THE INDONESIAN FOOD AND DRUG AUTHORITY
OF THE REPUBLIC OF INDONESIA

REGULATION OF THE CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY THE REPUBLIC OF INDONESIA
NUMBER 16 OF 2015
ON
PROCEDURES AND ASSESSMENT OF NEW DEVELOPED DRUGS

BY THE BLESSINGS ALMIGHTY GOD

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

Considering : that to implement the provisions of Article 27 section (2) of 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 of Drug Registration as amended by the Regulation of the the Chairperson of the Indonesian Food and Drug Authority Number 3 of 2013, it is necessary to establish a Regulation of the the Chairperson of the Indonesian Food and Drug Authority on Procedures and Assessments of New Developed Drugs;

Observing :

1. 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);
2. Presidential Decree Number 103 of 2001 on the Position, Duties, Functions, Authority, Organizational Structure and Work Procedures of Non-Departmental Government Institutions as several times amended, last by Presidential Regulation Number 3 of 2013;
3. Presidential Decree Number 110 Of 2001 on Echelon I Organizational Units of Non-Departmental Government Institutions as several times amended, last by Presidential Decree Number 4 Of 2013;

4. Regulation of the Minister of Health Number 1010/Menkes/Per/XI/2008 on the Registration of Drugs as amended by the Regulation of the Minister of Health Number 1120/Menkes/Per/XII/2008;
5. Regulation of the Minister of Health Number 1799/Menkes/Per/XII/2010 on Pharmaceutical Industries as amended by the Regulation of the Minister of Health Number 16 of 2013 (State Bulletin of the Republic of Indonesia of Number 442 Of 2013);
6. Decision of the Chairperson of the Indonesian Food and Drug Authority Number 02001/SK/KBPOM Of 2001 on the Organizational and Work Procedure of the Indonesian Food and Drug Authority as amended by the Decision of the the Chairperson of the Indonesian Food and Drug Authority Number HK.00.21.4231 Of 2004;
7. Regulation of the the Chairperson of the Indonesian Food and Drug Authority Number HK.03.1.23.10.11.08481 Of 2011 on the Criteria and Procedures of Drug Registration (State Bulletin the Republic of Indonesia of 2011 Number 134) as amended by the Regulation of the the Chairperson of the Indonesian Food and Drug Authority Number 3 of 2013 (State Bulletin of the Republic of Indonesia of 2013 Number 540);
8. Regulation of the the Chairperson of the Indonesian Food and Drug Authority Number HK.03.1.33.12.12.8195 of 2012 on the Application of Guidelines for Good Drug Manufacturing (State Bulletin of the Republic of Indonesia of 2012 Number 122);

HAS DECIDED:

To issue: REGULATION OF THE CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY ON THE PROCEDURES AND ASSESSMENTS OF NEW DEVELOPED DRUGS.

CHAPTER I
GENERAL PROVISIONS

Article 1

In this Regulation:

1. Drugs mean manufactured drugs including biological products that are a material or combination of materials used to affect or investigate physiological systems or pathological conditions in the framework for the determination of diagnosis, prevention, cure, rehabilitation and improvement of health, and contraception for humans.
2. New Developed Drugs (*Obat Pengembangan Baru*), hereinafter referred to as OPB, means drugs or drug materials in the form of new molecules, biology/biotechnology products that are being developed and manufactured by research institutions or pharmaceutical industries in Indonesia and/or abroad to be used in non-clinical and/or clinical trial phases in Indonesia with the purpose to obtain circulation license in Indonesia.
3. Non-clinical trials mean biomedical studies that are not conducted on human subjects consisting of in vivo and in vitro trials, performed prior to clinical trials and may proceed during clinical developments (potential toxicity trials).
4. Clinical trials mean research activities by involving human subjects with the intervention of trial products, to discover or confirm clinical effects, pharmacological and/or other pharmacodynamics and/or identify any adverse reactions and/or study the absorption, distribution, metabolism and excretion with the purpose to ensure the safety and/or effectiveness of the product researched.
5. Assessment of OPB is the assessment phase of new developed drugs consisting of the drug quality development / CMC (Chemistry Manufacturing and Control) including the development of active substances, manufacturing processes, analysis methods, non-clinical trials, and the assessment of clinical trial programs including clinical trial protocols.
6. Chairperson of the Authority is the Chairperson of the Indonesian Food and Drug Authority.

CHAPTER II
PROCEDURES AND ASSESSMENTS OF NEW DEVELOPED DRUGS
Part One
General

Article 2

OPB assessments must be conducted in accordance with the Guidelines on the Procedures and Assessments of OPB as contained in Annex I which is an integral part of this Regulation.

Part Two
Assessment

Article 3

(1) The request for OPB assessment is filed by pharmaceutical industries or research institutions to the Chairperson of the Authority in writing, by using the letter format as contained in Annex II which is an integral part of this Regulation.
(2) The request as referred to in section (1) is submitted and attached with OPB documents as contained in Annex III which is an integral part of this Regulation.
(3) Assessments on OPB documents that fulfill the provisions as referred to in section (1) is performed by the OPB assessment team.
(4) In assessing OPB documents, the OPB assessment team may request considerations of experts according to their competence.
(5) The OPB assessment team is established by the Chairperson of the Authority.

