Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

MAR 06 2020

ADMINISTRATIVE ORDER
No. 2020- 0010

SUBJECT: Regulations on the Conduct of Clinical Trials for Investigational Products

I. RATIONALE

Republic Act No. 9711, otherwise known as the "Food and Drug Administration (FDA) Act of 2009," and its Implementing Rules and Regulations has declared the policy of the state to adopt, support, establish, institutionalize, improve and maintain structures, processes, mechanism and initiatives that are aimed, directed and designed to: (a) protect and promote the right to health of the Filipino people; (b) help establish and maintain an effective health products regulatory system; and (c) undertake appropriate manpower development and research responsive to the country's health needs and problems.

In relation to these and in furtherance with the objectives of the Republic Act No. 11223, otherwise known as the "Universal Healthcare Act," which seeks to "ensure that all Filipinos are guaranteed equitable access to quality and affordable health care goods and services, and protected against financial risk," the FDA, as the National Regulatory Authority (NRA), recognizes that conduct of clinical trials is beneficial to the country. Clinical trials allow for the identification and access to new treatment modalities which are crucial in addressing the high burden of communicable (e.g., HIV/AIDS, tuberculosis, and malaria) and non-communicable (e.g., cancer, diabetes, etc.) diseases. While a large number of clinical trials are being conducted in other countries, representation of Filipino patients is important to account for race, genetic factors, and co-morbid conditions that play pivotal roles in response to a drug or intervention.

The first general standards and policies for the approval and conduct of clinical trials in the Philippines was provided for in 1989 thru Administrative Order (AO) No. 67 wherein clinical trials were required for the registration of investigational drugs, new drugs, and other tried and tested drugs. Over the last 30 years, subsequent regulations and guidelines have been issued to expand the policies for the approval, conduct, and monitoring of clinical trials. However, these issuances have to be rationalized to provide a clear framework of clinical trial regulation in the Philippines.

Consistent with the aim of RA No. 11032 or the "Ease of Doing Business and Efficient Government Service Delivery Act of 2018," the existing regulations related to the conduct of clinical trials were streamlined to create a clear, simplified and transparent regulation, boost local competitiveness and attract more local and foreign entrepreneurs.

II. OBJECTIVES

This Administrative Order aims to achieve the following:

1. Ensure the full protection of the rights and safety of human subjects and the integrity of clinical trial data through the adoption and implementation of International Council of Harmonization-Good Clinical Practice (ICH GCP) standards;
2. Ensure efficient and effective process for the approval of clinical trials;
3. Provide standards and requirements for the regulation and importation of Investigational Products; and
4. Strengthen the monitoring of compliance of all organizations, institutions and entities to GCP and other related FDA regulations through regulatory inspections.

III. SCOPE AND COVERAGE

This Administrative Order shall apply to the sponsors, Contract Research Organizations (CROs), investigators, and Research Ethics Committees (RECs) involved in the approval, conduct, monitoring and inspection, in all phases of clinical trials for Investigational Products intended for eventual product registration and marketing.

Products with issued Marketing Authorization shall follow these requirements provided the following apply:

1. The study will be conducted to support a new indication or intended to be used to support any other significant change in the labelling of the drug; or
2. The study will involve a route of administration or dosage level or use in a patient population or other factors that present more than minimal risk; or
3. The study will assess a known risk related to the use of the drug, assess signals of serious risk related to the use of the drug and/or identify an unexpected serious risk when available data indicates the potential for a serious risk.

Combination products containing at least one investigational product shall also be required to follow the requirements stated in this Order.

IV. DEFINITION OF TERMS

Definitions contained in the International Council for Harmonization on Good Clinical Practice Glossary and ICH Safety and Efficacy Guidelines (E2A) are hereby adopted and the following are emphasized:

1. **Adverse Event (AE):** any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH E2A).

2. **Adverse Drug Reaction (ADR):** all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions (ICH E2A).

3. **Clinical Trial/Study:** Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous. (ICH GCP 1.12)

4. **Contract Research Organization (CRO):** A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions. (ICH GCP 1.20)

5. **Institutional Review Board (IRB):** An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, of protocols and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects. (ICH GCP 1.31)

6. **Investigational Product (IP):** A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. (ICH GCP 1.33)

7. **Investigator:** A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. (ICH GCP 1.34)

8. **Protocol Amendment:** A written description of a change(s) to or formal clarification of a protocol. (ICH GCP 1.45)

9. **Serious Adverse Event or Adverse Drug Reaction:** Any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect (ICH E2A).

10. **Sponsor:** An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of clinical trial. (ICH GCP 1.53)

11. **Unexpected Adverse Drug Reaction:** An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product) (ICH E2A).

Additional definition for terms applicable for this Order are found in Appendix A.

V. GENERAL GUIDELINES

1. All clinical trials of Investigational Products shall be conducted in accordance with the current ICH GCP and its subsequent revisions (Annex A).
2. Likewise, the ICH Safety and Efficacy Guidelines and its subsequent revisions are hereby adopted (Annex B).
3. All establishments that will conduct clinical trials in the Philippines, for purposes of product registration, shall secure a License-to-Operate (LTO) from FDA, as a clinical trial sponsor and/or a CRO.
4. Clinical trials shall only commence once the approval from the FDA and Institutional RECs have been issued.
5. All clinical trials on IPs covered in this AO, including amendment/s thereof, shall undergo mandatory review and approval from FDA.

6. All IPs to be used in the conduct of clinical trials shall be in compliance to Good Manufacturing Practice (GMP) and labeling requirements as required by this Order.
7. Only establishments with a valid LTO as importer shall be allowed to import IPs.
8. Imported IPs shall secure an Import License (IL). The IL shall also include imported Ancillary Supplies, if applicable.
9. All clinical trials shall be uploaded to the Clinical Trial Registry which is made available to the public for transparency.
10. Reporting of all Suspected, Unexpected Serious Adverse Reaction (SUSAR) shall comply with all applicable regulatory requirements and the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2A) which is hereby adopted (Annex C).
11. Promotional claims of safety or effectiveness of the investigational product for a use for which it is under investigation shall be prohibited.
12. All clinical trial related inspections by other regulatory authorities and results thereof shall be reported to the FDA.
13. FDA shall have the authority to enter the facilities of investigational sites, sponsors, CROs and RECs engaged in the conduct of clinical trials for inspection of compliance with the investigational plan/protocol and regulations and/or for verification of submitted documents in relation to any application.

VI. SPECIFIC GUIDELINES

1. Clinical Trial Application

1.1 A clinical trial shall gain authorization from the FDA for its conduct in the Philippines thru the process of approval illustrated in Appendix B.

1.2 Filing

1.2.1 A sponsor and/or CRO shall submit a clinical trial application to the FDA in accordance with the existing guidelines on the process of submission of application.

1.2.2 An application for the conduct of clinical trial is deemed filed upon complete submission of the documentary requirements (Appendix C), including payment of fees and charges.

1.3 Evaluation and Regulatory Decision

1.3.1 The evaluation of all applications shall be based on the completeness and veracity of the submitted documents and compliance with appropriate standards.

1.3.2 FDA shall give the final decision to approve or deny a regulatory application. Decision on applications shall be based on the evaluation of the scientific, technical and administrative documents submitted. This evaluation shall be conducted by FDA Regulatory Reviewers and a duly constituted Scientific Advisory Committee (SAC), if appropriate.

The composition and constitution of the FDA Regulatory Reviewers and SAC shall be covered by separate issuance/s. Further, they shall be required to follow the Department of Health guidelines on the disclosure and management of Conflict of Interest (COI).

1.3.3 FDA shall provide a written decision within 60 calendar days after filing of application. Should there be a need for clarification on the application,

a notification, either written or electronic, shall be sent to the applicant (clock stops). The applicant is expected to respond to the query within 30 calendar days. If no response is received from the applicant within the required period, the application shall be disapproved.

1.3.4 In case the applicant falsified, misrepresented material facts or documents, or withheld any material data or information, the application shall be disapproved and additional sanctions may be imposed by the FDA.

2. **Investigational Products and Clinical Trial Import License**

2.1 The responsibility of ensuring the quality of products used in the conduct of clinical trials shall rest upon the sponsor(s) and CRO(s) involved in the conduct of the studies.

2.2 The License to import IPs to be used for clinical trials shall be issued together with the Clinical Trial Approval (CTA) and shall be valid for three (3) years. The IL can be used repeatedly within the validity period.

2.3 Extension of Validity and Addition of Quantity

2.3.1 Two-year extension of the validity of the IL shall be issued upon submission of an application within 120 days prior to the expiration of the validity of the IL. For complete list of documentary requirements, please see Appendix D.

2.3.2 Likewise, an application for addition of quantity for the importation of IPs can also be submitted following the same documentary requirements as item 2.3.1.

2.3.3 The FDA shall provide a written decision on these applications within 15 calendar days upon filing of application. The FDA may have queries regarding the request which shall be sent electronically to the applicant (clock stops). The applicant is expected to respond to the query/queries within seven calendar days. If no response is received from the applicant within the required period, the application shall be disapproved.

