specification limits for raw materials/intermediates.	1. Changes in specifications for raw materials/intermediates within the approved limits. 2. There are no specification changes of Active Pharmaceutical Ingredient beyond the approved limits. 3. There is no change in the impurities of Active Pharmaceutical Ingredient profile beyond the approved limits.	A. Quality documents 1. Quality information and testing of the proposed materials/ intermediates. 2. Summary procedures, if new analytical procedures are used.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
7.	Changes in inclusion of Pharmacopoeia editions for Active Pharmaceutical Ingredients.	1. The Active Pharmaceutical Ingredient testing method remains unchanged. 2. Specifications for Active Pharmaceutical Ingredients and Drugs remain unchanged.	A. Quality documents 1. Relevant Pharmacopoeia references.
8.	Tightening Active Pharmaceutical Ingredient specification limits.	1. Changes are within the applicable standard limits. 2. The testing procedure remains unchanged.	A. Quality documents 1. Specifications of New Active Pharmaceutical Ingredient . 2. Active Pharmaceutical Ingredient certificate of analysis with new specifications.
9.	Changes to the Active Pharmaceutical Ingredient specification to meet the latest Pharmacopoeia requirements.	1. The specifications (release and *shelf life*) of the drug remain unchanged. 2. Specification *impurity* and Active Pharmaceutical Ingredient remains unchanged (particle size profile, *polymorphism*). 3. Additional validation of new or amended Pharmacopoeia methods is not required.	A. Quality documents 1. Active Pharmaceutical Ingredient specifications and testing methods 2. Active Pharmaceutical Ingredient certificate of analysis. 3. Analysis results of two production-scale Active Pharmaceutical Ingredient batches for all new specification testing. 4. Relevant Pharmacopoeia references.
10.	Changes to the Active Pharmaceutical Ingredient specification to meet the latest non-Pharmacopeial requirements.	1. Testing method has been verified . 2. Specification of *impurity*and Active Pharmaceutical Ingredient remains unchanged (particle size profile, *polymorphism*). 3. There is no significant changes in the qualitative and quantitative composition except for tightening specifications. 4. Additional validation of new or amended Pharmacopoeia methods is not required.	A. Quality documents 1. Active Pharmaceutical Ingredient specifications and testing methods 2. Active Pharmaceutical Ingredientcertificate of analysis. 3. Batch Analysis of two production-scale Active Pharmaceutical Ingredientfor all new testing specification. 4. Batch analysis of two production-scale batches of Drugs with Active Pharmaceutical Ingredients that meet approved and proposed specifications (if necessary). 5. Drug dissolution profile data of at least one pilot-scale batch (if necessary). 6. Relevant Pharmacopoeia references.
11.	Additionoftesting parameters and specification limitsforprocess control of Active Pharmaceutical Ingredient manufacturing process.	1. Changes are not influenced by manufacturing process of the drug or its stability issues. 2. Active Pharmaceutical Ingredient specifications remain unchanged. 3. The testing method has beenvalidated.	A. Quality documents 1. Manufacturing procedure. 2. Comparison of approved and proposed*in-process* testing during the manufacturing process of Active Pharmaceutical Ingredients. 3. Analysis method details and validation data of new analytical methods. 4. Batch analysis data using two batches of Active Pharmaceutical Ingredient(three batches for Biological Products) for all testing in the proposed specification.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
12.	Minor changes to the Active Pharmaceutical Ingredient analytical procedure.	1. The analytical method remains unchanged (e.g. changes in column length or temperature, but method and column type remained unchanged). 2. Revalidation study has been conducted in accordance with the protocol. 3. Results of the method validation demonstrate that the proposed analytical procedure is identical/equivalentas the approved procedure. 4. The specifications (release and *shelf life*) of the drug remain unchanged. 5. Not applicable for additiontesting procedures.	A. Quality documents 1. Active Pharmaceutical Ingredient specifications and testing methods 2. Active Pharmaceutical Ingredient certificate of analysis. 3. Comparison of the validation results or analysis results indicating that the proposed and approved procedure areidentical/equivalent.
13.	Changes in the analytical method of Active Pharmaceutical Ingredient as sayin accordance with Pharmacopoeial monographs.	1. Active Pharmaceutical Ingredient specifications remain unchanged. 2. The specifications (release and *shelf life*) of the drug remain unchanged.	A. Quality documents 1. Analytical method of Active Pharmaceutical Ingredients. 2. Verification of Active Pharmaceutical Ingredient analytical procedure. 3. Active Pharmaceutical Ingredient certificate of analysis. 4. Reference standard
14.	Changes in the storage conditions of Active Pharmaceutical Ingredient.	1. Stability test results remain in compliancewiththe requirements of the previously approved specifications. 2. Changes are not influenced by Active Pharmaceutical Ingredient manufacturing process or its stability issues. 3. There is no change in Active Pharmaceutical Ingredient retest period.	A. Quality documents 1. Active Pharmaceutical Ingredient stability report. 2. Specifications of Active Pharmaceutical Ingredients.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
