Clinical Trial Regulation

"Regulations on the Conduct of Clinical Trials for Investigational Products"

Clinical Research Section (CRS)
Product Research and Standards Development Division
Center for Drug Regulation and Research (CDRR)
Food and Drug Administration

Development of Drugs & Vaccines

DISCOVERY

Researchers discover new molecular compounds with potential benefits against a disease

PRE-CLINICAL RESEARCH

Discovered beneficial compounds undergo laboratory and animal testing to identify dosing and toxicity levels

The findings will be used to decide whether the beneficial drug qualifies for testing in human subjects

PHASE I

Participants:
20 - 100 healthy volunteers

Length of study:
several months

Purpose:
determine safety & dosage

about 70% will move to the next phase*

PHASE II

Participants:
hundreds of volunteers with the target condition or with exposure to the disease

Length of study:
several months to years

Purpose:
assess efficacy & safety (short-term side effects)

about 33% will move to the next phase*

PHASE III

Participants:
300 to 3,000 volunteers with the target condition or with exposure to the disease

Length of study:
<1 to 4 years

Purpose:
assess efficacy & safety (monitoring of adverse reactions)

about 25-30% will move to the next phase*

*Source: USFDA

FDA PRODUCT REGISTRATION

APPROVAL

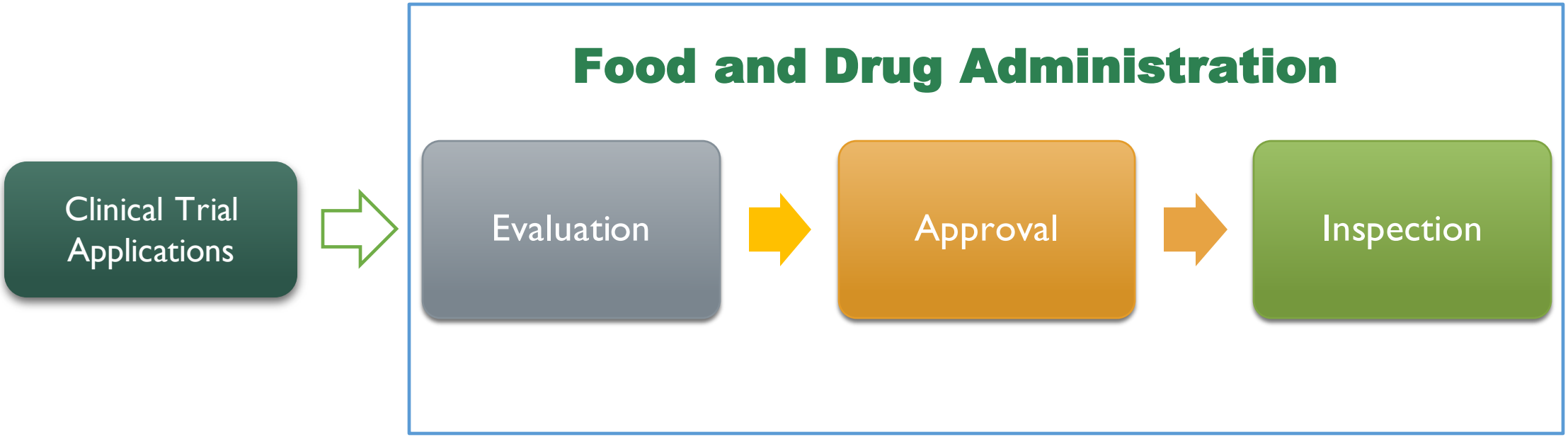
Certificate of Product Registration (CPR)