2.4 Notification

2.4.1 The sponsor or CRO shall notify FDA quarterly of every shipment of IPs and ancillary supplies entering the country.

2.4.2 Documentary requirements for notification are found in Appendix D.

3. **Labeling of Investigational Products**

3.1 The label of an investigational product shall not bear any statement that is false or misleading in any particular and shall not represent that the investigational product is safe or effective for the purposes for which it is being investigated.

3.2 The labeling shall follow the stated requirements in Appendix C8.

4. **Uploading to the Clinical Trial Registry**

4.1 It is the responsibility of the study sponsor or CRO to ensure that the required information is uploaded to the Clinical Trial Registry within 30 calendar days after receipt of the FDA clinical trial approval and/or approval of any amendments. Information and documents required to be uploaded are indicated in Appendix E.

4.2 The sponsor or CRO shall update the registry within 30 calendar days after the termination of the study.

4.3 The FDA shall upload violations, violating entities and regulatory actions in the

registry.

5. **Amendments**

5.1 Clinical trial protocol amendments shall be classified as (1) notification and (2) prior approval (Appendix F).

5.2 Notification amendment can be implemented without prior approval from FDA provided that the documentary requirements are submitted.

5.3 Amendments in the clinical trial that have the potential to affect the benefit-risk assessment of the trial shall not be implemented without prior approval from the FDA, unless otherwise justified. These amendments include those where they are likely to have a significant impact on:

5.3.1 the safety or physical or mental integrity of the subjects

5.3.2 the scientific value of the trial

5.3.3 the conduct or management of the trial

5.3.4 the quality or safety of any IP used in the trial

5.4 Documentary requirements for notification and prior approval amendments are found in Appendix D.

5.5 The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted.

5.6 FDA shall provide a written decision on the amendment applications within 20 to 30 calendar days after filing of requirements. The FDA may have queries regarding the applications which shall be sent electronically to the applicant (clock stops). The applicant is expected to respond to the query/queries within 15 calendar days. If no response is received from the applicant within the required 15 calendar days, the application shall be disapproved.

6. **Safety Reporting**

6.1 The sponsor or the CRO is responsible for expediting the reporting of all SUSARs to the FDA, in accordance with the Standards for Expedited Reporting of the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2A). The terminology recommended by the Medical Dictionary for Regulatory Activities (MedDRA) term shall be used in coding the adverse reaction(s).

6.1.1 Reports to the FDA shall be submitted as follows:

6.1.1.1 Fatal or Life-Threatening Unexpected Adverse Reaction.

FDA shall be notified as soon as possible but no later than seven calendar days after first knowledge by the sponsor that a case qualifies, followed by as complete a report as possible within eight additional calendar days. This report shall include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal products.

6.1.1.2 All Other Serious, Unexpected Adverse Reaction

Serious, unexpected adverse reactions that are not fatal or life-threatening shall be filed as soon as possible but no later than 15

calendar days after first knowledge by the sponsor that the case meets the minimum criteria for expedited reporting.

6.2 If the results of a sponsor's investigation show that an adverse reaction not initially determined to be reportable under the identified expedited reporting is reportable as a SUSAR, the sponsor and/or CRO shall report such as soon as possible but in no case later than seven calendar days (Fatal or Life-Threatening Unexpected ADR) or 15 calendar days (All Other Serious, Unexpected ADRs) after the determination is made.

6.3 Local expected serious adverse event (SAE) shall be included in the Interim/Annual Report.

6.4 Development Safety Update Report (DSUR) shall be submitted annually following the month and year of the Development International Birth Date (DIBD).

6.5 Documentary Requirements for Reporting are listed in Appendix D.

7. **Interim/Annual Report**

The sponsor or CRO shall submit a study progress report annually (within the second quarter of the year ending on June 30) to the FDA, provided that the clinical trial has been approved for at least 12 months, until the study ends. An interim report should be submitted for each protocol. Please refer to Appendix G for the format of an Interim/Annual Report.

8. **Termination of Clinical Trial**

8.1 End of Trial

The sponsor/CRO shall inform the FDA within 30 calendar days when the following occur:

8.1.1 The trial is completed in the Philippines (i.e. last investigational site has closed); or

8.1.2 when the trial has been completed globally.

8.2 Early Trial Termination

The sponsor/CRO shall inform the FDA when a clinical trial is terminated earlier than scheduled, within 30 calendar days of the earlier termination of the trial. The reason(s) for early termination must be explained and, if applicable, follow up measures should be described.

8.3 Documentary requirements for reporting are found in Appendix D.

9. **Promotions**

9.1 A sponsor, CRO or investigator, or any person acting on its behalf, shall not promote the investigational product as safe and effective for the for the purposes for which it is under investigation.

9.2 A sponsor, CRO or investigator shall not commercially distribute or test market an investigational product.

9.3 A sponsor shall not unduly prolong an investigation after finding that the results of the investigation appear to establish sufficient data to support a marketing application.

10. **Inspection**

10.1 Inspection by the FDA

10.1.1 The FDA shall conduct inspections to ensure that the rights, safety, and well-being of study subjects have been protected, to ensure integrity of the scientific data collected and to assess adherence to GCP Principles and other applicable FDA regulations. Inspections shall be classified as follows:

10.1.1.1 Routine: Inspections shall be carried out as a routine surveillance of GCP compliance in the absence of specific trigger elements.

10.1.1.2 For Cause: Inspections shall be conducted for concerns related to either the actual issues observed or the potential impact of deviations from GCP and/or FDA regulations on the conduct of the study.

10.1.2 The sponsor, CRO or the investigator shall be responsible for securing agreement from all involved parties to ensure that FDA, for the purpose of inspection and verification, can have access to (and if needed, obtain copies of) any records and reports relating to a clinical trial conducted. Also, upon written request by FDA, the sponsor, CRO or the investigator shall submit the records or reports (or copies of them) to FDA.

10.1.3 The FDA shall provide the inspected entity a report on the results of inspection within 45 calendar days after the completion of inspection.

10.2 Inspection by Other Regulatory Agencies

10.2.1 The sponsor, CRO or the investigator shall inform the FDA of any clinical trial-related inspection to be conducted in the Philippines by another regulatory agency, 15 calendar days within the receipt of inspection notice. A Notice of Inspection by Other Regulatory Agencies (Appendix H) shall be submitted to the FDA.

10.2.2 Results of the inspection shall be submitted to the FDA within 30 days of receipt of the inspection report.

11. **Records and Archiving**

All documents related to the trial shall be retained by the sponsor, CROs and investigator at least two years after the last approval of a marketing application and until there are no pending or contemplated marketing applications; or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product; and/or five years after the completion of the clinical trial.

VII. FEES

The appropriate fees as prescribed under existing regulations shall apply. FDA, from time to time, may prescribe changes in fees, which shall be promulgated in appropriate issuances.

VIII. PENALTIES

Violation of any of the provisions of this Order shall be subject to the penalties/sanctions provided for under Book III, Article XI of the Rules and Regulations

Implementing Republic Act No. 9711 or the "Food and Drug Administration Act of 2009", and other penalties provided by other applicable laws.

IX. TRANSITORY PERIOD

A transitory period of not more than three months from the date of effectivity of this Order shall be provided to allow all covered establishments to comply with the new guidelines.

Establishments found to be violating the provisions of this Order beyond the transitory period shall be subject to appropriate regulatory actions after due process.

X. REPEALING CLAUSE

This Order supersedes the following administrative order and circulars or parts thereof inconsistent with this Order are hereby repealed accordingly:

1. Administrative Order No. 67 s. 1989;
2. Bureau Circular No. 5 s. 1997;
3. Administrative Order No. 47-a s. 2001;
4. Administrative Order No. 46-a s. 2003;
5. Administrative Order No. 2006-0021;
6. Administrative Order No. 2011-0009; and
7. FDA Circular No. 2012-007.

XI. SEPARABILITY CLAUSE

If any portion or provision of this Order is declared invalid or unconstitutional, the validity and enforceability of the remaining portions or provisions shall not be affected thereby.

XII. EFFECTIVITY

This Order shall take effect 90 days upon approval and after publication in a newspaper of general circulation. Copies of this Order shall be filed with the U.P. Law Center pursuant to the Administrative Code of 1987. This Order shall be reviewed periodically for its effective implementation and for recommendations of any appropriate action.

