Republic of the Philippines
Department of Health
FOOD AND DRUG ADMINISTRATION

June 7, 2012

FDA Circular
No. 2012-007

SUBJECT: Recognition of Ethical Review Board/Committee (ERB/ERC) For Purposes of the Conduct of Clinical Trials on Investigational Medicinal Products in the Philippines and for Other Purposes

I. RATIONALE AND BACKGROUND

The Philippines Emerges as a Top Destination for Global Clinical Trials

In recent years there has been an increase in the number of clinical trials in the Philippines. Of 10 countries in Southeast Asia, the Philippines ranks third in terms of the number of clinical trials (US NIH, http://clinicaltrials.gov/ct2/search/browse?brwse=locn_cat_SE, Accessed on May 19, 2012).Based on the 2009 report by the European Medicines Agency, the Philippines is ranked as number 8 among the top 10 countries worldwide with a high annual growth rate of 30.9 % in clinical trials. Clinical trials emanating from the European Union increased from 2 in 2005 to 25 in 2008 with a corresponding increase in the number of trial participants from 67 to 3,042 respectively. Likewise, trials emanating from the US increased from 3 in 2000 to 363 in 2009. The Philippines currently ranks third in Southeast Asia with 528 ongoing global trials, after Thailand with 1094, and Singapore with 958 (www.clinicaltrials.gov, accessed on June 5, 2012). FDA received 396 clinical trial applications in 2009; 339 in 2010, and 335 in 2011.

As recruitment for volunteers become more intense with the anticipated increase in clinical studies and given the vulnerabilities of the majority of our people because of poor health, economic status, abuse or poor orientation and lack of awareness of their rights, there is an urgent need to improve regulatory function and promote cooperation between DOH-FDA and other quasi-regulatory agencies suchas the Philippine Health Research Ethics Board (PHREB) of the Philippines National Research Health System (PNHRS) to better ensure that every Filipino patient who volunteers to participate in clinical research studies is accorded due protection as embodied in the Philippine Constitution.

As part of the quest to attain a higher level of competitiveness for the country, there is a need to find a more efficient system that should be benchmarked with global models.

II. OBJECTIVES

In addition to the objectives laid down in the Rules and Regulations implementing Republic Act No. 9711, this Order is hereby formulated to:

- To accord due protection to human subjects of clinical trials and ensure the generation of research findings of strong scientific merit, FDA grants recognition and empowersselected institution-based Ethical Review Board/Committees (ERB/ERCs)undertaketheethical and technical evaluation of clinical trials for the purpose of recommending, to the FDA, the approval of such studies for conduct in the Philippines.
- To require mandatory ethical and technical reviews by accredited independent review committees of experts in accordance with existing national regulations (PNHRS Ethics Guidelines) as well as Good Clinical Practice (GCP ICH-E6 1996) guidelines and any supplements and amendments thereof, which are hereby adopted.
- To require mandatory inclusion for all clinical trials (Phases I, II, III and IV) in the Philippine Clinical Trials Registry (http://registry.healthresearch.ph).

III. COVERAGE AND SCOPE

This Circular covers the recognition of ERB/ERCs to serve as ethical and technical reviewers for clinical trial applications and is for the compliance is for the compliance of the sponsor companies, Clinical Research Organizations (CROs), and Ethical Review Board/Committees (ERB/ERCs).

This regulation covers Phase I, II, III and IV clinical trials of investigational medicinal products defined as any substance or combinationof substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis. Investigational medicinal products cover new chemical entities under the investigational phase of drug development as well as existing drug preparations already in the market seeking approval for new or additional indications.

IV. DECLARATION OF POLICIES

Pursuant to the mandates provided under the 1987 Constitution to protect and promote the right to health of the people, Republic Act 3720, as amended by Executive Order 175, otherwise known as the "Food, Drugs and Devices, and Cosmetics Act", to adopt measures that ensure the purity and safety of foods and cosmetics, and, in addition to purity and safety, the efficacy and quality of drugs and devices in the country and as reiterated by Republic Act No. 9711 or the "The Food and Drug Administration (FDA) Act of 2009," the adoption of the International Conference on Harmonization Guideline for Good Clinical Practice or ICH GCP (E6) in the review, approval and regulation of clinical trials not only for vaccines but for all pharmaceutical products as may be applicable or supported by local guidelines as expressed under Administrative Order 47-a, series of 2001 entitled Rules and Regulations on the Registration, Including Approval and Conduct of Clinical Trials and Lot or Batch Release Certification of Vaccines and Biologic Products is hereby reiterated.