Phase IV Clinical Trial
to assess long-term efficacy & safety

Post-Marketing Surveillance
Pharmacovigilance
Compliance Monitoring

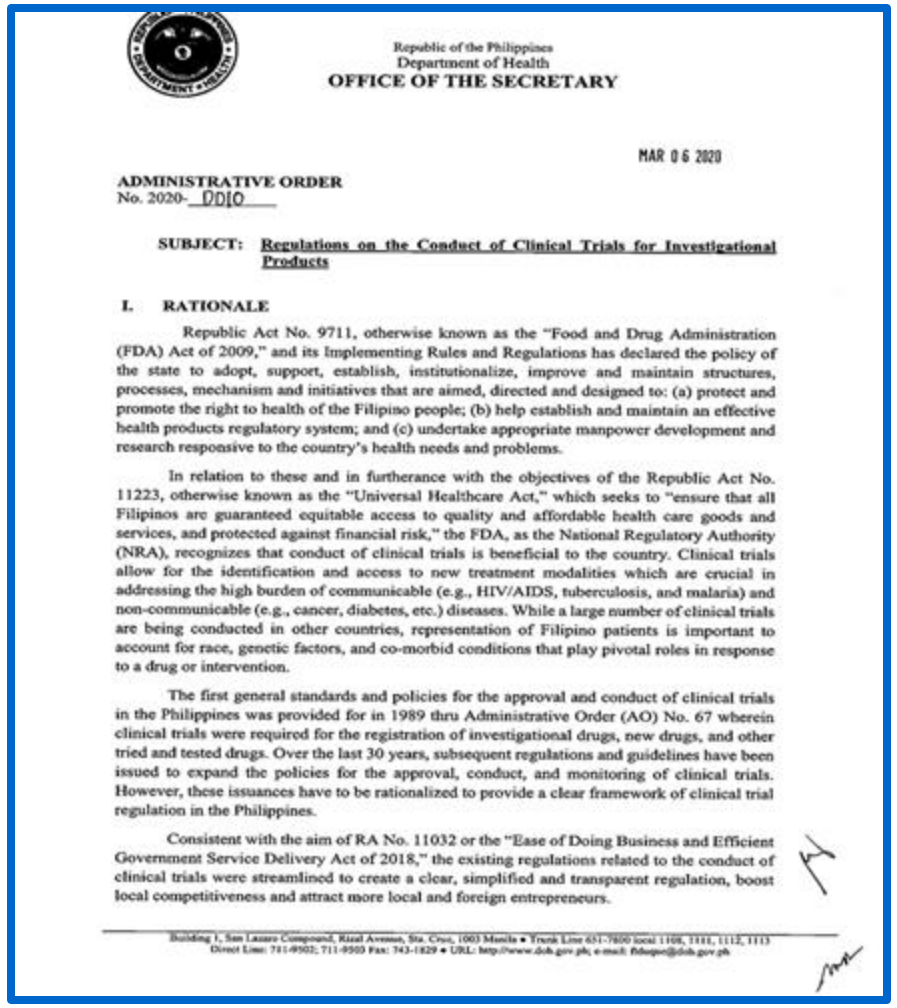
Policy Background

- Republic Act No. 9711 otherwise known as “The Food and Drug Administration Act of 2009”
  - "supervise, monitor and audit research studies on health and safety issues of health products undertaken by entities duly approved by the FDA"



Administrative Order No. 2020-0010

- Approved and signed by the Secretary of Health on March 6, 2020
- Enabled an efficient clinical trial application and review process
- Details a clear, simplified, and transparent regulation



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.

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Direct Line: 711-9502; 711-9503 Fax: 743-1829 • URL: http://www.doh.gov.ph; e-mail: fdaopo@doh.gov.ph

AO No. 2020-0010 Objectives

1. Ensure the full protection of the rights and safety of participants and the integrity of clinical trial data through the adoption and implementation of **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

4. Strengthen the **monitoring of compliance** to GCP and FDA regulations through **regulatory inspections**

*ICH-GCP: International Council on Harmonization - Good Clinical Practice

Scope

WHO

- Sponsors
- Contract Research Organizations (CROs)
- Investigators
- Research Ethics Committees (RECs)

WHAT

- All phases of Clinical Trials
- Investigational Products intended for eventual product registration and marketing
- Registered products with new indication, dose/route change, or to assess risks related to the drug
- Combination products containing at least one investigational products

Highlights

- Adoption of International Guidelines on Conduct of Clinical Trials - ICH-GCP
  - International Conference on Harmonization - Good Clinical Practice (ICH-GCP) and its subsequent revisions
  - ICH Safety and Efficacy Guidelines
  - ICH E2A: Definitions and Standards for Expedited Reporting
  - Good Manufacturing Practice (GMP)

Highlights

- License to Operate (LTO) - Sponsor or CRO
- Mandatory review & approval by FDA and REC of the clinical trial protocol and related documents prior to initiation of study
- Import License (IL)
- Prohibits promotional claims of the IP under study
- Public Transparency – Philippine Health Research Registry (PHRR)
- Clinical Trial Regulatory Inspections

License to Operate

AO No. 2020-0017 – Revised Guidelines on the Unified Licensing Requirements and Procedures of the Food and Drug Administration Repealing Administrative Order No. 2016-0003.