FRANCISCO T. DUQUE III, MD, MSc
Secretary of Health

ATTACHMENTS

Annexes

	Title
A	International Council for Harmonisation (ICH) Harmonized Guideline - Guideline for Good Clinical Practice (GCP) E6(R2) Link: database.ich.org/sites/default/files/E6_R2_Addendum.pdf
B	ICH Safety and Efficacy Guidelines Safety: www.ich.org/page/safety-guidelines Efficacy: www.ich.org/page/efficacy-guidelines
C	ICH Harmonised Tripartite Guideline - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A Link: database.ich.org/sites/default/files/E2A_Guideline.pdf
D	Council for International Organizations of Medical Sciences (CIOMS) -I Form Link: cioms.ch/cioms-i-form/
E	ICH Harmonised Tripartite Guideline - Structure and Content of Clinical Study Reports E3 Link: database.ich.org/sites/default/files/E3_Guideline.pdf

Appendices

	Title		Form
A	Additional Definition of Terms		
B	Clinical Trial Approval Process Flow Chart		
C	Documentary Requirements for Clinical Trial Applications		
C1	Table of Contents for Clinical Trial Application		*FDA-CRS Form 1.0*
C2	Cover Letter for Application		*FDA-CRS Form 2.0*
C3	Clinical Trial Application Form		*FDA-CRS Form 3.0*
C4	Investigational Products and Ancillary Supplies		*FDA-CRS Form 4.0*
C5	Import License Application Form		*FDA-CRS Form 5.0*
C6	Letter of Authorization		*FDA-CRS Form 6.0*
C7	Pharmaceutical Data		
	C7.1	Pharmaceutical Products	
	C7.2	Herbal Medicines	
C8	Labelling Requirements for Investigational Products		
D	Other Documentary Requirements		
D1	Amendment Application Form		*FDA-CRS Form 7.0*
D2	Cover Letter for Reporting		*FDA-CRS Form 8.0*
D3	Investigational Product Importation Report		*FDA-CRS Form 9.0*
D4	Ancillary Supplies Importation Report		*FDA-CRS Form 10.0*
E	Minimum Requirements to be Uploaded to the Clinical Trial Registry		
F	Types and Examples of Amendments		
G	Interim/Annual Report		*FDA-CRS Form 11.0*
H	Notice of Inspection by Other Regulatory Authority		*FDA-CRS Form 12.0*

Appendix A

Additional Definition of Terms

1. **Ancillary Supplies:** Products other than the test product, placebo or comparator that may be used in a trial. These may include laboratory kits, reagents and other materials used by participants in a trial.

2. **Center for Drug Regulation and Research (CDRR):** An office within the FDA created under Republic Act No. 9711 which has a jurisdiction on the manufacture, importation, exportation, distribution, sale, offer for sale, transfer, promotion, advertisement, sponsorship of, and/or where appropriate, the use and testing of drugs (to include veterinary medicine, vaccines and biologicals) and, when appropriate, certify batches of antibiotic and antibiotic preparations.

3. **Clinical Trial Registry:** An official platform for the registration of clinical trials in the Philippines. The registry provides a publicly-accessible database containing information on the design, conduct and administration of clinical trials.

4. **Combination Product:** A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity.

5. **Development International Birth Date (DIBD):** The date of the sponsor's first authorization to conduct a clinical trial in any country worldwide.

6. **Establishment:** A sole proprietorship, a partnership, a corporation, an institution, an association or an organization engaged in the manufacture, importation, exportation, sale, offer-for-sale, distribution, donation, transfer, use, testing, promotion, advertising or sponsorship of health products, including the facilities and installation needed for its activities.

7. **FDA:** The Food and Drug Administration.

8. **Import License:** A permit granted by the FDA to the study sponsor or CRO, to allow importation of investigational product and ancillary supplies necessary for the conduct of clinical trial.

9. **Institutional Research Ethics Committee (REC):** This term is synonymous with the Institutional Review Board (IRB) as defined by the ICH.

10. **License-to-Operate (LTO):** An authorization or permission embodied in a document granted by FDA to any natural or juridical person engaged in manufacture, distribution, importation, exportation, sale, offer for sale, testing and transfer of drug products.

11. **Marketing Authorization (MA):** An official document issued by the FDA for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy, and quality. In the Philippines, the MA is in the form of a Certificate of Product Registration (CPR).

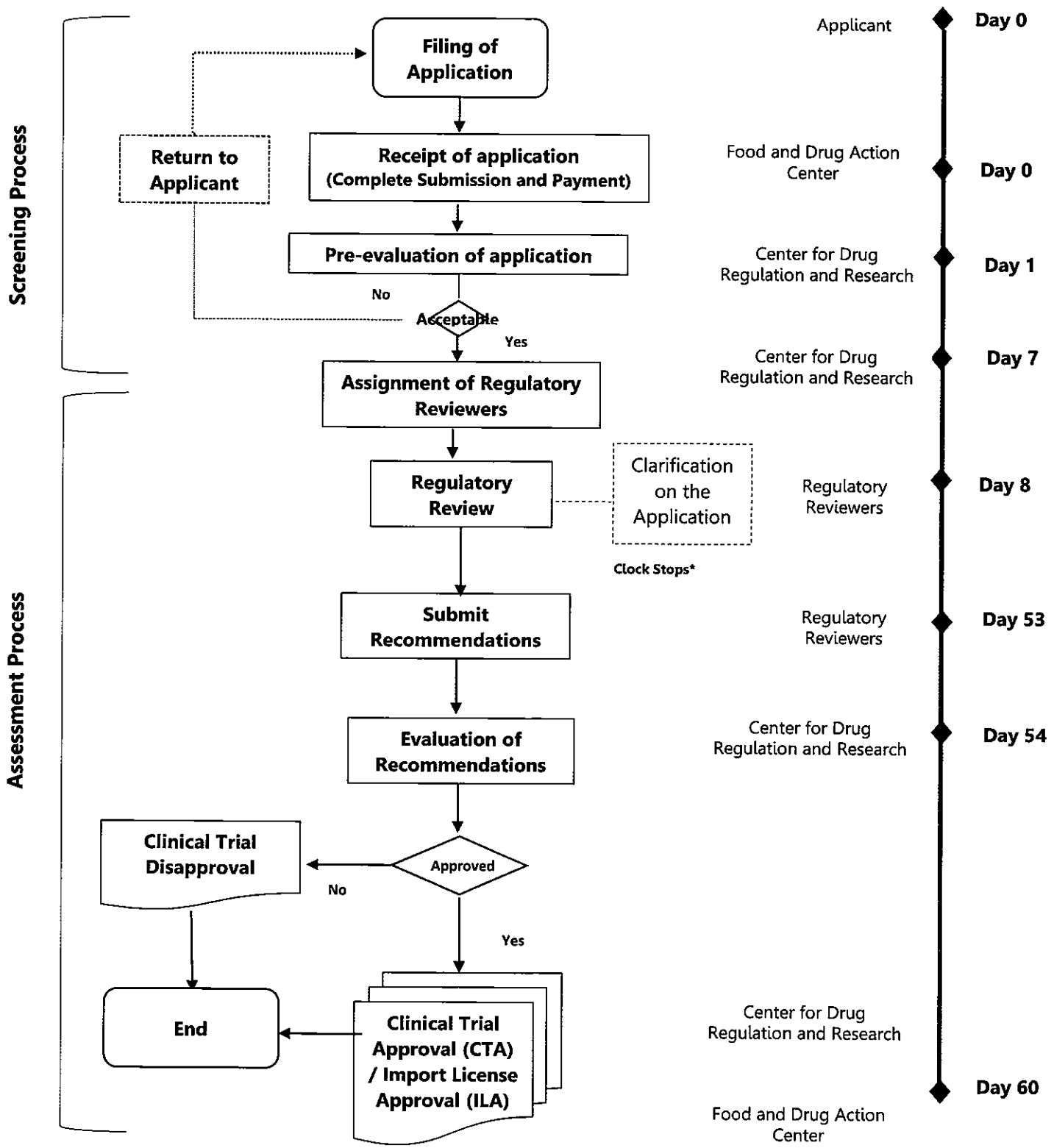
12. **Regulatory Reviewer:** An individual/organization/institution duly recognized and managed by the FDA to assist in the review of technical and scientific soundness, merit and regulatory compliance of a clinical trial application and provide recommendation.

13. **Scientific Advisory Committee (SAC):** An independent expert group created by FDA which may be consulted by the FDA or the Regulatory Reviewers to give recommendatory opinion, if deemed necessary, in the review of applications.

14. **Suspected, Unexpected, Serious Adverse Reaction (SUSAR):** a serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information (e.g. investigator's brochure for investigational product or summary of product characteristics for authorized product).