Article 4

(1) OPB assessments are performed in a period of no longer than 100 (one hundred) work days since the date the OPB documents are submitted and declared complete.
(2) In the event that clarifications or additional data are required then the assessment time calculation is stopped (clock-off) up till the applicant provides the requested additional data.
(3) Clarifications or additional data as referred to in section (2) are submitted in writing to pharmaceutical industries or research institutions as applicants of the OPB assessments.

Part Three
Providing Decisions

Article 5

(1) Decisions on the OPB assessment may be in the form of:
a. assessment results of the OPB process;
b. approval of clinical trial implementation; and/or
c. rejection / suspension / termination.
(2) Decisions in the form of assessment results of the OPB process, the approval to implement clinical trials, and/or rejection / suspension / termination as referred to in section (1) are submitted in writing to the pharmaceutical industries or research institutions as applicants of the OPB assessments.

CHAPTER III
REPORTING

Article 6

(1) Pharmaceutical industries or research institutions that receive an approval to implement the OPB process are obligated to submit a report on the development of the OPB process.
(2) The reports on the development of the OPB process as referred to in section (1) include information as contained in the Guidelines on the OPB Procedures and Assessments as referred to in Article 2.
(3) The reports as referred to in section (1) are submitted to the Chairperson of the Authority periodically at least 1 (one) time in one of after the date of approval.

CHAPTER IV
COST OF ASSESSMENTS

Article 7

(1) Requests for OPB assessment applications are charged as non-tax state revenues in accordance with the provisions of legislation.
(2) Payments of OPB assessment requests costs as referred to in section (1) only apply for 3 (three) years since the assessment results of the OPB process as referred to in Article 5 section (1) point a.
(3) To apply for an approval for clinical trials implementations as referred to in Article 5 section (1) point b that is conducted apart from the 3 (three) year period as referred to in section (2) costs are charged as non-tax state revenues in accordance with the provisions of legislation.
(4) In the event that the OPB process as referred to in section (1) is rejected, then the costs paid cannot be withdrawn.

CHAPTER V
CLOSING PROVISION

Article 8

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

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

Issued in Jakarta
on 10 December 2015

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

signed

ROY A. SPARRINGA

Promulgated in Jakarta
on 15 December 2015
DIRECTOR GENERAL OF THE 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 2015 NUMBER 1854

ANNEX I
REGULATION OF CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY NUMBER 16 YEAR 2015
REGARDING
GUIDELINES ON THE PROCEDURES AND ASSESSMENTS OF NEW DEVELOPED DRUGS

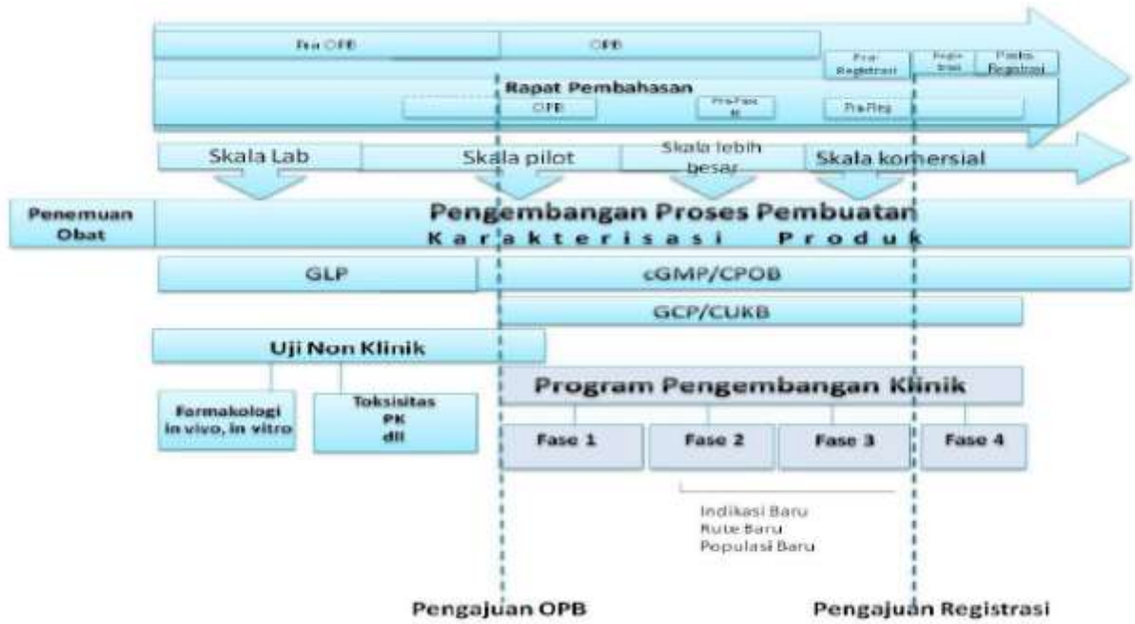
1. PREFACE

Prior to be marketed in Indonesia, a new drug goes through a long development process, starting from the concept of developing a new drug, development of active substances, process of manufacturing, analysis method and non-clinical trials, up till the clinical trial program that is the evidence phase of safety, efficacy and quality of drugs for humans, which data will be used for the registration of the drug.

Developing new drugs require regulatory guidelines to prevent phases that are not in accordance with the regulation requirements for drug registration purposes. Therefore, upstream communications are needed between regulators and product developers. With early communication on the development of new drugs it is expected that clinical trials implemented fulfill the provisions of the requirements in effect and the available data can be used as evidence of the aspects of quality, safety and efficacy of new drugs for registration purposes. Through this communication, the regulator can guide and provide requirements at every phase of the new drug developments so that it is expected that data resulted are implemented in accordance with the requirements at the time the drug is registered. Communication between the regulator and product developer will be the main purpose of the New developed Drugs process guidance.