Requirements

- Accomplished e-application form with Declaration of Undertaking
- Proof of Business Name Registration
- Proof of Income (Latest Audited Financial Statement with Balance Sheet)
- Proof of Payment

Applications are submitted via eService:

- CRO: FDA eServices Portal
- Sponsor: FDA eServices Portal

Requirements for Clinical Trial Application

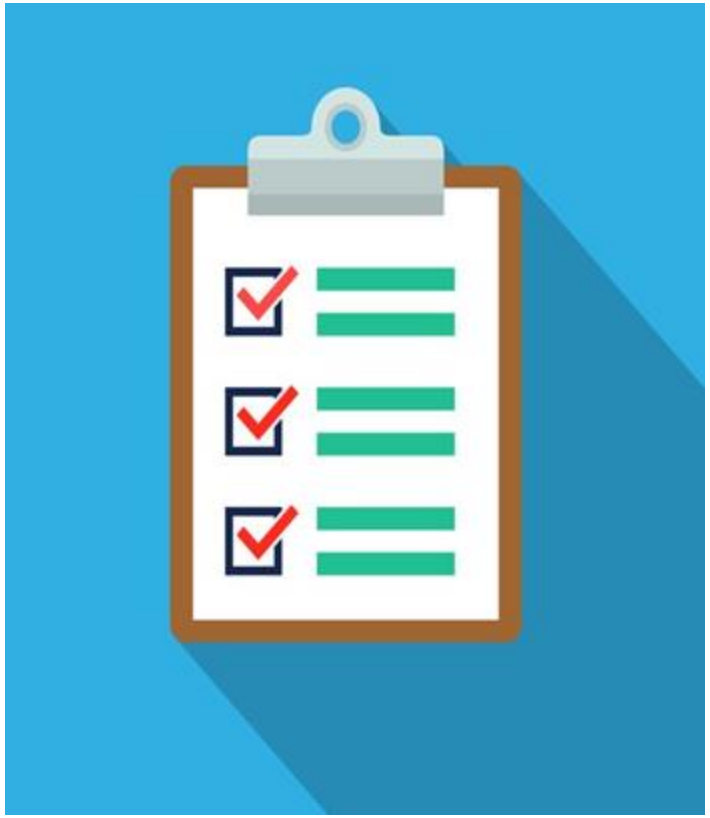
- Cover Letter
- Clinical Trial Application Form
- Investigational Products and Ancillary Supplies Information
- Import License Application Form
- Letter of Authorization
- Proof of Payment
- Clinical Trial Protocol
- GCP Certificates and CV of PI
- Informed Consent Form
- Investigator's Brochure
- Investigational Product: Pharmaceutical Data, GMP/Evidence of GMP Compliance, Shipping Conditions for IP
- Labeling Materials