Appendix B

Clinical Trial Approval Process Flow Chart



**In cases where regulatory reviewers request for supplementary information from the applicant, the clock stops on the day the request is sent via email. Review will commence on the day the response is received.*

Appendix C

Documentary Requirements for Clinical Trial Applications

No.	Document	Format and/or Requirements
1	Table of Contents for Clinical Trial Application	C1
2	Cover Letter for Application	C2
3	Clinical Trial Application Form	C3
4	Investigational Product and Ancillary Supplies Information	C4
5	Import License Application Form This shall be submitted if Investigational Product/s and Ancillary Supplies are to be imported into the Philippines	C5
6	Proof of Payment	
7	Letter of Authorization This shall be submitted in cases where; a. Sponsor or a Principal Investigator (PI) decides to use a service of CRO for the conduct of a clinical trial; or b. The applicant is not the sponsor or product owner	C6
8	Clinical Trial Protocol and Protocol Amendment(s), where applicable This shall be submitted in the format specified by the latest ICH-GCP	
9	GCP Certificate and Curriculum Vitae (CV) for Investigator/PI of each trial site	
10	Informed Consent Form, Assent Form (if applicable) The informed consent form (ICF) provided can be in either English or Filipino (Initial version)	
11	Investigator's Brochure The format and content of the IB shall follow the Appendix 1 of the ICH-GCP E6 (R2) and its subsequent revisions	
12	Pharmaceutical Data The requirements for Pharmaceutical data in the ASEAN Common Technical Dossier, and Quality data for Herbal Medicines shall be followed. In addition, the following shall be submitted: a. GMP Certificate from National Regulatory Authority and/or Evidence of GMP compliance; and b. Shipping Condition for IP and trial related materials For products with approved marketing authorization, this requirement may not be submitted.	C7
13	Labeling Requirements for Investigational Products Sample or draft label of the Investigational Product shall be submitted and shall meet the labeling requirements as prescribed in this document.	C8

Appendix C1

FDA-CRS Form 1.0

Table of Contents for Clinical Trial Application

Section	Description		Page/s
1	Cover Letter		
2	Clinical Trial Application Form		
3	Investigational Products and Ancillary Supplies Information		
4	Import License Application Form		
5	Letter of Authorization		
6	Proof of Payment		
7	Clinical Trial Protocol and Protocol Amendment/s		
8	GCP Certificate and Curriculum Vitae (CV) for Investigator/PI of each trial site		
9	Informed Consent Form		
10	Investigator's Brochure		
11	11.1	Pharmaceutical Data	
	11.2	Good Manufacturing Practice (GMP) Certificate and/or Evidence of GMP Compliance	
	11.3	Shipping Condition for IP and trial related materials;	
12	Labeling Materials		

Appendix C2

FDA-CRS Form 2.0

Cover Letter for Application

[Company Letterhead]

[Date]

[Director General]
Director General
Food and Drug Administration
1781 Civic Drive, Filinvest City
Alabang, Muntinlupa City

Attention: [CDRR Director]
Center for Drug Regulation and Research

Re: Clinical Trial Application/Import License Application/ Extension/Notification
Full title of the trial:
Investigational Product Name/Code: _____
Clinical Trial Approval No: _____ (for approved CT)

[Salutation],

[Body] Must include the following:

- A brief description of the IP including its name, indication, and proposed formulation
- A brief description of the clinical trial protocol and study design/amendment, for clinical trial application and amendments only
- IP manufacturer's name and contact information
- IP importer's name and contact information, if applicable
- Points of contact for the application

[Complimentary Close],

[Signature]
[Name of Responsible Person]
[Sponsor/ Clinical Research Organization]
[Address]
[Contact Number]

Appendix C3

FDA-CRS Form 3.0

CLINICAL TRIAL APPLICATION FORM

CLINICAL TRIAL INFORMATION					
Full Title of the Clinical Trial					
Abbreviated Title of the Clinical Trial					
Phase of Clinical Trial to be Conducted	☐ Phase I	☐ Phase II	☐ Phase III	☐ Phase IV	☐ Others *(Specify)*____
Contents	☐ Table of Contents *(FDA-CRS Form 1.0)* ☐ Cover Letter *(FDA-CRS Form 2.0)* ☐ Investigational Product (IP) and Ancillary Supplies Information *(FDA-CRS Form 4.0)* ☐ Import License (IL) Application Form *(FDA-CRS Form 5.0)* ☐ Letter of Authorization *(FDA-CRS Form 6.0)* ☐ Proof of Payment ☐ Clinical Trial Protocol ☐ Good Clinical Practice (GCP) Certificate and Curriculum Vitae (CV) of Principal Investigator (PI) for each Trial Site ☐ Informed Consent Form ☐ Pharmaceutical Data ☐ Good Manufacturing Practice (GMP) Certificate and/or Evidence of GMP compliance ☐ Shipping Condition for IP and trial related materials; ☐ Labeling Materials ☐ Investigator's Brochure				
Clinical Trial Protocol Number					
Protocol Version Number					
Name/Code of Investigational Product					
Proposed Indication for Use					
Target Population/ Characteristics of Trial Subjects					
Total Number of Subjects in the Philippines					
Expected Start Date					
Expected End Date					

STUDY SITES

If the study will be conducted in more than one study site, assign a sequential number (e.g. Site1, Site2, Site 3 and so on) for each study site. Provide tabulation on a separate sheet when necessary.

Site Sequential Number	Name of Study Site	Principal Investigator	Contact Details of PI (Mobile No. & Email Address)

SPONSOR INFORMATION			
Name of Sponsor			
LTO Number			
Address			
Contact Information	**Telephone No.**		
	Mobile No.		
	E-mail Address		
Is any part of the clinical trial to be conducted by a Contract Research Organization?	Yes Name of CRO: _____ LTO No.: _____ *Attach Letter of Authorization (FDA-CRS Form 6.0)* *Also attach a copy of the Signed Agreement between the study Sponsor and CRO*		☐ No Type of Organization: _____
Person responsible for monitoring the conduct and progress of the clinical trial	**Name**		
	Designation		
	Telephone No.		
	Mobile No.		
	E-mail Address		

APPLICANT STATEMENT		
I/We hereby confirm that: - The above information given is true, correct and complete, and that all relevant information are provided - I/We shall abide and adhere by the FDA Regulations - I/ We shall not initiate the above-named trial until approval both from the responsible Research Ethics Committee (REC) of the trial site/s and the FDA are obtained. - I/ We will declare the effective date of commencement of the trial and submit necessary reports to the to the FDA and REC concerned as soon as available - All manufacturing and assembly operations are carried out under Good Manufacturing Practice (GMP) conditions - I/ We shall inform FDA of any changes to the information submitted in the application as required - The study will be conducted in compliance with the protocol, FDA requirements, and the principles of Good Clinical Practice - I/ We undertake to indemnify the Government/the Hospital against any and all actions, claims or proceedings in respect of any injury to or death of any person whomsoever arising out of or in connection with the carrying out of the clinical trial.		
Name of applicant		
Signature		
Designation		
Organization		
Contact information	**Telephone No.**	
	Mobile No.	
	E-mail Address	
Date of submission		

Appendix C4

FDA-CRS Form 4.0

Investigational Products and Ancillary Supplies Information

INVESTIGATIONAL PRODUCT *If more than one Investigational Product (IP) will be used in the trial, assign a sequential number (e.g. IP1, IP2, IP3, and so on.) for each IP and tabulate required information on a separate sheet. Provide one tabulation per IP.*		
IP Sequential Number *where applicable*		
Use of IP		☐ IP being tested ☐ IP used as a comparator
Name of IP		
Product Code *where applicable*		
Dosage Strength		
Dosage Form		
Route of Administration		
Proposed Shelf-life		
Packaging		
Storage Condition		
Type of IP		☐ Chemical origin ☐ Biological/Biotechnological origin ☐ Vaccine ☐ Others, *please specify*: _____
Manufacturer	**Name**	
	Address	
	Contact Details	
Repacker	**Name**	
	Address	
	Contact Details	
Is this IP to be used in the trial a registered product in Philippines?		☐ Yes ☐ No
Drug registration number: *if registered*		
Is the IP modified compared to the registered form? *if registered*		☐ Yes. *Please specify*: _____ ☐ No

PLACEBO *If more than one placebo will be used in the trial, assign a sequential number (e.g. P1, P2, P3, and so on.) for each placebo and tabulate required information on a separate sheet. Provide one tabulation per placebo.*		
Placebo Sequential Number *where applicable*		
IP Sequential Number *of IP associated with the Placebo*		
Name of Placebo		
Dosage Form		
Composition		
Packaging		
Manufacturer	**Name**	
	Address	
	Contact Details	
Repacker	**Name**	
	Address	
	Contact Details	

OTHER MEDICATION *If more than one other medication is to be used in the trial, assign a sequential number (e.g. OM1, OM2, OM3, and so on.) for each medication and tabulate required information on a separate sheet. Provide one tabulation per medication.*	
Product Name	
Active Ingredient	
Dosage Form	
Dosage Strength	
Packaging	
Registration Number *where applicable*	

PRODUCTS USED PER STUDY SITE

Site Sequential Number must be consistent with FDA-CRS Form 3.0. Tabulation may be provided on a separate sheet when necessary.

Site Sequential Number	IP/P/OM Sequential Number	Total Amount to be Used*

**Provide an estimate and attach justification when necessary*

APPLICANT STATEMENT

I/We hereby confirm that:

- The above information given is true, correct and complete, and that all relevant information are provided.
- The Pharmaceutical and/or Quality Data of the Investigational Product included in this application is consistent with that submitted to the FDA in support of the related Clinical Trial application.