These guidelines aim to guide the implementation of the OPB process conducted by research institutions as well as pharmaceutical industries with the purpose to be registered in Indonesia.

The New developed Drug Process (OPB) is as follows:



OPB goes through non-clinical and clinical trials prior to the registration of drugs. During the non-clinical and clinical phases, non-clinical trials of drugs are conducted that include in vitro and in vivo trials on animals as well as the characterization and validation of OPB that is produced on laboratory scales by using a predetermined phase process to prepare a pilot scale. If OPB is conducted by research institutions, then upon starting the OPB process, the research institution must at least prepared manufacturing facilities that fulfill the requirements of CPOB to implement the pilot scale and/or must cooperate with pharmaceutical industries for the manufacture of large-scale OPB according to CPOB. At the time OPB starts the clinical trial phase, then OPB must be produced in larger scales in facilities that meet CPOB, ranging from pilot scales to commercial scales wherein the product has been characterized. At this phase, the implementation of OPB clinical trials must observe the aspects of the Good Clinical Test Method (CUKB) as a form of protection for the subjects of clinical trials. After the clinical trial phase is implemented, then OPB enters the drug registration phase to obtain a circulation license number (NIE). After obtaining the NIE, it is not ruled out that an OPB goes through post-marketing clinical trials, in general, clinical trials to confirm the safety of an OPB.

The Indonesian FDA guidance for OPB starts at the time it enters the clinical trial phase, however, if required research institutions or pharmaceutical industries may perform communications during the non-clinical phase (Pre-OPB), as the most early communication phase prior and/or after non-clinical trials are implemented.

The Pre-OPB can be disregarded and product developers can immediately apply for OPB assessments if the Pre-OPB is in accordance with the requirements.

2. SCOPE

A. These guidelines include the role of Indonesian FDA in guiding OPB to be registered as a new drug to obtain a circulation license. Guidance of the Indonesian FDA against product developers since the early phase of the drug development until the registration is an OPB Assessment and requirement communication phase as well as the related provisions as set forth by the Indonesian.
These guidelines are intended to support the guidelines or requirements for clinical trials and drug registration in effect.

B. The guidelines are addressed to OPB that can be one of the following possibilities:
   1. OPB developed by research institutions or pharmaceutical industries in Indonesia, are manufactured by pharmaceutical industries in Indonesia, and at least one clinical trial is implemented in Indonesia.
   2. OPB developed by research institutions or pharmaceutical industries overseas, manufactured by pharmaceutical industries in Indonesia, and at least one clinical trial is implemented in Indonesia.
   3. OPB developed by research institutions or pharmaceutical industries overseas, manufactured by pharmaceutical industries overseas, and at least starting from the 2nd phase clinical trial are performed in Indonesia.

C. OPB proposed are drugs or drug materials in the form of new molecules or biology/ biotechnology products.

3. TERMS

Drugs are finished drugs including biological products, that are materials or a combination of materials used to affect or examine the physiological systems or pathological conditions in the framework to determine the diagnosis, prevention, cure, restoration and improvement of health and contraception for humans.

New developed Drugs (OPB) are drugs or drug material in the form of new molecules, biological products/ biotechnology that are being developed and manufactured by research institutions or pharmaceutical industries in Indonesia and/or overseas to be used in the non-clinical trial and/or clinical trials phase in Indonesia with the purpose to obtain a circulation license in Indonesia.

Product Developers (Registrants) are research institutions and/or pharmaceutical industries in Indonesia filing for OPB.

OPB Assessment is the phase of assessing new drug developments including the development of the drug quality/ CMC (Chemistry Manufacturing and Control), including the development of active substances, manufacturing process, analysis methods, non-clinical trials, and assessments of the clinical trial program and the clinical trial protocol.

OPB Filing is the filing for an OPB assessment.
Clinical Development Program are information on clinical trials that have been, or will be conducted, including any rational implementation of each study and the expected results, proving the safety and efficacy of OPB required to obtain a circulation license in Indonesia.

Pre-OPB is the pre-consultation phase of active substances, the manufacturing process, methods of analysis and non-clinical trials to support the filing of OPB.

Clinical trials are research activities by involving human subjects and intervention of trial products, to discover or ensure clinical effects, pharmacological and/or pharmacodynamics and/or identification of any adverse reaction, and/or study the absorption, distribution, metabolism and excretion with the aim to ensure safety and/or effectiveness of the product researched.

4. NEW DEVELOPED DRUGS (OPB)

At the time of filing OPB, the OPB document submitted must demonstrate a security guarantee on the use of OPB on clinical trial subjects and have the potential of achieving scientific objectives of the new drug. The completeness of OPB documents that must be provided by product developers are adjusted to the novel of OPB and how far the research and trials have been implemented prior to filing for the OPB, including the information of the clinical trial phase to be performed, duration of the clinical trials and dosage forms.

In the early phases of drug development, the assessments of Pre-OPB are implemented by the Indonesian FDA based on OPB data availability, namely summary of data quality (Chemistry, Manufacturing, Control/CMC) consisting of information on active substances, manufacturing process, testing of physical-chemical and biology, as well as non-clinical trial results supporting the safety of OPB. During the OPB process, new as well as additional information regarding the characteristics of OPB, results of clinical trials implemented and clinical trials to be performed, will be relevant information for the approval to conduct clinical trials in the framework of OPB. During this phase, the OPB quality document must include among others information on the composition, more detailed manufacturing process, quality control of active substances, finished OPB products, OPB stability evidence during the implementation of clinical trials, and the OPB labeling.
If available, then the Drug Master File (DMF) must be submitted.