15.	Increase/decrease in batch size (including range of batch size) of Active Pharmaceutical Ingredients or *intermediates* used in its manufacturing process up to ten folds.	1. Biological Products Excluded. 2. Changes do not affect specifications of Active Pharmaceutical Ingredient/*intermediates*; any changes in the manufacturing process of and/or process control with respect to change related to the batch size, such as the use equipmentsof different sizemust be reported. 3. The process validation results in accordance with the previously approved batch. 4. Changes do not affect the reproducibility and/or consistency of the Active Pharmaceutical Ingredient or *intermediates* 5. Changes are not influenced by manufacturing process of the drug or its stability issues.	A. Quality documents 1. Batch analysis comparison of the approved and proposed batch. 2. A statement letter declaring that: a. Changes do not result in negative changes to the process reproducibility. b. Changes are not to any impact during manufacturing process or its stability issues ; c. Active Pharmaceutical Ingredient specifications remain unchanged.
16.	Manufacture of New (Working Cell Bank) WCB.	1. *New Cell bank*isderivedfrom pre-approved MCB/MSL . 2. *New Cell bank* is obtained fromthe same passage number is the same as which has been the previously approved. 3. *New Cell bank* is released in accordance with the previously approved protocol/process .	A. Quality documents 1. The procedure of cell bank or seed lot qualification has been approved by the Indonesian FDA.. 2. Characterization and testing of MCB/WCB as well as cell from end of production or post-production passage.
17.	*Change of seed lot: new generation of Working Sheet Log.*	*1. New seed lot is derived from the pre-approved Master Sheet Log.* *2. New seed lot is obtained from the same release specification of the previously approved.* *3. New seed lot is released in accordance with the protocol/process previously approved or as described in the original submission.*	A. Quality documents 1. Comparability study on of the physicochemical characterization, biological activity and impurity profile of approved and proposed API. 2. Quality control results as quantitative data for proposed new seed lot (in tabular format). 3. Commitment to provide stability data of API obtained from proposed seed and report to the Indonesian FDA if any results do not meet the specifications.
18.	Reduction of Active Pharmaceutical Ingredients shelf life.	1. Changes are not caused by repeated events or stability issues occurred during the manufacturing process. 2. The specifications (release and *shelf life*) of Active Pharmaceutical Ingredientremain unchanged.	A. Quality documents 1. Active Pharmaceutical Ingredient stability report.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
19.	Deletion of non-significant *in-process* testing in the manufacture of Active Pharmaceutical Ingredient.	1. The deleted parameters are not critical, including but not limited to, assay, impurities, and particle siz.. 2. The changes are not caused by repeated events or stability issues during manufacturing. 3. The test is not related to critical parameters (e.g., composition, impurity, other physical critical characteristics ormicrobialpurity).	A. Quality documents 1. Information of controlforthe critical step during manufacture and of the proposed intermediate ofActive Pharmaceutical Ingredient. 2. Justification/risk assessment that attributes are insignificant.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
C. Changes related to the quality of drugs.			
1.	Minor changes to the drug manufacturing process.	1. Biological products and sterile preparations are excluded. 2. The overall manufacturing process principals remains unchanged. . 3. New manufacturing process producestheproduct with the same quality (validated), specifications, safety, and efficacy. 4. There is no change in terms of qualitative and quantitative *impurity* or physicochemical properties; 5. Specifications of drugs and intermediate products remain unchanged. 6. There is no change in specification limits of process control in the drug-manufacturing. 7. Drug stability testing has been conducted for at least three months of pilot or production scale batch. 8. The manufacturing site remains unchanged. 9. Changes have no negative effect on the quality, efficacy, and safety of the drug. 10. The dissolution profile remains unchanged.	A. Quality documents 1. Drug manufacturing process. 2. Batch analysis data. 3. For solid dosage form, comparative dissolution profile from one representative productionbatch and comparative data from the last three production batches from the approved drug manufacturing process. 4. Drug stability reports and stability commitments if the stability reports are incomplete. 5. Justification for not conducting BE study.
2.	Tightening the limits of drug-release specifications.	1. Changes are within the approved range of specification limits. 2. The testing procedures remain unchanged or only minor changes made toits procedures.	A. Quality documents 1. Comparison of approved and proposed drug-release specifications. 2. New drug certificate of analysis.
3.	Changes in drug specifications (release and *shelf life)* to meet the requirements of Pharmacopeia.	1. The change is not due to previous assessments. 2. Changes are not due to any impact from manufacturing process of the drug. 3. Changes are within the approved range of specification limits. 4. The testing procedures remain unchanged or only minor changes made toits procedures. 5. There is no change in terms of qualitative and quantitative *impurity* profile or physicochemical properties or dissolution profile.	A. Quality documents 1. New drugs Specifications of (release and *shelf life*). 2. Comparison of approved and proposed drug specifications (release and *shelf life*). 3. Drug batch analysis data for all testing of the new specifications (two batches).