Signature		
Name of Applicant		
Title/Designation		
Organization		
Contact Details	**Telephone No.**	
	Address	
	E-mail Address	
Date of Submission		

Appendix C5

FDA-CRS Form 5.0

IMPORT LICENSE APPLICATION FORM

APPLICANT INFORMATION			
Name of Establishment *Sponsor/CRO with valid LTO*			☐ Sponsor ☐ CRO
LTO Number			
Address			
Contact Information	**Telephone No.**		
	Mobile No.		
	E-mail Address		
Type of Submission	☐ Initial Import License Application *Must be submitted together with the Clinical Trial Application* ☐ Extension of Validity ☐ Addition of Quantity ☐ Amendment		
Contents	☐ Cover Letter *(FDA-CRS Form 2.0)* ☐ Investigational Product Information *(FDA-CRS Form 4.0)* ☐ Rationale for Request and/or Supporting Data ☐ Proof of Payment ☐ List of Attachments		
CLINICAL TRIAL INFORMATION			
Full Title of the Clinical Trial			
Abbreviated Title of the Clinical Trial			
Clinical Trial Approval Number *for applications other than initial IL*			

PRODUCTS FOR IMPORTATION

Sequential Number and Study Site assignment must be consistent with FDA-CRS Form 4.0.
Accomplish in a separate sheet when necessary

I. Investigational Product/s, Placebo, and Other Medication

Product Name/ Sequential No.	Total Quantity to be Imported*	Amount to be Used per Study Site*		
		Site 1	Site 2	Site 3

II. Ancillary Supplies

Product Name**	Total Quantity to be Imported*	Amount to be Used per Study Site*		
		Site 1	Site 2	Site 3

III.Importer Information

Name of Importer* **		
Address		
Contact Information	**Telephone No.**	
	Mobile No.	
	E-mail Address	

** For Initial IL Application, provide an estimate and attach rationale for indicated amount.*

*** For Laboratory Kits, kit type may be indicated provided that a Packing List is for each kit type is included as attachment.*

**** If the study will use more than one importer, accomplish this table per Importer assigned.*

APPLICANT STATEMENT		
I/We hereby confirm that: - The above information given is true, correct and complete, and that all relevant information are provided. - The Pharmaceutical and/or Quality Data of the Investigational Product included in this application is consistent with that submitted to the FDA in support of the related Clinical Trial application.		
Signature		
Name of Applicant		
Title/Designation		
Organization		
Address		
Contact Details	**Telephone No.**	
	Mobile No.	
	E-mail Address	
Date of Submission		

Appendix C6

FDA-CRS Form 6.0

Letter of Authorization

[Sponsor Letterhead]

[Date]
[Director General]
Director General
Food and Drug Administration
1781 Civic Drive, Filinvest City
Alabang, Muntinlupa City

ATTENTION: **[Name of CDRR Director]**
Center for Drug Regulation and Research

[Name of Sponsor] with business address at [Sponsor's Business Address] hereby authorize [Name of Local Company with business address at [Local Applicant's Business Address] to represent our establishment in the Clinical Trial Registration in the Philippines of:

Title of the Clinical Trial : .....
Protocol No : .....

[Local Applicant Company] is authorized to be the representative of the [Sponsor] and will be responsible for all matters pertaining to the clinical trial application for the above mentioned study protocol. In addition, the [Local Applicant Company] is authorized to conduct the following activities with regard to the above mentioned clinical trial:

- ☐ All tasks of the sponsor
- ☐ Monitoring
- ☐ Regulatory
- ☐ Data management
- ☐ SUSAR reporting
- ☐ Quality assurance (QA) auditing
- ☐ Other duties subcontracted
  If yes to other please specify:_____

[Complimentary Close],

[Signature]
[Name of Responsible Person]
[Sponsor]
[Address]
[Contact Number and email]

Appendix C7

Pharmaceutical Data

7.1 Pharmaceutical Products

Pharmaceutical Data submitted for Clinical Trial Applications shall be in accordance with the ASEAN Common Technical Dossier. The following are the minimum requirements for pharmaceutical products as stated:

No.	Parameters	Components
S	**Drug Substance**	
S1	General Information	
	1.1 Nomenclature	Information from the S1
	1.2 Structure	Pharmaceutical: Structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass. Biotech: A brief description of the predicted structure should be provided. Higher order structure, schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass should be included, as appropriate.
	1. 3 General Properties	Physico-chemical characteristics and other relevant properties including biological activity for biotech
S2	Manufacture	
	2.1 Manufacturer(s)	Name and address of the manufacturer(s).
	2.2 Description of Manufacturing Process and Process Controls	The description of the drug substance manufacturing process and process control that represents the applicant's commitment for the manufacture of the drug substances. Biotech: Information on the manufacturing process, which typically starts with a vial(s) of the cell bank, and includes cell culture, harvest(s), purification and modification reaction, filling, storage and shipping conditions
	2.3 Control of Materials	Starting materials, solvents, reagents, catalysts, and any other materials used in the manufacture of the drugs substance indicating where each material is used in the process. Tests and acceptance criteria of these materials. Biotech: - Control of source and starting materials of biological origin. – Source, history and generation of the cell substrate. – Cell banking system, characterization and testing. – Viral safety evaluation
	2.4 Controls of Critical Steps and Intermediates	Critical steps: Tests and acceptance criteria, with justification including experimental data, performed at critical steps of the manufacturing process to ensure that the process is controlled.
		Intermediates: Specifications and analytical procedure, if any, for intermediates isolated during the process. Biotech: Stability Data supporting storage conditions.
	2.5 Process Validation and/or Evaluation	Process validation and/or evaluation studies for aseptic processing and sterilization

	2.6 Manufacturing Process Development	Description and discussion of significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing non- clinical, clinical, scale-up, pilot and if available, production scale batches. Biotech: The development history of the manufacture process as described in S.2.2
S3	Characterisation	
	3.1 Elucidation of Structure and other characteristics	Confirmation of structure based on e.g. synthetic route and spectral analyses. Biotech: – Details on primary, secondary and higher- order structure and information on biological activity, purity and immunochemical properties (when relevant).
	3.2 Impurities	Summary of impurities monitored or tested for during and after manufacture of drug substance
S4	Control of Active Substance	
	4.1 Specification	Detailed specification, tests and acceptance criteria. Biotech: Specify source, including as appropriate species of animal, type of microorganism etc.
	4.2 Analytical Procedures	The analytical procedures used for testing of drug substance
	4.3 Validation of Analytical Procedures	Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance.
		Additional Information for phase II and III clinical trials The suitability of the analytical methods used should be demonstrated. A tabulated summary of the results of the validation carried out should be provided (e.g. results or values found for specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate). It is not necessary to provide a full validation report. For substances which comply with a monograph of the Ph. Eur., the pharmacopoeia of an EU country, USP or JP, reference to the relevant monograph will be sufficient
	4.4 Batch Analyses	Description of batches and results of the analysis to establish the specification.
	4.5 Justification of Specification	Justification for drug substance specification.
S5	Reference Standards or Materials	Information on the reference standards or reference materials used for testing of the drug substance.
S6	Container Closure System	Descriptions of the container closure systems.
S7	Stability	Stability report.

No.	Parameters	Components
P	**Finished Product**	
P1	Description and Composition	Description
		Composition Name, quantity stated in metric weight or measures, function and quality standard reference.
P2	Pharmaceutical Development	
	2.1 Information on Development Studies	Data on the development studies conducted to establish that the dosage form, formulation, manufacturing process, container closure system, microbiological attributes and usage instruction are appropriate for the purpose specified in the application.
	2.2 Components of the Drug Product	Active Ingredient - Justification of the compatibility of the active ingredient with excipients listed in P1
		Excipients - Justification of the choice of excipients listed in P1, which may influence the drug product performance.
	2.3 Finished Product	Formulation Development - A brief summary describing the development of the finished product, (taking into consideration the proposed route of administration and usage)
		Overages - Justification of any overage in the formulation(s) described in P1 - Physicochemical and Biological Properties Parameters relevant to the performance of the finished product e.g. pH, dissolution. **Additional information for phase II and phase III clinical trials** If changes in the formulation or dosage form compared to the IP used in earlier clinical trials have been made, the relevance of the earlier material compared to the product under testing should be described. Special consideration should be given to dosage form specific changes in quality parameters with potential clinical relevance, e.g. in vitro dissolution rate.
	2.4 Manufacturing Process Development	Selection and optimisation of the manufacturing process
		Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in P.3.2, if applicable
	2.5 Container Closure System	Suitability of the container closure system used for the storage, transportation (shipping) and use of the finished product.
	2.6 Microbiological Attributes	Microbiological attributes of the dosage form, where appropriate
	2.7 Compatibility	Compatibility of the finished product with reconstitution diluent(s) or dosage devices
P3	Manufacture	
	3.1 Batch Formula	Name and quantities of all ingredients
	3.2 Manufacturing Process and Process Control	Description of manufacturing process and process control
	3.3 Control of Critical Steps	Tests and acceptance criteria