Manufacturing of OPB clinical trial drugs follow the CPOB guidelines, while OPB non-clinical trials in laboratories shall follow the provisions of Good Laboratory Practice (GLP) or other provisions established. OPB information that must be available during the filing of OPB is as contained in the OPB filing form (Annex-1).

4.1. Active Substances

The quality document on active substances must contain descriptions on active substances including physical, chemical and biological characteristics. It is also must provided the information on the name and address of the manufacturers, facilities used for manufacturing the clinical trial lots, manufacturing process of active substances, the control process, specifications in general, method of analyses and content limit to indicate the identity, potency, quality and purity of the active substances during the planned toxicology tests and clinical trials.

In particular for vaccines and biological active substances, information must be provided on the raw material, components, derivates and specifications used in the manufacturing of active substances.

4.2 Finished Drugs

The document on the quality of drugs must contain the specification of active substances, additional substances, intermediate products and trial methods used. There should be validations for relevant critical processes, among others sterilization, virus removal, inactivation, purification, although the validation of the production process has not been completed yet.

During the OPB process, there can be amendments/ modifications in the manufacturing process or dosage form, however when filing for the phase 1 clinical trial, identification and control on active substances, intermediate products and finished drugs should already be available. Specifications should be determined although the specifications are subject to change until the end of the development process. The determination on the quality specifications may be used as a basis for the acceptance of test results of the specific active substances, intermediate products and finished drugs used in clinical trials.

The stability of active substances, intermediate products, and finished products must be guaranteed during the implementation of clinical trials and the entire phases of the clinical development program. Data on the longterm stability may be submitted in the last phase of the development to support the product stability at the time the drug is registered.

In the event that during the OPB development production scale changes occur, such as changes from the pilot scale into a larger production scale, then the product developers must submit an amendment/ improvement of the quality document.
Labeling of OPB must contain descriptions on Drugs for Clinical Trials.

5. ASSESSMENT ON NEW DEVELOPED DRUGS

The Indonesian FDA implements OPB assessments through phases as contained in Table 1. Filing for OPB are performed after non-clinical trial results (and previous clinical trials, if any) to support the clinical trials to be implemented in Indonesia. After the filing of OPB, the Indonesian FDA monitors the clinical trial phases and communicate with the product developers verbally and/or in writing regarding data needed for the drug registration.

Table 1. The New Developed Drug Phase

Phase	Product Developer	Indonesian FDA
Pre-OPB (optional)	1. Submit: - Pre-OPB documents according to attachments - Discussion material - Planning of clinical trials 2. Discussion Meeting	1. Determines time of discussion meeting 2. Study Pre-OPB documents 3. Discussion meeting with registrant
Filing of OPB	1. Submit: - OPB-1 Form according to Attachment 1 - OPB Process Document according to Attachment 2 - Requirements of phase 1 or phase 2 clinical trials 2. Discussion meeting 3. Program presentation on clinical developments	1. Providing an identity number 2. Assessment of the OPB process 3. Inspection of the CPOB manufacturers 4. Inspection of phase 1 CUKB facilities 5. Discussion meeting with the: -Expert Team -Product developers 6. OPB assessment results 7. Approval of clinical trial implementation/ recommendation for improvements/ termination 8. Suspension / termination of clinical trials
Filing subsequent clinical trials**	1. Submit the OPB Process Document according to annex 2 2. Discussion Meeting (optional)	1. Assessment 2. Discussion Meeting (optional) with the: - Expert Team - Registrant 3. Approval/ rejection of clinical trial implementation 4. Suspension/ termination of clinical trials.
Filing of clinical trials phase 3**	1. Submit: - OPB Process Document Phase Product Developers Indonesian	1. Assessment 2. Discussion Meeting with the: - Expert Team - Product developers

	FDA according to Attachment 2 - Discussion material 2. Discussion Meeting: Pivotal Pre-clinical trials - prior to filing for registration	3. Approval/ rejection of clinical trial implementation 4. Suspension/ termination of clinical trials
Filing phase 4 of clinical trials / Post- marketing of OPB **	Submit clinical trial phase 4 document / commitment	Asessment

* Identity number consists of 9 digits with the format of [aabbbcc/dd]
** Implementation of Clinical Trials follow the provisions of Guidelines on Good Clinical trial Methods (CUKB) and the Provisions of Clinical Trial Procedures

5.1. Pre-OPB

Pre-OPB is the initial meeting of product developers and the Indonesian FDA prior to filing for the OPB.

Documents submitted are non-clinical data and the summary of the quality document on OPB implemented, together with a statement that the data submitted is true. However, with special justification, the discussion can also start for the finished phase of non-clinical data implementation if the purpose of the product development is for drug registration.

At this phase, the Indonesian FDA implements discussions with product developers regarding the OPB concept, rational design of clinical trials or other topics as needed.

If the non-clinical data fulfills the provisions, then the product developers may immediately file for an OPB assessment without the pre-OPB phase.

5.2. Filing of OPB

Filing of OPB are conducted by product developers through phases as contained in Table 1 by using the form stated in Annex 1 and submitting the documents stated in Annex 2.

After the filed OPB document is received, the Indonesian FDA will provide an Identity Number.