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
4.	Addition of testing parameters and specification limits to process control of drug manufacturing process.	1. Changes are not influenced by manufacturing process of the drug. 2. Drug specifications remain unchanged. 3. The testing method has been validated. .	A. Quality documents 1. Manufacturing procedure. 2. Details of analytical method and data of new analytical methods validation . 3. Batch analysis data of three batches for all tests with new specifications.
5.	Tightening *in-process specification limits* during drug manufacturing process	1. The change is not resulting from previous assessments. 2. There are no changes in finished product contamination profile beyond the approved limits. 3. Changes are not influenced by manufacturing process of the drug or its stability issues . 4. The specifications (release and *shelf life*) of the drug remain unchanged. 5. Changes are within the approved standard limits. 6. The testing procedures remain unchanged or changes are still categorized as minor.	A. Quality documents 1. The proposed in-process specification during the manufacturing process 2. Comparison of approved and proposed *in-process* testing during the manufacturing process.
6.	Deletion of non-significant *in-process* testing.	1. There is no change in finished-product impurity profile beyond the approved limits. 2. The changes are not caused by repeated events or stability issues during manufacture. 3. Tests are not related to critical parameters (such as: assay, volume, impurity, other physical critical characteristics or microbial purity).	A. Quality documents 1. Justification/risk assessment indicates that this is insignificant.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
7.	Changes of IPC testing site.	1. There are no specification changes of the finished product beyond the approved limits. 2. There is no change in finished-product impurity profile beyond the approved limits. 3. Changes are notcaused by repeated events or stability issues during manufacturing process. 4. The proposed analytical procedure must remain unchanged or tighten the precision, accuracy, specificity and sensitivity, if performed. 5. There is no change in the IPC limit beyond the approved limits.	A. Administrative Documents 1. current Good Manufacturing Practices (cGMPs) Certificate. B. Quality documents 1. Batch analysis data from three batches of drugs. 2. Report of analytical method transfer.
8.	Addition of drug testing parameters.	1. Changes are not influenced by manufacturing process of the drug. 2. Drug specifications other than the added testingparameters,remainunchanged.	A. Quality documents 1. Drug Specifications. 2. Drug analytical procedure. 3. Batch analysis results (two batches). 4. Validation report of drug analytical procedure (if necessary).
9.	Changes in the analytical procedure of drug in accordance with the pharmacopoeia monograph.	1. Biological Products Excluded. 2. There are no qualitative and quantitative changes of *impurity*/ physico-chemical profile. 3. Drug analytical methods remain unchanged.	A. Quality documents 1. Drug specifications and testing methods 2. Drug batch analysis data with the approved and proposed analytical procedures. 3. Validation/verification results of analytical methods.
10.	Changes and/or additions to manufacturers of excipients.	1. Biological Products Excluded. 2. Excipient specifications remainunchanged. 3. The drug Specifications (release and	A. Quality documents 1. Certificate of Analysis of Excipient