	and Intermediates	**Additional information for phase III clinical trials** If critical manufacturing steps have been identified; their control as well as possible intermediates should be documented.
	3.4 Process Validation and/or Evaluation	Description, documentation, and results of the validation and/or evaluation studies for critical steps or critical assays used in the manufacturing process
P4	Control of Excipients	
	4.1 Specifications	Specifications for excipients
	4.2 Analytical Procedures	Analytical procedures used for testing excipients where appropriate.
	4.3 Excipient of Human or Animal Origin	Information regarding sources and or adventitious agents.
	4.4 Novel Excipients	For excipient(s) used for the first time in a finished product or by a new route of administration, full details of manufacture, characterisation and controls, with cross reference to supporting safety data (non-clinical or clinical)
P5	Control of Finished Product	
	5.1 Specification	The specification(s) for the finished product.
	5.2 Analytical Procedures	Analytical procedures used for testing the finished product
	5.3 Validation of Analytical Procedures	Information including experimental data, for the analytical procedure used for testing the finished product
		Non-compendial method A tabulated summary of the results of the validation should be provided (e.g. results or values found for specificity, linearity, range, accuracy, precision, and quantification and detection limit, as appropriate). It is not necessary to provide a full validation report.
	5.4 Batch Analyses	Description and test results of all relevant batches. – Information on the characterisation of impurities
	5.5 Characterisation of Impurities	Information on the characterisation of impurities
	5.6 Justification of Specifications	Justification of the proposed finished product specification(s). The choice of specifications and acceptance criteria for parameters which may affect efficacy or safety should be briefly justified.
P6	Reference Standards for Materials	Information on the reference standards or reference materials used for testing of the finished product.
P7	Container Closure System	Specification and control of primary and secondary packaging material, type of packaging and the package size, details of packaging inclusion (e.g. desiccant, etc)
P8	Stability	Stability report: data demonstrating that product is stable through its proposed shelf life. **Additional information for phase I clinical trials** For phase I clinical trials, it should be confirmed that an ongoing stability program will be carried out with the relevant batch(es) and that, prior to the start of the clinical trial, at least studies under

		accelerated and long-term storage conditions will have been initiated. Where available, the results from these studies should be summarized in a tabulated form. Supportive data from development studies should be summarized in a tabular overview. An evaluation of the available data and justification of the proposed shelf-life to be assigned to the IP in the clinical study should be provided. **Additional information for phase II and phase III clinical trials** The available stability data should be presented in a tabulated form. An evaluation of the available data and justification of the proposed shelf-life to be assigned to the IP in the clinical study should be provided. Data should include results from studies under accelerated and long-term storage conditions

7.2 Pharmaceutical Data for Herbal Medicines

Pharmaceutical Data submitted for Clinical Trial Applications shall be in accordance with the current requirements on herbal medicines.

The following are the minimum requirements for herbal medicines on basis of the provisions of Administrative Order No. 172 s. 2004, subject to updates through FDA issuance/s:

No.	Parameters	Components
1	**Unit Dose and Batch Formulation**	
	1.1 Formulation	Complete list of all ingredient/s whether active or inactive with the corresponding amount per unit dose, expressed in the metric system.
	1.2 Identity of Plant Material	Statement of the active ingredient/s (plant material/s) using scientific name with the common/local name printed below the scientific name. Specific plant part/s used shall be stated after the common name.
	1.3 Other Ingredients	Ingredient/s which are used in the manufacture, but which may not be present in the finished product shall be included in the list (e.g. alcohol). Alcohol, if present, in the formulation shall be expressed in percentage (%)
2	**Manufacture of Product**	
	2.1 Name and address of the Manufacturer	Complete name, business address and contact details of the product manufacturer.
	2.2 Manufacturing Procedure	The description of the drug substance manufacturing process including in-process quality control procedures.
	2.3 In-process Controls	
	2.4 Facilities and Equipment	Description of facilities and equipment used in each stage of the manufacturing process.
	2.5 Master Packaging Procedure	Full description of the packaging materials used and packaging procedure including specifications for container closure system.
3	**Raw Materials**	
	3.1 Authenticity of Raw Materials	For plant materials from the Philippines, the Certificate of Authenticity shall be obtained from the Philippine National Museum or an FDA-recognized taxonomist.
		For imported plant materials, the Certificate of Authenticity must be from the country of origin's government agency. This shall be authenticated by the Philippine Consulate.
	3.2 Quality of Raw Materials	Certificate of Analysis of active raw material/s from supplier of active raw material and manufacturer of finished product.
4	**Finished Product**	
	4.1 Physical Description of Finished Product	Organoleptic and microscopic description of the finished product. Include information on the product's moisture content, pH (if applicable), and alcohol content (if applicable)

	4.2 Purity and Quality of Finished Product	Tests and standards shall be in full compliance with the pharmacopeial requirements. For plant materials which are not included in any official pharmacopeia, standards set by Annex A of AO 172 s. 2004 shall be followed.
5	**Quality Control**	
	Quality Control Procedures	Complete and detailed description of quality control tests and procedures for raw material, in-process and finished product.
6	**Stability Studies**	
	Stability of Finished Product	Stability report: data demonstrating that herbal medicine is stable at the proposed storage conditions and shelf life.

Appendix C8
Labelling Requirements for Investigational Products

The following are the minimum labelling requirements for Investigational Products:

No	Particulars	Secondary Packaging	Primary Packaging *where primary and secondary packaging remain together throughout*	Primary Packaging *blisters or small packaging units*
1	Name, address and telephone number of the sponsor, CRO or investigator (the main contact for information on the product)	✓	✓	✓
2	Name of Product/code	✓	✓	✓
3	Strength of active Substance	✓	✓	✓
4	Pharmaceutical Dosage Form and Pack Size	✓	✓	Optional
5	Route of Administration	✓	Optional	Optional
6	Batch and/or code number to identify the contents and packaging operation	✓	✓	✓
7	Trial subject identification number/treatment number and where relevant, the visit number	✓	✓	✓
8	Directions for use (can be in a leaflet)	✓	-	-
9	For clinical trial use only" or similar wording	✓	-	-
10	Storage conditions	✓	-	-
11	Period of use (use-by date, expiry date or re-test date as applicable), in month/ year format and in a manner that avoids any ambiguity.	✓	-	-
12	"Keep out of reach of children" except when the product is for use in trials where the product is not taken home by subjects.	✓	-	-

Appendix D

Other Documentary Requirements

I. CLINICAL TRIAL

A. Amendments

a. Cover Letter (FDA-CRS Form 2.0)
b. Application Form (Appendix D1)
c. Original version, corresponding amendment/s and rationale in a tabulated format
d. Supporting data
e. Proof of Payment

B. Safety Reporting

a. Cover Letter (Appendix D2)
b. DSUR Executive Summary, supplemented with line listings of serious adverse reactions (SARs), as appropriate

C. Termination of Clinical Trial

a. Cover Letter (FDA-CRS Form 8.0)
b. Clinical Study Report, in the format recommended by the "ICH Guideline E3: Structure and Content of Clinical Study Reports" (Annex E) or a letter of commitment stating that the sponsor and/or CRO shall submit the CSR as soon as available.
c. Investigational Product Importation Report (Appendix D3) and evidence of disposition, when available.

II. INVESTIGATIONAL PRODUCTS IMPORT LICENSE

A. Extension of Validity and Addition of Quantity

a. Cover Letter (FDA-CRS Form 2.0)
b. Investigational Product Information (FDA-CRS Form 4.0)
c. Import License Application Form (FDA-CRS Form 5.0)
d. Rationale for the request and/or Supporting data
e. Proof of Payment

B. Notification

a. Cover Letter (FDA-CRS Form 2.0)
b. Proof of payment
c. Investigational Product Importation Report (FDA-CRS Form 9.0)
d. Ancillary Supplies Importation Report (Appendix D4), if applicable
e. Copy of Proforma Invoice/s

Appendix D1

FDA-CRS Form 7.0

AMENDMENT APPLICATION FORM

CLINICAL TRIAL INFORMATION		
Full Title of the Clinical Trial		
Name or Abbreviated Title of the Trial		
Clinical Trial Approval Number		
Protocol Number(s) Affected by the Amendment		
APPLICANT INFORMATION		
Sponsor		
Address		
Contact Information	**Telephone Number**	
	Mobile Number	
	E-mail Address	
CRO, *if applicable*		
Address		
Contact Information	**Telephone Number**	
	Mobile Number	
	E-mail Address	

DOCUMENTARY SUBMISSION CHECKLIST
Submit original copy of listed documents as attachment to this form.

- ☐ Cover Letter *(FDA-CRS Form 2.0)*
- ☐ List of Amendment/s, Rationale and Supporting Data
- ☐ Proof of Payment
- ☐ List of Documents Appended

Attach copies of all modified documents with this form.

TYPE OF AMENDMENT

- ☐ Change/Addition of Principal Investigator
- ☐ Change in Sponsor
- ☐ Change /Addition of Trial Site
- ☐ Change in Protocol
- ☐ Change of Manufacturer
- ☐ Change of Chemistry, Manufacturing Controls (CMC) Information (if CMC had been submitted in the initial CT application)
- ☐ Other Amendment related to pharmacology and toxicology

Please Specify:

_____

APPLICANT STATEMENT

I/We hereby confirm that the above information given is correct and have disclosed all relevant information which may influence the approval of this application.

I/We shall abide and adhere by the all relevant regulations.