Submission of Application and Requirements via FDAC: fdac.letter.cdrr@fda.gov.ph

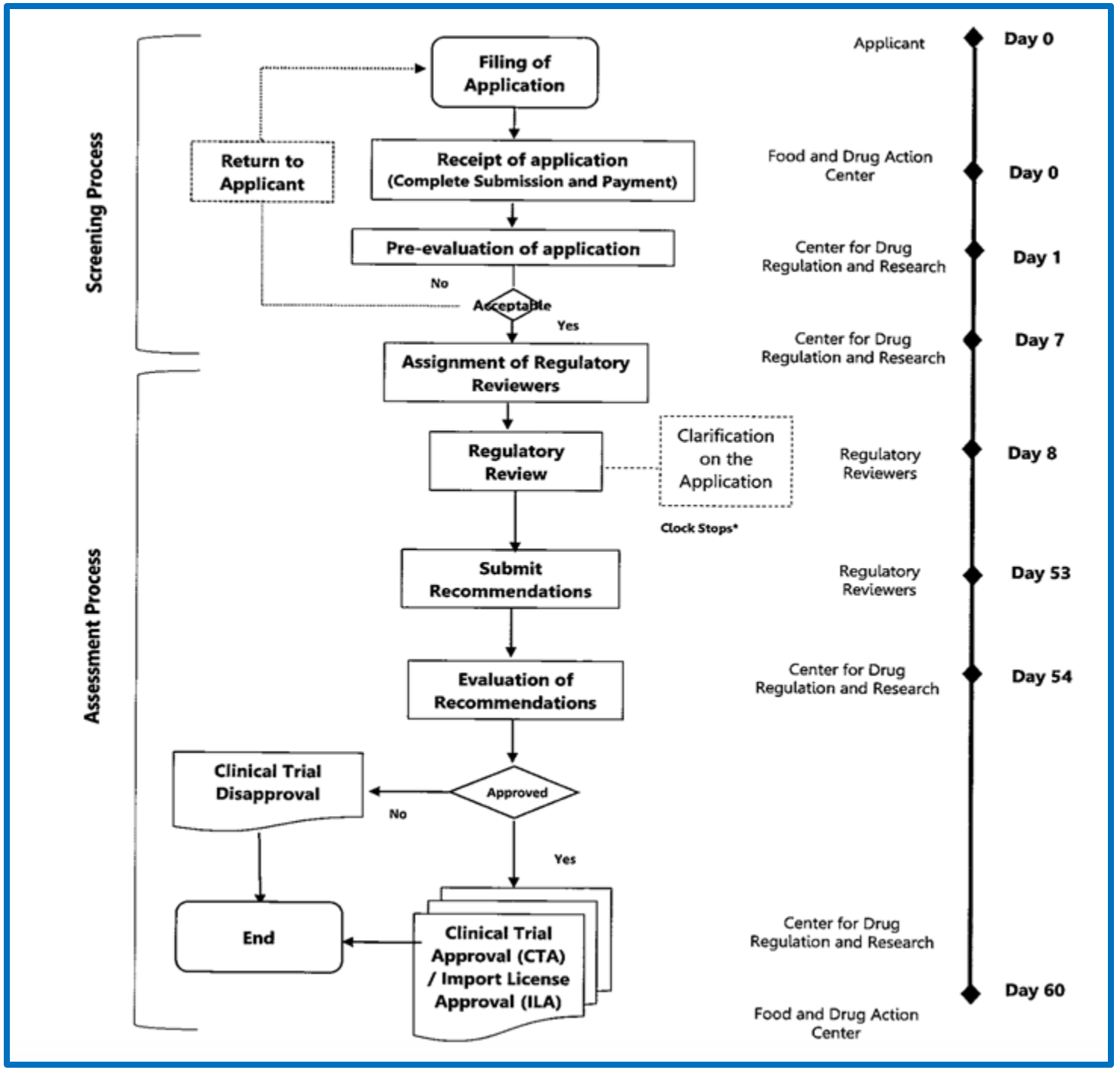
Import License

Import License is a permit granted by the FDA to the study sponsor or CRO, to allow importation of investigational products and ancillary supplies necessary for the conduct of clinical trial.

- Details of Licensed Establishment (Sponsor/CRO)
- The clinical trial information
- Details of the investigational product, placebo and other medications
- Ancillary supplies
- Information of the Licensed Importer



Clinical Trial Application Process Flow Chart



Clinical Trial Registry

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).

*FDA is currently developing registry in the FDA website for clinical trials under FDA regulation.

Clinical Trial Reports

Safety Reports

- 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).
- Coding of Adverse Events - Medical Dictionary for Regulatory Activities (MedDRA)

Clinical Trial Reports

- **Annual Reports** - Sponsor/CRO shall submit a study progress report annually (within the second quarter of the year ending on June 30) provided that clinical trial has been approved for at least 12 months, until the study ends. An interim report should be submitted for each protocol.