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
		shelf life) remainunchanged. 4. Raw materials used have fulfilled the criteria of *pharmaceutical grade* or *food grade*.	
11.	Tightening limit of Excipient specification.	1. Changes are not due to the previous assessments. 2. Changes are not influenced by manufacturing process of the drug. 3. Changes are within the applicable standard limits. 4. The testing procedure remains unchanged. 5. The acceptance criteria for residual solvents are within approved limits (e.g, within ICH limit for third-class residual solvents or Pharmacopoeia requirements).	A. Quality documents 1. New Excipient Specifications. 2. Certificate of Analysis of Excipient with new specifications.
12.	Minor changes to the Excipient analytical procedure.	1. The analytical method remains unchanged (e.g. changes in column length or temperature, but method and column type remained unchanged). 2. Analytical procedure is not a biological/immunological /immunochemical analysis or an analytical procedure that uses biological reagents.	A. Quality documents 1. Excipient specifications and analytical methods. 2. Certificate of Analysis of Excipient
13.	Changes to the excipient analytical procedure in accordance with Pharmacopoeia monograph or as relevant.	1. Excipient specifications remain unchanged (for example, particle size, polymorphism).	A. Quality documents 1. Excipient Specifications. 2. Excipient analytical procedure. 3. Certificate of Analysis of Excipient 4. Pharmacopoeia references or relevant supporting documents.
14.	Additionoftesting parameters to excipient specifications.	1. Excluding *adjuvant* excipients for Biological Products. 2. Changes are not influenced by manufacturing process of the drug.	A. Quality documents 1. Excipient specifications and testing methods. 2. Batch analysis data from excipients with approved and proposed specifications.
15.	Changes to the excipient analysis procedure, including changing the testing method.	1. Revalidation study was conducted according to the protocol. 2. The results of the method validation demonstrate that the new analytical procedure is the same as the approved procedure. 3. The specifications (release and*shelf life*) of the drug remains unchanged.	A. Quality documents 1. Excipient specifications and testing methods. 2. Revised *impurity* specification (if any). 3. Comparative validation results demonstrating that the new testing procedure is equivalent to the approved test.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
16.	Changes to the excipient specification to fulfill the Pharmacopoeia requirements.	1. The new testing methods has been verified and the result fulfill the required specifications. 2. The specifications (release and*shelf life*) of the drug remain unchanged.	A. Quality documents 1. Excipient specifications and testing methods. 2. Certificate of Analysis of Excipient 3. Drug Specifications. 4. Batch analysis results of two production-scale batches of drugs. 5. Relevant Pharmacopoeia references.
17.	Changes in sources ofexcipient or reagents at-risk of BSE/TSE .	1. The release specifications for excipient and drug as well as the *shelf-life* specification remain unchanged. 2. Excluding for excipients or reagents used in the production of biological products or drugs containing biologically Active Pharmaceutical Ingredients.	A. Quality documents 1. A statement from the excipient or reagent manufacturer that the substance is derived from plant or animal origin or synthetic. 2. BSE/TSE free-certificate. 3. Certificate of Analysis of Excipient
18.	Change in weight of tablet coating or capsule shell in the immediate release *oral dosage form.*	1. Drug dissolution profile with tablet coating or new capsule shell weight (at least two pilot-scale batches) is comparable to the approved drug. 2. Drug specifications only change in weight and dimensions. 3. Stability tests have been conducted according to the protocol with a minimum of two pilot- or production-scale batches with a minimum of three months of data that meet specifications. 4. The coating is not a critical factor for drug release mechanism.	A. Quality documents 1. Descriptions and Formulas 2. Drug Specifications. 3. Results of drug batch analysis with approved and proposed weight of tablet/capsule shell coating. 4. Comparative dissolution testing data of minimum one pilot-scale batch between drugs approved and proposed formula (if required). 5. Drug stability reports and stability commitments if the stability reports are incomplete.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
19.	Increase, addition, deletion or replacement—coloring and/or odoring agents.	1. There is no change in drug specifications (release and *shelf life*), except coloring and/or odoring agents. 2. There is no change in drug functional characteristics (e.g., disintegration time, dissolution profile). 3. New coloring agents and/or odoring agents are not prohibited for pharmaceutical use. 4. New coloring and/or odoring agents are not from human/animal origin requiring viral safety data. 5. Changes are not due to production or stability issues. 6. Stability tests have been conducted according to the protocol with a minimum of two pilot or production scale batches with a minimum of three months of data that meet specifications.	A. Quality documents 1. Descriptions and Formulas 2. Batch formula. 3. Manufacturing process and process control. 4. New coloring and/or odoring agents specifications. 5. Testing procedures of new coloring and/or odoring agents 6. Certificate of analysis of new coloring and/or odoring agents. 7. Drug Specifications. 8. Results of Drug Analysis. 9. Comparison of drug batch analysis data from two production-scale batches of approve and propose formulas. 10. BSE/TSE-free certificate (if necessary). 11. Drug stability reports and stability commitments if the Drug stability reports are incomplete.