Name of Applicant		
Signature		
Title/ Position		
Organization		
Contact Information	**Telephone Number**	
	Mobile Number	
	E-mail Address	
Date of Submission		

Appendix D2

FDA-CRS Form 8.0

Cover Letter for Reporting

[Company Letterhead]

[Date]

[Director General]
Director General
Food and Drug Administration
1781 Civic Drive, Filinvest City
Alabang, Muntinlupa City

Attention: [CDRR Director]
Center for Drug Regulation and Research

Re: Safety Reporting/Drug Safety Update Report/Annual Progress Report/Termination/End of Trial
Full Title of the Trial:
Clinical Trial Approval Number:
Protocol Number:

[Salutation],

[Body] Must include the following:

- For Safety Reports: The report identification or manufacturing control no., description of the SUSAR or event term, report status (initial or follow up report), date of the report, outcome of the event and assessment
- For DSUR: Description of report
- For Annual Progress Report: A brief description of the IP, clinical trial protocol and study design
- For Termination/ End of Trial: Date of termination and/or end of trial and attachments

[Complimentary Close],

[Signature]
[Name of Responsible Person]
[Sponsor/CRO]
[Address]
[Contact Number]

Appendix D3

FDA-CRS Form 9.0

Investigational Product Importation Report

Import License Notification Number	
TO BE FILLED OUT BY FDA	
Received by:	
Signature:	
Date:	
Payment Details	
Amount Paid: **OR No.:** **OR Date Issued:**	

CLINICAL TRIAL INFORMATION	
Clinical Trial Approval No.	
Protocol Title	
Protocol Number	
Investigational Product	
Import License Number	
IL Validity Period	
Sponsor	
CRO, *if applicable*	
Total number of Subjects in the Philippines	

IMPORTATION SUMMARY
Sequential Number assignment must be consistent with that in the IL approval letter.

IP/P/OM Sequential No.	Product Name/Code	Total Quantity Approved for Importation	Total Quantity Imported During the Period	Balance

Importation Period *DD-MM-YYYY*	
Importer	

IMPORTATION DETAILS
Accomplish on a separate sheet when necessary.

No.	Date of Importation	Batch Number	Airway Bill No. /Invoice No.	Quantity Imported	Balance
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					

STUDY SITE SUMMARY
Accomplish on a separate sheet as necessary.

No.	Study Site	Name of PI	Quantity Imported for Study Site
1			
2			
3			
4			
5			

SUBMISSION DETAILS

Submitted by		
Signature		
Designation		
Organization		
Contact Details	**Telephone Number**	
	Mobile Number	
	E-mail Address	
Date of Submission		

Note:

1. The Sponsor/CRO is required to submit an Investigational Product Importation Report for each investigational product, placebo or other medication as listed in the approval letter for import license. For example, the total quantity to be imported may appear as illustrated below in the approval letter:

Item No.	Product Name	Quantity
1	Drug X 5mg Tablet/Placebo to Match Drug X 5mg Tablet	150 boxes*
2	Drug X 10mg Tablet/ Placebo to Match Drug X 10mg Tablet	150 boxes*
3	Drug X 25mg Tablet/ Placebo to Match Drug X 25mg Tablet	150 boxes*
*Each box contains 100 tablets		

   In the abovementioned, the Sponsor/CRO is required to submit three (3) Investigational Product Importation Reports for the items listed above.

2. Please attach a copy of invoice for each shipment.

Appendix D4

FDA-CRS Form 10.0

Ancillary Supplies Importation Report

Import License Notification Number	
TO BE FILLED OUT BY FDA	
Received by:	
Signature:	
Date:	
Payment Details	
Amount Paid: **OR No.:** **OR Date Issued:**	

CLINICAL TRIAL INFORMATION	
Clinical Trial Approval No.	
Protocol Title	
Protocol Number	
Import License Number	
IL Validity Period	
Sponsor	
CRO, *if applicable*	
Total number of Subjects in the Philippines	

IMPORTATION SUMMARY			
Product Name	**Total Quantity Approved for Importation**	**Total Quantity Imported During the Period**	**Balance**
Importation Period *DD-MM-YYYY*			
Importer			

IMPORTATION DETAILS
Accomplish on a separate sheet when necessary.

No.	Date of Importation	Airway Bill No. /Invoice No.	Product/s Imported	Quantity Imported	Balance
1			a.		
			b.		
			c.		
2					
3					
4					
5					

STUDY SITE SUMMARY
Accomplish on a separate sheet as necessary.

No.	Study Site	Name of PI	Product	Quantity Imported for Study Site
1			a.	
			b.	
			c.	
2				
3				
4				
5				

SUBMISSION DETAILS

Submitted by		
Signature		
Designation		
Organization		
Contact Details	**Telephone Number**	
	Mobile Number	
	E-mail Address	
Date of Submission		

Note:

1. The Sponsor/CRO may submit one (1) Importation report for all ancillary supplies imported during the reporting period.

2. Please attach a copy of invoice for each shipment.

Appendix E

Minimum Requirements to be Uploaded to the Clinical Trial Registry

I. Documents

Title	Rationale for Inclusion	Description
1. Approval Letter from FDA	To ensure that the study has completed technical, scientific and ethical review of the FDA and has been authorized for conduct in the Philippines.	Proof of clinical trial protocol approval from FDA.
2. Approval Letter from PHREB-accredited Level 3 REC and Institutional Endorsement Letter *Provide for each study site*	To ensure that the trial has completed Institutional Research Ethics Committee (REC) review and has been approved for conduct in the Study Site. To confirm that the institution or site can offer its facility and resources as entailed in the clinical trial protocol. To ensure that the site signifies accountability for maintenance of subject safety and rights as well as reliability of clinical trial data.	Proof of clinical trial protocol approval from Institutional REC and endorsement letter from the Institution. Includes the version number and date of the document(s) reviewed by the REC.
3. Subject Recruitment Plan *Provide if the clinical trial will use advertisement schemes. Document must be in English.*	To demonstrate that recruitment measures are appropriate and not coercive	Advertising that is intended to be seen or heard by prospective subjects to solicit their participation in a study (e.g. newspaper, radio, TV, bulletin boards, posters, and flyers that are intended for prospective subjects).

II. Clinical Trial Information

Title	Description
1. Scientific Title	The title should contain information on participants, the intervention, the condition being studied, and the outcome.
2. Public Title	Layman's term for easy understanding and reference.
3. Clinical Trial Registration (CTR) Number	Unique identification number assigned by FDA to the study.
4. Date of CTR	Date of release of CTR
5. Protocol Code Number	Unique identification number assigned by the Sponsor to the clinical trial protocol.

6. Protocol Version	Latest version of the clinical trial protocol.
7. Date of Protocol Version	Date of approval of the latest version of the protocol.
8. Sponsor	Individual, company, institution or organization which takes responsibility for the initiation, management and/or financing of the clinical trial. Provide the following information on the Sponsor: ▪ Institution Name ▪ Address ▪ LTO No.
9. Funding Agency	Major source(s) of monetary or material support for the trial.
10. Amount of Funds	Funds allocated for the clinical trial
11. Contract Research Organization (CRO) Information	Individual or organization contracted by the Sponsor to performs one or more of the Sponsor's trial-related duties and functions. Provide the following information on the CRO: ▪ Institution Name ▪ Address ▪ LTO No.
12. Project Description	Brief description of the study mentioning study design, phase and intervention.
13. Contact for Public Queries	Name, address and contact details of point person.
14. Contact for Scientific Queries	Name, address and contact details of point person.
15. Start Date	Date of start of the clinical study; the estimated or actual date of enrolment of first participant.
16. Duration	Expected enrollment date of the first participant to expected end date that the last participant in a clinical study to be examined or received an intervention.
17. Recruitment Status	Status of recruitment in the Philippines: ▪ Pending: participants are not yet being recruited or enrolled at any site ▪ Recruiting: participants are currently being recruited and enrolled ▪ Suspended: there is a temporary halt in recruitment and enrolment ▪ Complete: participants are no longer being recruited or enrolled ▪ Other
18. Countries of Recruitment	Countries from which participants will be, are intended to be, or have been recruited at the time of registration.

19. Total Number of Trial Subjects Locally	Total number of subjects that is planned to be enrolled in the Philippines.
20. Total Number of Trial Subjects Globally	Total number of subjects that is planned to be enrolled globally.
21. Therapeutic Area	Provide primary therapeutic area that the conduct of the trial addresses
22. Health Condition/s or Problem/s Studied	The specific medical condition being studied (e.g. asthma, myocardial infarction, hyperlipidemia, depression). Include ICD 10 classification code.
23. Intervention/s	Provide the name and a brief description of the intervention.
24. Primary Outcome	Describes the primary outcomes(s) that will answer the primary question (or most important) question being asked by the trial For each primary outcome provide: ▪ The name of the outcome (do not use abbreviations) ▪ The metric or method of measurement used (be as specific as possible) ▪ The timepoint(s) of primary interest
25. Key Secondary Outcome	Secondary outcomes are outcomes which are of secondary interest or that are measured at timepoints of secondary interest. A secondary outcome may involve the same event, variable, or experience as the primary outcome, but measured at timepoints other than those of primary interest. As for primary outcomes, for each secondary outcome provide: ▪ The name of the outcome (do not use abbreviations) ▪ The metric or method of measurement used (be as specific as possible) ▪ The timepoint(s) of interest
26. Key Inclusion Criteria **27. Key Exclusion Criteria**	List the most important Inclusion and Exclusion criteria for participant selection.
28. Amendments	Provide the type of amendment and rationale. ▪ Information Amendment ▪ For Approval Amendment If the amendment is for approval, provide date of FDA approval.
29. Type of Study	Determine the type of study, phase, and design. Phases of Clinical Trial:

30. Phase	0 (Exploratory trials) I (Human pharmacology) II (Therapeutic Exploratory) III (Therapeutic confirmatory) IV (Therapeutic use)
31. Study Design	Identify the investigative methods used in the clinical trial
32. Results	Provide a brief summary of the results of the clinical trial. Include the following information: ▪ Baseline characteristics ▪ Participant Flow ▪ Adverse Events ▪ Outcome Measures
33. IPD Sharing Statement	Indicate whether or not Individual Participant-Level Data (IPD) will be shared. If so, provide a description that indicates by what mechanism, with whom and for what types of analyses the IPD shall be shared.