- **Termination of a Clinical Trial** - The Sponsor/CRO shall inform FDA within 30 calendar days when (1) trial is completed in the Philippines (2) trial has been completed globally

Amendments

- Classified as either :
  - **Notification** - can be implemented without prior approval
  - **Prior Approval from FDA**
    - Amendments that have potential to affect benefit-risk assessment of the trial; these have significant impact on the following:
      - Safety of the study participants
      - Scientific value of the trial
      - Conduct or management of the trial
      - Quality or safety of any IP used in the trial
- FDA decision in 20-30 calendar days

Regulatory Inspections

- **Conduct of 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.
- FDA shall have the authority to enter the facilities of investigational sites, sponsors, CROs and RECs engaged in the conduct of clinical trials
- **Regulatory Inspection**
  - Routine
  - For cause
- **Inspections by other Regulatory Authorities**
  - 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

Records and Archiving

- At least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications
- At least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product; and/or
- 5 years after the completion of the clinical trial

Policy under Development

FDA Circular on Regulatory Reliance for Clinical Trials

Reliance is defined by the World Health Organization as:

"the act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision. The relying authority remains independent, responsible, and accountable for the decisions taken, even when it relies on the decisions, assessments, and information of others."

Reference Drug Regulatory Agency (RDRA) refers to a stringent regulatory authority whose regulatory decisions and/or regulatory work products are relied upon by another regulatory authority to inform its own regulatory decisions.

FDA Circular – Guidelines on Regulatory Reliance on the Conduct of Clinical Trials

Objective

- To facilitate the evaluation of clinical trial applications; and
- To improve the access of investigational drug products for public health emergencies, rare diseases, and emerging and re-emerging infectious diseases of public health threats.

Scope and Coverage

- Sponsors, Contract Research Organizations (CRO), Investigators and Research Ethics Committees (RECs)
- All phases of Multi-Regional Clinical Trials (MRCTs) for investigational drug products addressing public health emergencies, rare diseases, and emerging and re-emerging infectious diseases of public health threats intended for eventual product registration and marketing.

FDA Circular – Guidelines on Regulatory Reliance on the Conduct of Clinical Trials

Abridged Regulatory Pathway refers to regulatory procedures facilitated by reliance, whereby the regulatory decision is solely or partially based on the application of reliance.

Applications under abridged regulatory pathway will undergo facilitated review through reliance. This pathway shall be applied only when the following criteria are met:

1. Investigational drug will address: Declared public health emergency, rare diseases, or Emerging or re-emerging infectious diseases declared as public health threat
2. All aspects of the clinical trial application are identical to that currently approved by the identified RDRA at the time of submission, notwithstanding changes made in adherence to national regulations or guidelines (e.g. local customization of information consent form or other patient materials).
3. The clinical trial protocol and investigational product should have not been rejected, withdrawn, suspended, or pending deferral by any RDRA for any reason.

FDA Circular – Guidelines on Regulatory Reliance on the Conduct of Clinical Trials

Requirements - the same as in AO No. 2020-0010, with the addition of the following:

- A formal letter written request from the applicant notifying the FDA of its intent to avail of the abridged review, identifying the RDRA
- Copy of the clinical trial approval or any equivalent from the identified RDRA. Proof of conduct of the clinical trial in the country of RDRA such as clinical trial registry
- A Sworn Assurance (Annex B) duly signed by the Sponsor or the authorized CRO stating the requirements under Section V. A.7.b and A.7.c. of this Circular

Processing Time – 20 Working Days

Reference Drug Regulatory Agency (RDRA)

List of Reference Drug Regulatory Agencies (RDRAs)* - Annex A

- Therapeutic Goods Administration (TGA) – Australia
- Federal Agency for Medicines and Health Products (FAMHP) – Belgium
- Health Canada (HC) - Canada
- European Medicines Agency (EMA) - European Union
- French National Agency for Medicines and Health Products Safety (ANSM) - France
- Federal Institute for Drugs and Medical Devices (BfARM) – Germany
- Paul-Ehrlich-Institut (PEI) – Germany
- Italian Medicines Agency (AIFA) – Italy
- Pharmaceuticals and Medical Devices Agency (PMDA) – Japan
- Medicines Evaluation Board (MEB) – Netherlands
- Health Sciences Authority (HSA) – Singapore
- Swiss Agency for Therapeutic Products (Swissmedic) - Switzerland
- Medicines and Healthcare Products Regulatory Agency (MHRA) - United Kingdom
- US Food and Drug Administration (USFDA) – United States of America

**Selection criteria include the founding members of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), WHO Listed Authorities (WLAs) for medicines and vaccines, and other regional and national regulatory authorities performing or operating at maturity level 4.*

Thank you!

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FDA
Food and Drug Administration
PHILIPPINES