If at the time of the OPB Assessment new information is available, then the information may be added as an amendment.

5.2.1. OPB Identity Number

The identity number consists of 9 digits with the format of [aabbbcc/dd] and the following details:
the 2 first digits indicate the year of the OPB process filing
the 3 second digits indicate the registrant code
the 2 third digits indicate the product serial number
the last 2 digits indicate the phase and filing serial

5.2.2. Assessment

The Indonesian FDA will assess the documents submitted when filing the OPB.

Assessments are implemented by the Assessment Team from various science disciplines established by the Indonesian FDA. The Chairperson of the Authority may request adhoc expert feedback. The Assessment Team and experts must not have conflict of interests and are obligated to maintain the confidentiality of OPB documents assessed.

Assessment of an OPB may be performed on one or more clinical trial phases with the purpose to ensure the rights, safety and well-being of clinical trial subjects at each clinical trial phase, and may assist in providing quality assurance of OPB scientific assessment which results of safety testing and efficacy will later be assessed at the time of drug registration. The assessment of the OPB quality aspect is performed during the development of active substances and drugs (see Part 4).

The assessment of the clinical development program is performed by considering the OPB quality aspect, non-clinical trial and clinical results implemented. The clinical development program muat go through clinical trial phase 1 up till phase 3, unless the specificity of OPB as bio-similar products, copy drugs, and vaccines. Assessment on the clinical development program is different at each phase. The assessment on the phase 1 OPB process is assigned for drug safety, while phase 2 and 3, muat consist of the efficacy and safety of the drug (see Part 6).

Assessments on the clinical development program are among others performed on the methodology of OPB clinical trials that refers to the applicable efficacy and safety assessment guidelines. In terms of OPB specificity, the methodology of clinical trials are set forth in a separate guideline, among others:

- General Guidelines Biosimilar Product Assessment

- o Guidelines for Bioequivalence Tests
- o Guidelines for Assessing the Efficacy and Safety of Vaccines
- o Guidelines for Assessing the Efficacy and Safety of Combined Vaccines

OPB assessments are performed within 100 (one hundred) work days from the submission of documents. In the event that clarifications or additional data is needed, then the calculation of the assessment time is stopped (clock-off) up till the product developers submit the requested additional data.

5.2.3. Discussion Meeting

The Indonesian FDA implements discussion meetings prior or during the OPB process assessment.
Discussion meetings can be in the form of discussion meetings between the Indonesian FDA and product developers or the Indonesian FDA and the expert team. In the discussion meeting with the product developers, the Indonesian FDA may invite the expert team. The purpose of discussion meetings are to submit information on the new drug development process verbally, discussions and solving scientific problems that may arise during the process of the new drug development, and answering questions of product developers submitted before the meeting.

Discussions are prioritized on the clinical development program, the purpose and design of clinical trials, and/or discussions on the adequacy of the quality document, non-clinical trials and other technical information aimed to support the clinical trials and/or drug registration.

Discussion meetings are implemented at each phase of the OPB assessment and at the request of the product developer (optional), however at least held in the pre-OPB phase, at the time filing the OPB, before the pivotal clinical trial, and prior to the registration process. The Indonesian FDA prepares the implementation plan at a time agreed upon by the product developers and the Indonesian FDA and prepares a documentation of the minutes of the meeting. Discussion material must be delivered to the Indonesian FDA at least 7 days prior to the discussion meeting. The OPB Assessment Team may provide additional questions or recommendations to the product developer related to the information submitted or the clinical trial design of the clinical development program, within 30 days after the meeting. The product developer must response within the time period specified by the Indonesian FDA.

5.2.3.1. Pre-OPB Discussion Meeting

Pre-OPB meetings may be requested by product developers during the production process, formulation and passed specifications have been determined, however prior to the completion of the pharmacology and toxicology non-clinical trials. In these meetings, the product developer submits information/ documents to the Indonesian FDA and communicates to identify the data needed by the Indonesian FDA for the clinical development program.

The meeting is aimed to discuss :
- Rationalization of the OPB design;
- Production process and OPB quality standard;
- Non-clinical development program;
- Clinical development program;
- Regulations and policies of the Indonesian FDA related to the OPB process;
- Other relevant issues.

5.2.3.2. Discussion Meeting on the Filing of OPB

This meeting is held to discuss the clinical development program and other relevant issues, among others:
- CPOB status of OPB manufacturers, formulation, packaging and stability;
- Non-clinical information available and support of the clinical development program.
- Design and rational of the clinical development program
- List of questions for discussion material.

5.2.3.3. Discussion Meeting Prior to the Pivotal Clinical Trial

This meeting is held prior to the start of the phase 3 study, to discuss:
- CPOB status of OPB manufacturers, formulation, packaging and stability;
- Drug safety to proceed to phase 3
- Protocol of clinical trial phase 3
- Adequacy of available studies to assess the safety and efficacy for the next phase
- Identification of additional information needed to support the registration

Product developers must submit information/ documents, at least 1 month prior to the meeting, consisting of:

- Summary of clinical trial phase 1 and 2
- Protocol of clinical trial phase 3
- Implementation plan and duration of clinical trial phase 3

– formulation, form of dosage and method of OPB application

– plan on additional non-clinical trials (if any)

5.2.3.4. Discussion Meeting Prior to the Request for Registration

This meeting is held prior to the registration with the purpose to discuss:

- CPOB status of OPB manufacturers, formulation, packaging and stability;
- Identification of clinical trials relied on as clinical trials that are adequate and controlled to support the drug efficacy for registration;
- Identification of current clinical trial status or that are needed to assess the safety and efficacy;
- Submit general information required for drug registration;
- Concept of the Risk Management Plan (RMP);
- Discuss unresolved major issues.