This circular strengthens the technical and ethical review through the use of independent ethical and technical panels that have been audited and accredited by Philippine Health Research Ethics Board (PHREB), the national body constituted under the Philippine National Health Research System (PNHRS)under the Department of Science and Technology (DOST) to ensure that ERB/ERCs comply with international and national standards in the performance of their function. In keeping with international standards to safeguard the quality of research and protect the public from the negative effects of biased reporting and

publication, clinical trials are hereby mandatorily required to be posted on the clinical trials registry established under the mandate of PNHRS.

A. FDA Recognition of PHREB-Accredited IRBs to Serve as Ethical and Technical Reviewers for Clinical Trial Applications

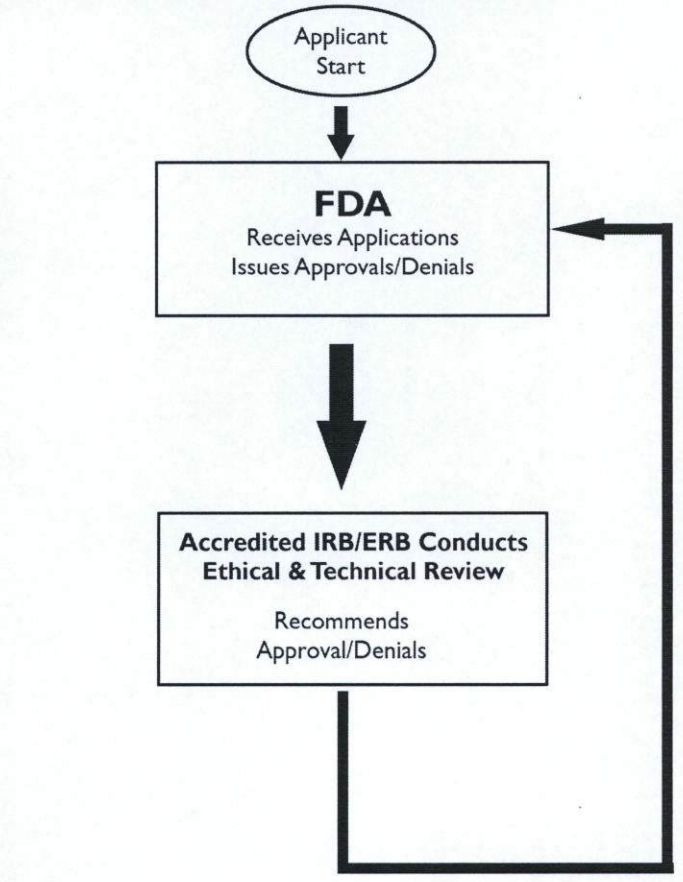
The FDA recognizes the following IRBs/ERCs of institutions based on the recommendation of the PHREB:

1. University of the Philippines Manila –National Institutes of Health (UPM-NIH)
2. De La Salle University Health Sciences Institute
3. St. Luke's Medical Center for Clinical Trials

The list will be subject to updating based on PHREB's continuing accreditation of institutions and compliance with other requirements of FDA.

As shown in Figure 1, the ERB/ERCs will submit recommendations to the FDAfor the approval or denial of clinical trial protocols subjected to review. FDA, after due deliberation will renderthe decision for approval or denial.

Figure 1
Approval Process for Clinical Trial Applications



The FDA will also coordinate with the ERB/ERCs as well as the PHREB on all matters related to the applications under review to resolve whatever issues will arise.

B. Mandatory FDA Approval for All Phase I to IV Clinical Trials

All clinical studies, from Phase I to IV, including amendment(s) thereto, require mandatory approval from the FDA to ensure that clinical trials intended to be conducted in the country that involve the recruitment of Filipinos as volunteer subjects conform to the highest ethical and technical standards of clinical research. Approval will be based on results of the evaluation that will be carried out by accredited ERB/ERBs.