20.	Reduction or deletion mission of one or more components of the coloring and/or odoring agent.	1. There is no change in drug specifications, except coloring and/or odoring agent. 2. Stability tests have been conducted according to the protocol with a minimum of two pilot or productions scale batches with at least six months of data that meet specifications.	A. Quality documents 1. Descriptions and Formulas 2. Batch formula. 3. Drug manufacturing procedures. 4. Drug Specifications. 5. Batch analysis data of two production-scale batches. 6. Drug stability reports and stability commitments if the Drug stability reports are incomplete.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
21.	Change or addition of imprint, *bossing* or other marking (except break lines) on tablet or *printing* on capsule, including replacement or addition of ink used for product labelling.	1. Drug Specifications (release and *shelf life*) remain unchanged (except for descriptions). 2. The ink used must meet the requirements of pharmaceutical regulations. 3. Proposed descriptions should not cause an ambiguity in the approved drugs.	A. Product and Label Information 1. Product Information (if necessary). B. Quality documents 1. Drug Specifications. 2. certificate of analysis of Ink/*printing*material . 3. Batch analysis data of two production-scale batches.
22.	Change of color of capsule shell.	1. There is no change in capsule shell specifications, except color. 2. There is no change in drug specifications (release and *shelf life*), except color of capsule shell. 3. There is no change in drug functional characteristics of the capsule shell. (e.g., disintegration time, dissolution profile). 4. Changes are not due to the production or stability issues. 5. Stability tests have been conducted according to the protocol with a minimum of two pilot or production scale batches with a minimum of three months of data that meet specifications.	A. Quality documents 1. Description 2. Drug Specifications. 3. BSE/TSE-free certificate. 4. Information of gelatin ~~re~~sources as raw material for capsule shells. 5. Capsule shell specifications. 6. Certificate of analysis of Capsule shell. 7. Results of drug batch analysis with approve and propose/capsule shell. 8. Drug stability reports and stability commitments if the Drug stability reports are incomplete.
23.	Changes in synthesis of excipient (non-Pharmacopoeial).	1. Excluding of Excipient of Biological Products. 2. Excluding *adjuvant* agents. 3. Changes do not affect excipient specifications. 4. There is no qualitative and quantitative change *impurity* profile or physicochemical characteristics; 5. Route of Synthesis and specification of excipient are identical and there is no qualitative and quantitative change in the *impurity* profile~~.~~	A. Quality documents 1. Comparison of batch analysis data for Excipient of at least two pilot scale batches manufactured according to the approved and proposed manufacturing process Excipient. 2. Comparison of drug dissolution profile data of at least two pilot scale batch.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
24.	Changes of specification of non-Pharmacopoeial excipient to fulfill the Pharmacopoeia requirements.	1. Excipient specifications remain unchanged (e.g, particle size, polymorphism). 2. Drug specifications remain unchanged.	A. Quality documents 1. Excipient specifications and testing methods. 2. Results of excipient analysis. 3. Relevant Pharmacopoeia references.
25.	Replacement or addition of secondary packaging–site for Drugs.	1. Results of cGMP inspection for the last two years aresatisfactory.	A. Administrative Documents, Product Information and Labels 1. cGMP certificate of the secondary packaging site. 2. Images of ready-to-market primary and secondary packaging from all sides and sample of product information 2. (if necessary).
26.	Tightening the specification limits of primary packaging for drugs.	1. Changes are not due to the previous assessments. 2. Changes are within the applicable standard limits. 3. The testing procedures remain unchanged and or only minor changes in testing procedures.	A. Quality documents 1. Packaging specifications. 2. Certificate of analysis of packaging.
27.	Qualitative and/or quantitative changes in the composition of primary packaging materials for drugs (for all dosage forms).	1. Excluding Biological product and sterile preparations 2. Changes only made to the same packaging type and material. 3. The proposed packaging materials are identical or equivalent to those approved. 4. Stability tests have been conducted according to the protocol with a minimum of two pilot or production scale batches with a minimum of six months data that meet specifications.	A. Quality documents 1. Spesification of testing methods packaging and its material. 2. certificate of analysis of Packaging. 3. Drug stability reports and stability commitments if the stability reports are incomplete. 4. For liquid and semisolid dosage forms, there is an evidence demonstrating no interaction between the drug and the proposed type/packaging material.
28.	Addition or replacement of measuring device that is not part of the primary packaging (excluding *spacer device for metered dose inhaler*).	1. The proposed measuring device must include the accurate dose in accordance with the approved posology and supported with the appropriate data. 2. The new measuring device is compatible with the drug . 3. The changes do not affect the product information.	A. Product and Label Information 1. Image of measuring device, primary and secondary packaging from all sides and samples of ready-to-market packages with the new labeling , including product information (if necessary). B. Quality documents 1. Measuring device specifications and testing methods. 2. Calibration data of the measuring device.