Product developers must submit the following information/ documents no less than 1 month prior to the meeting, consisting of:

- Summary of clinical trial to be submitted for registration;
- Information on current clinical trial status or that are needed;
- Discussion material.

5.2.4. Decision

The Indonesian FDA will provide a decision on the OPB assessment results in the form of an OPB Assessment Result, Approval of the Clinical Trial Implementation, Rejection/ Suspension/Termination.

5.3. Control on Clinical Trial Implementations

Each clinical trial implemented during the OPB process must obtain an approval of the Ethical Commission and Approval of the Clinical Trial Implementation from the Indonesian FDA. Every filing for the clinical trial approval shall follow the Guidelines of the Good Clinical Test Method (CUKB) and the applicable clinical trial regulations.

After approval of the clinical trial implementation on the filing of OPB, the product developer may request for a subsequent clinical trial phase, separately. The product developer files for the approval of the clinical trial implementation by attaching the report summary and previous clinical trial approval. The clinical trial team of the Indonesian FDA will study the clinical trial protocol to further provide an Approval for the Clinical Trial Implementation and Approval for Drug Import for the Clinical Trial, if the clinical trial drug is not produced in Indonesia. After providing an approval, the Indonesian FDA will monitor the clinical trial implementation as follows:

- Inspect the clinical trial implementation at the clinical trial site;
- Monitor the Serious Adverse Drug Reaction (ADR)

The product developer may be requested to provide a commitment to implement clinical trial phase 4 as an additional clinical trial to determine the drug safety and efficacy on specific populations, as contained in the Risk Management Plan (RMP).

5.4. Studies in the Framework of Drug Registration

After the clinical trial phase contained in the clinical development program is completed, then a drug registration process will be performed by studying the efficacy, safety and quality as well as a risk-benefit discussion implemented by the drug registration team and the National Committee Team following the guidelines and applicable regulations on drug registration.

5.5. Reporting on the Process of the New Developed Drug

Product developers are obligated to submit annual reports to the Indonesian FDA on the development of the OPB process. The Periodic Reports on the Development of the OPB Process must contain the following information:

a. Information on clinical trials

Summary of the clinical trial status, either the ongoing as well as the completed trials.

- Title of the clinical trial, protocol number, purpose, subject population and information whether the clinical trial has been completed.

- Planned number and participating subjects (grouped based on age, gender and race), who participate in the clinical trials to completion and drop-outs as well as the reasons.
- A brief explanation on clinical trial results that have been completed.

b. Summary of information

Contains information obtained from previous clinical trials and non-clinical trials.

- Summary on Serious Adverse Drug Reaction (ADR) that most often occur, in the form of descriptions or tables;
- Summary of the entire report on the safety of the OPB process;
- List of subjects who died during the participation in the clinical trial, together with information on the cause of death;
- List of subjects who dropped-out during the research because of Adverse Events (SAE) either related to the drug or not;
- A brief description related to the drug action, for instance information on the dosage response, information on controlled trials and bio-availability;
- List of non-clinical trials that have been or are still implemented (included trials on animals) and a summary of non-clinical major findings;
- A summary on changes of the manufacturing process or microbiology, if any.

c. Descriptions on future clinical trial plans to replace the clinical development program filed in the previous year.

d. A summary on the changes of the Investigator's Brochure (IB) and submit the latest IB version, if any.

e. Descriptions of changes on the clinical trial protocol, if any.

f. Status of circulation in other countries, including information whether it was ever withdrawn from the market or whether the circulation was suspended.

6. CLINICAL DEVELOPMENT PROGRAM

The filing of OPB may be performed for one or more clinical trial phases. The filing for the approval of OPB clinical trial implementation shall follow the Clinical Development Program that has been approved during the OPB Assessment. Changes on the Clinical Development Program may be performed based on information derived from other clinical trials, ongoing clinical trials or other information sources. This should be discussed at the Discussion Meeting.

In general, clinical trials are divided into 4 phases. The implementation of the clinical trial phases are conducted in sequence, although it may be possible to coincide or overlap. The four phases are:

a. Phase 1

Clinical trial phase 1 is a study on the initial administering of OPB on humans. This clinical trial is normally applied to healthy subjects. The clinical trial is designed to determine the OPB metabolism and pharmacology mechanism on humans, observe the adverse reaction profile related to increased dosage and if possible to obtain an initial phase effectiveness evidence.

The phase 1 clinical trial is also a drug metabolism study, structure and activity relationship and the action mechanism in humans, including studies where OPB used is to determine biological phenomena or disease processes.

During the phase 1 clinical trial, information must be obtained on adequate pharmacologic and pharmacokinetic effects, so that it can continue into phase 2 clinical trials that are well controlled and scientifically valid. The total number of subjects varies according to the type of drugs and the amount according to statistical calculations.

b. Phase 2

Phase 2 clinical trials are studies using comparisons that are implemented to assess the effectiveness of OPB for indications to be filed and to determine the short term general adverse reactions or risks related to the drug. Generally, phase 2 clinical trials are implemented by involving a relatively small number of ill subjects according to statistical calculations.

c. Phase 3

Phase 3 clinical trials are advanced studies by using or not using comparisons. This study is designed after obtaining initial evidences of the effectiveness of a drug, and is intended to obtain additional information regarding the effectiveness and safety needed to assess the entire risk-benefit of a drug, and becomes the basis of adequate information on the labeling. Phase 3 clinical trials usually involve more ill subjects than phase 2 subjects according to statistical calculations.

d. Phase 4

Phase 4 clinical trials are studies on marketed drugs to obtain the profile of the drug effectiveness and safety on the actual use in the community. Phase 4 clinical trials may also be studies to support changes such as dosage changes, administering schedules and different populations.