Clinical Trial Site/s and Details of the Investigator/s

Title	Description
1. Name of Trial Site	All trial sites must be listed.
2. Address	Address of trial site
3. Principal Investigator	For each trial site, the list the following information on the Principal Investigator: ▪ Name ▪ Expertise ▪ Contact Details
4. Research Ethics Committee/s	For each trial site, list the following information on the REC: ▪ Name of the REC ▪ Status of Approval ▪ Once approved, indicate the date of approval and upload the approval letter

Appendix F

Types and Examples of Amendments

Notification Amendment	Supporting Data
Change of Principal Investigator	CV and GCP Certificate of Principal Investigator
Change in Sponsor	Letter of Transfer of Sponsor
Change/Addition of Study Site	Justification of Change/Additional trial site CV and GCP Certificate of Principal Investigator, if applicable

Prior Approval Amendment	Supporting Data
Change in Protocol	Clinical Trial Protocol and Protocol Amendments, where applicable Summary of Protocol Amendment
Change of Manufacturer	GMP Certificate and/or Evidence of GMP from other Regulatory Authorities Certificate of Analysis
Change of Chemistry, Manufacturing, Controls (CMC) Information [if CMC had been submitted in the initial clinical trial application]	Supporting CMC, where relevant
Other Amendment related to pharmacology and toxicology	Supporting documents such as pharmacology/toxicity data, clinical/safety data, clinical/pharmacology data and statistics, where relevant

Examples of for approval amendments:

A. Changes in Protocol	
1. Objectives of the trial / Endpoints / Design of the trial	a. Modification to the main objective of the trial b. Addition of an interventional ancillary study e.g. pharmacokinetics or pharmacogenetics sub-study. c. Change to the primary endpoint and/or a secondary endpoint likely to have a significant impact on the safety of CT participants e.g. addition of an invasive test d. Change to the primary endpoint and/or a secondary endpoint without impact on the safety of CT participants e. Change to the design of the trial (e.g. addition of an arm / addition of a placebo group)
2. Clinical trial participants	a. Change in planned number of subjects to be included b. Change to the inclusion / non-inclusion criteria (including the age of the participants) c. Extension to the period of recruitment with change to the duration of the clinical trial

3. Treatment(s) administered	a. Change in the mode of administration of the IPs b. Change of dose c. Addition of new dose ranges d. Change in the duration of exposure to the IP e. Change of comparator f. Modification to the list of concomitant treatments prohibited / authorised
4. Duration of Clinical Trial	a. Change to the duration of the study, without change to the duration of exposure to the IP nor to the duration of treatment with the IP, but with change to the monitoring of the participants. b. Change to the duration of the study, without change to the duration of exposure to the IP nor to the duration of treatment by the IP, without change to the monitoring of the participants
4. Monitoring of clinical trial participants	Change to the monitoring of clinical participants
5. Monitoring of the clinical trial	a. Addition or withdrawal of an independent data monitoring committee b. Change in the independent data monitoring committee
6. Other Changes	a. Temporary halt of a clinical trial b. Restart of the clinical trial after a temporary halt c. New clinical safety data relative to the IP(s), reported from a clinical trial or not, likely to have a significant impact on the safety of the participants and/or on the trial protocol d. New clinical safety data relative to the IP(s), reported from a clinical trial or not, without impact on the safety of the participants and/or on the trial protocol e. Change in the definition of the end of trial
C. Change of Manufacturer	
D. Change of Chemistry, Manufacturing, Controls (CMC) Information	a. Manufacturing process for active substance of biological origin • Change of manufacturer and/or change to the manufacturing process, and/or size of the batch and/or analytical method(s) for the active substance, that may have a significant impact on the safety of the CT participants b. Manufacturing process for active substance of chemical origin • Changes in the manufacturing process resulting in the presence or discover of new impurities c. Manufacture of the finished product • Change of manufacturer or formulation, and/or change in the manufacturing process, and/or the size of the batch, and/or the analytical method(s), and/or the site of primary packaging for the

	finished product, that may have a significant impact on the safety of the CT participants d. Manufacture of the placebo • Change of formulation likely to have a significant impact on the safety of the CT participants e. Stability of the finished product or placebo • Restriction of the storage conditions motivated by a safety issue f. Packaging and labelling of the IP (including packaging of the placebo) • Change of IP dispensing system • Change of packaging of an IP, where the IP is a gene therapy or cell therapy drug g. Other modifications related to the quality of the IP or of the placebo • Withdrawal or modification of a filter to be placed on the perfusion line upon administration of the drug h. Amendments in viral safety data of biotechnological IP • Modification to data presented in the viral safety

* This list is not inclusive and does not preclude the submission of amendments for approval at the Sponsor's initiative.

Appendix G

FDA-CRS Form 11.0

Interim/Annual Report

PROTOCOL INFORMATION	
Protocol Title	
Protocol Number	
Study Drug	
Sponsor	
Contract Research Organization	
Clinical Trial Approval Number	
Date of Clinical Trial Approval	

CLINICAL TRIAL SITES

Accomplish on a separate sheet when necessary

Clinical Trial Site	Name of PI	Contact Details of PI (Telephone No. & E-mail)	External Technical Recommending Body

COMMENCEMENT AND TERMINATION DATES	
Has the study started?	☐ Yes ☐ No
If yes, what was the actual start date?	
If no, what are the reasons for the study not commencing?	
When is the expected start date?	
When is the expected completion date?	

RECRUITMENT OF PARTICIPANTS

Accomplish on a separate sheet when necessary

Clinical Trial Site	No. of participants recruited	No. of participants currently enrolled in the trial	Proposed in original application:	Actual number to date:
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				

WITHDRAWAL OF PARTICIPANTS

Accomplish on a separate sheet when necessary

Clinical Trial Site	Number of withdrawals due to				Total No. of Withdrawals
	Lack of Efficacy	Adverse Events	Self-withdrawal	Non-compliance	
1.					
2.					
3.					
4.					
5.					
6.					
7.					
8.					
9.					
10.					

Have there been any serious difficulties in recruiting participants? (Yes/No) *If Yes, provide details.*	
Do you plan to increase the number of participants into the trial? *Any increase in planned recruitment should be notified to the FDA as an amendment for approval.*	

SAFETY REPORTS	
Have there been any Suspected Unexpected Serious Adverse Reactions (SUSARs) in this trial? (Yes/No) *If yes, include the line listing of SUSARs*	
Have these SUSARs been notified to the FDA within 7/15 days under ICH E2A? *If no, please arrange urgently and give reasons for late notification.*	
AMENDMENTS	
Have any for approval amendments been made to the trial protocol during the year? *If yes, please give the date of approval for each amendment made.*	
PROTOCOL DEVIATIONS	
Are there any protocol deviations in the trial reported to the FDA? *If yes, please provide a list with the corresponding reasons and action taken.*	
APPLICANT STATEMENT	
I/We hereby confirm that: - The above information given is true, correct and complete, and that all relevant information are provided - I/We shall abide and adhere by the FDA Regulations	
Signature	
Name	
Designation	
Organization	
Date of Submission	

Appendix H

FDA-CRS Form 12.0

Notification of Inspection by Other Regulatory Authority

[Company Letterhead]

[Date]

[Director General]
Director General
Food and Drug Administration
1781 Civic Drive, Filinvest City
Alabang, Muntinlupa City

Attention: [CDRR Director]
Center for Drug Regulation and Research

Re: Clinical Trial Related Inspection by Other Regulatory Authority
Name of Individual/Establishment Subject to Inspection:
Date of Inspection: [indicate tentative date if inspection date is not yet finalized]

[Salutation],

[Body] Must include the following:

- Name and Contact Information of Other Regulatory Authority
- Type of inspection [If For Cause, indicate the reason for inspection]
- If the inspection involves a specific clinical trial:
  - Full Title of the Clinical Trial
  - Clinical Trial Approval Number
  - Sponsor/Contract Research Organization (CRO)

[Complimentary Close],

[Signature]
[Name of Responsible Person]
[Address]
[Contact Number]