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
29.	Minor changes to analytical procedure for the primary packaging of drug .	1. The results of the method validation demonstrate that the proposed analytical procedure is identical/equivalent to the approved procedure. 2. The testing method remains unchanged (e.g, changes in column length or temperature but not for column type).	A. Quality documents 1. Specifications and analytical procedures of packaging materials.
30.	Changes in the testing procedure of the primary packaging material of the drug, including the replacement or addition of the testing procedure.	1. Method validation results demonstrate that the proposed testing procedure is similar/equivalent to the approved procedure. 2. The proposed analytical method does not use new non-standard techniques or any standard techniques with new methods.	A. Quality documents 1. Spesification of testing methods Packaging and its material.
31.	Changes or additions of manufacturer of packaging component or medical devices included withthe drug, excluding manufacturer of *spacer devices* for *metered dose inhaler.*	1. Specifications of packaging materials or medical devices remain unchanged.	A. Product and Label Information 1. Statement letter regarding replacement or addition of manufacturers. B. Quality documents 1. Marketing authorization of Medical device . 2. Packaging material specifications. 3. Certificate of analysis of Medical device. 4. Specific for Biological Products are also equipped with comparison of testing result (*control*) packaging components or medical devices included with the drug between proposed and approved manufacturers.
32.	Reduction of manufacturer for packaging component or medical devices included with the drug, excluding manufacturers of *spacer devices* for *metered dose inhalers.*	1. There should be no removal of packaging component or medical devices included with the drug.	A. Product and Label Information 1. A statement letter regarding reductionof manufacturer.
33.	Addition of testing parameters for primary packaging of drug.	1. Changes are not due to manufacturing process of the drug.	A. Quality documents 1. Spesification and testing methods of Packaging material. 2. Primary packaging test
34.	Changes in secondary packaging materials.	1. Labeling remains unchanged.	A. Quality documents 1. Specifications and analytical procedures for secondary
35.	Changes in claims for drug storage condition (redactional).	1. The drug specifications (release and *shelf life*) remain unchanged. 2. Changes are not due to the manufacturing process of the drug or because its stability issues.	A. Product and Label Information 1. Images of primary and secondary packaging from all sides and samples of ready-to-market packaging (including Product Information).