Table 2. Clinical Development Program

No	Phase	Type of Trial	Title	Design	Number of subjects	Purpose	Plan on the start and completion of the trial
		1. Pharmaco-dynamic 2.Pharmacokinetic 3. Efficacy 4.Imunogecity 5. Safety				1. Primer 2.Secondary	

7. SUSPENSION / TERMINATION OF THE NEW DEVELOPED DRUG PROCESS

If there are unresolved issues in the Clinical Development Program, the OPB Assessment Team will request the indonesian FDA to suspend or terminate a clinical trial or the entire Clinical Development Program. Unresolved issues of the Clinical Development Program have certainly been communicated with the product developers by requesting clarifications or settlement of the issue.

The OPB suspension process is a temporary termination of the OPB filing or a temporary termination of an ongoing OPB development. OPB cannot be used on clinical trials that are still being filed. If there are ongoing clinical trials, then the subject recruitment and drug administering for the clinical trial shall be temporary terminated, unless approved by the Indonesian FDA to be still administered in relation to the safety of the subject.

The OPB termination process is a termination of the OPB process implementation and product developers MUST terminate the clinical trials and withdraw all the drugs of the clinical trials. The Indonesian FDA will deliver a written notification to the product developers. If the OPB process is terminated, the product developers is obligated to submit a report on the OPB process termination. If there are objections on the OPB process termination, product developers may apply for

reconsideration to the Indonesian FDA in writing together with the justification.

7.1. Reasons for the Suspension of the OPB Process

The basis for the OPB process suspension varies based on the clinical trial phase currently implemented.

a. Reasons of the OPB process suspension in Phase 1
   - Suspected actual safety risks.
   - The researcher/investigator does not have the qualifications conform his responsibility to implement a proper clinical trial.
   - The content of the Researcher Brochure is misleading.
   - Inadequate information to assess safety.

b. Reasons of OPB process suspension in Phase 2 or 3
   - All reasons as contained in phase 1.
   - Deficiencies are found in the design to fulfill the determined purposes.

c. Other reasons:
   - When no safety evidences and adequate efficacies are obtained to support the use.
   - The drug indicates limited efficacy in the study with a good method and comparison.
   - The unavailability of adequate drugs for the study implementation.

7.2. Reasons for the OPB Process Termination

a. Reasons for the OPB process termination in Phase 1
   - Actual safety risks.
   - The method, facilities, manufacturing process, and drug packaging are not adequate for clinical trials for determining the standard and maintaining the drug quality.
   - The clinical trial implementation differs from the protocol.
   - There is not adequate information to assess the safety.
   - There are no accurate annual reports.
   - There are no investigations and reports on Serious Adverse Drug Reactions (ADR).
   - Provides inaccurate information or omit information on the drug for clinical trials.

b. Reasons for OPB process termination in Phase 2 and 3
   - All reasons contained in phase 1.
   - The protocol proves that it cannot be used for the drug safety and efficacy evidences.
   - There are convincing evidences that the drug is not effective.

CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY,

Signed

ROY A. SPARRINGA

ANNEX II
REGULATION OF CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY
NUMBER 16 YEAR 2015
REGARDING
GUIDELINES FOR THE PROCEDURES AND ASSESSMENT OF NEW DEVELOPED DRUGS

FORM OPB -1

FORM FOR OPB FILING

I. GENERAL INFORMATION Identity Number: OPB aabbbcc/dd

Name of OPB:
Date of receipt (filled-out by the officer):
Name, address and telephone number of product developer :
Indication (in this filing)
Clinical trial phase: 1. ☐Phase 1 ☐Phase 2 ☐Phase 3 ☐Phase 4
2. List of other registered drugs that are the reference in this filing
3. Statement of not implementing clinical trials prior to the issuance of the Indonesian FDA Agency Approval
4. Approvals obtained for the same OPB (state in full): Date and Number of Approval :
5. Name and position of the person in charge of the implementation and reporting of the approval implementation Signature :
6. Purpose of submitting this document : (for example: initial filing, response, amendment, etc.)

II. INFORMATION ON OPB AND CLINICAL TRIAL PLAN

Content of active substances :
Class of pharmacology :
Structure of drug molecules :
Formula and dosage forms :
Method of administering :
General purpose :
Plan and time period of the clinical trial implementation :

Summary of experience on administering OPB or similar OPB on humans, if any :
Experience of studies or marketing in other countries related to the safety of OPB clinical trials filed :
. OPB already circulates in the market apart from Indonesia :☐ Yes ☐NIf yes, state the country the drug is marketed
. If the OPB has been withdrawn from the market because of safety and effectiveness reasons, state the name of the country wherein the filed OPB is terminated or withdrawn from the market;
. Reason of termination or withdrawal (related to the safety and effectiveness of OPB):
. Name of the country where the filed OPB is terminated during clinical trials:

III. PROTOCOL OF CLINICAL TRIAL

Protocol title for each study :
Version, number and date of protocol :
Purpose of clinical trial:
Name, address and qualification of each researcher :
Name of each sub-researcher :
Name and address of the clinical trial implementer site/center :
Name and address of the clinic laboratory :
Name and address of each Ethical Commission that reviews :
Inclusion criteria :
. Exclusion criteria :
. Planned number of subjects who participate in the study and receive the OPB :
. Description of the clinical trial design: . Type of the comparison group . Description of the method used to minimize bias on the subject, researcher and analyst
. Method to determine : . Dosage to be administered . Maximal dosage planned . Duration of subject treatment
. Description on the observation and measurements that shall be implemented to fulfill the clinical trial purpose
. Description of clinical examinations, laboratory test or other measurements to monitor OPB effects on the subject (humans) and minimize risks

IV. INFORMATION ON OPB PHARMACEUTICALS

1.	Composition of OPB:
2.	Process of manufacturing :

• Active substances : • Finished drug :
3. Specification and method of testing : • Active substances : • Finished drug :
4. Form of dosage :
5. Pharmaceutical information amendment on the production scale of the OPB development :

V. INFORMATION ON PHARMACOLOGY AND TOXICOLOGY

1. Profile of pharmacology and OPB non-clinical mechanism • Description on pharmacodynamics and working mechanism • Description on pharmacokinetics : - absorption : - distribution : - metabolism : - excretion:
2. Toxicology (depends on the OPB properties and clinical trial phase): • test results on single dosage of toxicity • test results on repeated toxicity dosage • drug effect on the reproductive system and teratogenicity • explicit toxicity test related to the specific OPB administering method (inhalation toxicity, dermal, ocular toxicology) • in vitro study 3. Immunogenicity 4. Follows the provisions of the Good Laboratory Practice (GLP) (for non-clinic laboratory studies): ☐ Yes ☐ No, reason :

VI. PREVIOUS CLINICAL TRIAL EXPERIENCES

1. Experience in using OPB clinical trials ☐ Yes ☐ No
2. Detailed information on experience using OPB safely :
3. Detailed information on experience using OPB effectively :
4. Is OPB a combination of drugs ever researched ? ☐ Yes ☐No If yes, provide information of each active component except researched/circulated in Indonesia

VII. ADDITIONAL INFORMATION

If OPB psychotropic or that may cause dependence and misuse : 1. Information on experience of study :
Radio-nuclear OPB: 2. Study data on animals or humans for dosage calculations absorbed against radiation on the body and critical organs administered on subjects (humans)
Plans on safety and effectiveness study on children (if any) :

CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY,

signed

ROY A. SPARRINGA

ANNEX III
REGULATION OF CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY NUMBER 16 YEAR 2015
REGARDING
REGULATIONS ON THE PROCEDURES AND ASSESSMENT OF NEW DEVELOPED DRUGS

COMPLETENESS OF DOCUMENT FOR OPB FILING

No	Document	Pre – OPB	Filing of OPB		
			Phase 1	Phase 2	Phase 3
1	Summary of OPB quality document : Information on active substances Manufacturing process of active substances Quality control, characterization, validation Determining content / potency of active substances Formulation and method of manufacturing drugs Stability	√			
2	Document on Quality :				
A	General Information :		√	√	√
	Source of raw material/antigen (active substances)		√	√*	√*
	Name of classification Chemical formula Summary of product characteristics		√	√*	√*
B	Manufacturing and control process				
C	Characteristics including validation for critical processes		√	√	
D	Overall characteristics on production lots/batches				√
E	Specification and testing method of active substances, additional substances and intermediate products		√	√*	√*
F	Specification and testing of packaging		√	√*	√*
G	OPB Stability Test		√	√*	√*
H	Consistency of lots from clinical lots (production scale, fulfillment of CPOB) **/*** and lot release **				√
3	Non-clinical overview and summary (Fulfillment of GLP)	√	√		

	-Toxicity				
	-Potency and immunogenicity **				
	-Genetic stability ***				
4	Clinical trial document				
A	Clinical trial according to CUKB requirements		√	√	√
B	Investigator's brochure****		√	√	√
C	Clinical trial phase 1 report on safety			√	
D	Clinical trial phase 2 report on safety and efficacy				√
E	Data on protection relations and antibody**				√
5	Labeling of OPB		√	√*	√*
6	Drug Master File (if any)		√	√*	√*
7	Clinical Development Program		√	√*	√*

√* : if there are information changes from previous clinical lots
**** : specifically for OPB vaccines**
***** : specifically for genetically engineered products**
****** : according to the CUKB guidelines in Indonesia**
GLP : Good Laboratory Practice

Summary of Product Characteristics

1. Name of Drug
2. Form of Dosage
3. Administering of drug
4. Drug composition (name and potency of active substances)
5. Method of drug action and/or pharmacodynamic and / or pharmacokinetic
6. Data on non-clinical safety (if necessary)
7. List of additional substances
8. Non-combined (if necessary)
9. Method of storage
10. Stability / circulation period (shelf life) of drug
11. Stability/ limit of use after reconstituted or after opened (in use stability) (if necessary)
12. Type and size of packaging
13. Instructions for use
14. Method of reconstitution (if any)
15. Classification of drug

16. Physicochemical properties or other relevant properties including biological activities for biological products
17. Immunogenicity (if relevant)

CHAIRPERSON OF THE
INDONESIAN FOOD AND DRUG
AUTHORITY,

Signed

ROY A. SPARRINGA

-