No	TYPES OF CHANGES	REQUIREMENTS	SUBMITTED DOCUMENTS
36.	Reduction of the drug shelf life : the packaging has not been opened.	1. The drug specifications (release and *shelf life*) remain unchanged. 2. The stability test has been conducted according to the approved protocol and meets the specification	A. Product and Label Information 1. Images and samples of Product Information that are ready to market (if necessary). B. Quality documents 1. Drug Specifications. 2. Drug stability report.
37.	Reduction of the drug shelf life: after the packaging has been opened or reconstituted.	1. The drug specifications (release and *shelf life*) of remain unchanged. 2. The stability test has been conducted according to the approved protocol and meets the specification	A. Product and Label Information 1. Images and samples of Product Information that are ready to market (if necessary). B. Quality documents 1. Drug Specifications. 2. Drug stability report after packaging has been opened or reconstituted.

CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY,
signed.

PENNY K. LUKITO

ANNEX XVII
REGULATION OF THE HEAD OF THE NATIONAL AGENCY OF DRUG AND FOOD CONTROL OF THE REPUBLIC OF INDONESIA
NUMBER 24 OF 2017
ON
CRITERIA AND PROCEDURES FOR DRUG REGISTRATION

RENEWAL DOCUMENTS REQUIREMENTS

1. Cover letter.
2. Applicant Statement
3. Marketing Authorization and all Registration Approval Variant Letters that have been issued by the Indonesian FDA their attachment
4. Registration form
5. Local Drugs
   a. Valid Applicant Pharmaceutical Industry Licenses
   b. GMP certificate of Drug Manufacturer in accordance with the proposed dosage forms.
   c. GMP certificate for Active Pharmaceutical Ingredients
   d. Valid Contract agreement (only for Contracted Drugs)
   e. Declaration letter from the licensing authority stating that there is still a cooperation between the licensor and licensee (only for Licensed Drugs).
   f. updated quality documents as follows:
      - Certificate of Analysis of Active Pharmaceutical Ingredient
      - Latest batch record of the manufactured drug and its Certificate of analysis (Maximum of the last two years)
      - bioequivalency study report or comparative dissolution test (CDT) for Active Pharmaceutical Ingredients with BE/ CDT requirements
      - Clarification for certain raw material sources derived from animals or plants
      - Statement letter whether themanufacturing process involves or does not involve the use of certain materials of porcine origin.
      - fulfillment of commitment from the previous registration
   g. Product Information and Labellingalong with photographs of the drug and the distributed packages (*hard copy* and*softcopy*).

6. Imported drugs
   a. Pharmaceutical Industry License of the Applicant
   b. Valid GMP certificate or equivalent document from Drug manufacturer and/or batch release site which in accordance with the proposed dosage form .
   c. GMP certificate of Active Pharmaceutical Ingredient Manufacturer
   d. Import Evidence from the last two years maximum
   e. Import justification
   f. CPP or equivalent documents from the exported country and/or country where batch release certificate is issued.
   g. updated quality document as follows:
      - Certificate analysis of Active Pharmaceutical Ingredient
      - Report on bioequivalencystudyreport or c comparative dissolution test (CDT) for Active Pharmaceutical Ingredients with BE/ CDT requirements
      - fulfillment of commitment from the previous registration
   h. Product Information and Labellingalong with photographs of the drug and the distributed packages (*hard copy* and *softcopy*).
   i. Latest approval letter from the pharmaceutical industry or product owner from outside the country is exempted for Applicants that area affiliations of the main company

7. For renewal that involves changes, other documents required will follow the type of changes proposed.

CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY,

signed.

PENNY K. LUKITO

ANNEX XVIII
REGULATION OF THE CHAIRPERSON THE INDONESIAN FOOD AND DRUG AUTHORITY OF THE REPUBLIC OF INDONESIA
NUMBER 24 OF 2017
ON
CRITERIA AND PROCEDURES FOR DRUG REGISTRATION

RE-EVALUATION PROCEDURE

1. The Chairperson notifies the Applicant in written on the drugs that need to be re-evaluation.

2. Applicants whose drugs should be re-evaluation will be given a chance to submit latest and authentic data and information to support Marketing Authorization of the drug being re-evaluated .

3. Data as referred to in number 2 should be submitted at the latest six month starting from the date of the notification

4. When data and information are submitted after the period stated in Number 3, data and information submitted by the Applicant will not be considered and the Marketing Authorization will be revoked.

5. Re-evaluation will be done on the data submitted by the Applicant based on the predetermined criteria of efficacy, safety, and quality.

CHAIRPERSON OF THE INDONESIAN FOOD AND
DRUG AUTHORITY,
signed.

PENNY K. LUKITO