V. IMPLEMENTATION GUIDELINES

A. In line with the recognition of accredited ERB/ERCs, the Policy Planning and Advocacy Division (PPAD) of the FDA is mainly responsible for providing supervision and oversight (VI. Supervision and Oversight) in the regulation of clinical trials. The Clinical Trial Management Unit under PPAD will be:

1. Responsible for handling the filing of the application, issuance of the ***Clinical Trial Reference No.*** and ***"Permit for ERB/ERC Review"*** and approval to conduct clinical trials. PPAD is also responsible for handling amendments to the clinical trial protocols that must be approved by the FDA Director.
2. Responsible for coordinating with the ERB/ERCs on matters relevant to the conduct of the ethical and technical review of clinical trial protocols.
3. Coordinating with PSD who will conduct the review of Part B- Pharmaceutical Data and the issuance of the ***Import Permit***.In addition, PPAD must ascertain that the Regulation Division I beproperly informed of ***Import Permit*** issuances to facilitate processing with the Bureau of Customs.
4. Receiving and acting on amendments and other changes to the clinical trial protocol and coordinating closely with ERB/ERCs
5. Monitoring compliance to mandatory requirement for participation in the Philippines Clinical Trial Registry
6. PPAD will be responsible for conducting on-site inspections of clinical trials; it is imperative that capacity for this be developed as soon as possible.
7. Coordinating with the FDA ADR Unit which is mainly responsible for receiving, analyzing and reporting on Safety Reporting
8. Responsible for maintaining data on statistics and formulating reports for submission regularly to the FDA Director.

B. The Product Services Division is responsible for evaluating the pharmaceutical data of new pharmaceutical products to ascertain that Chemistry, Manufacturing and Controls (CMC) and Good Manufacturing Practice (GMP) standards are met to ascertain the safety of the product for use by clinical trial subjects. Furthermore, PSD is also responsible for issuing the ***Import Permit***. The review of pharmaceutical data must be accomplished within a reasonably efficient timeframe not to exceed thirty (30) calendar days from receipt thereof from PPAD, and

issuance of the ***Import Permit*** not to exceed seven (7) working days from receipt of application.

C. The ADR Unit will be the unit responsible for receiving and analyzing reports on Adverse Events.

D. FDA reserves the right to terminate any clinical trial found to be violative of existing regulations or deviates from the approved protocol and monitoring plan.

E. Submission of Application to the FDA

1. Applicant company files applications to the FDA which will set one day of the week, schedule subject to announcement, for receiving applications from eight (8) in the morning to three (3) in the afternoon.

2. Steps in the filing:
   a. File application to PPAD-PAICS for assessment
   b. Go to Accounting Section for validation of Order of Payment
   c. Go to Cashier Section to pay the fee and secure an Official Receipt (OR)
   d. Return to PPAD-PAICS, present OR and secure Clinical Trial Reference Number. Submit documents and receive "Permit for ERB/ERC Review" which will signal the accredited ERB/ERCs to conduct the ethical and technical review.

3. Documents to be submitted will include those in Parts A, B and C and such other documents or data as hereinafter be required by FDA to ascertain safety, efficacy and quality of the products that will be subject to clinical study.

   a. PART A: Clinical Trial Protocol and other Pertinent Documents
      - Name and dosage form of product
      - Title and aim of the trial
      - Description of the trial design
      - Description of the subjects
      - Treatment profile
      - Operational aspects
      - Adverse events
      - Evaluation of results
      - Informed consent form, Case Report Form and Patient Information Sheet
      - Resumes of Principal and other Investigators
      - For multi-center studies, a list of Principal Investigators (and CVs) including trial sites

   b. PART B: Pharmaceutical Data
      To ascertain the quality and safety of the IPand to protect clinical trial subjects, FDA needs to ensure that the IP's CMC and manufacturing process is in compliance with acceptable standards (GMP).
      - GMP statement from manufacturing/Certificate from Regulatory Body
      - Certificate of Analysis
      - Stability Data (storage conditions)
      - Manufacturing Data & Formulation

- Product labeling (coded & labeled: blinding)

c. PART C: Investigator's Brochure (Efficacy and Safety Data)

Safety Data:

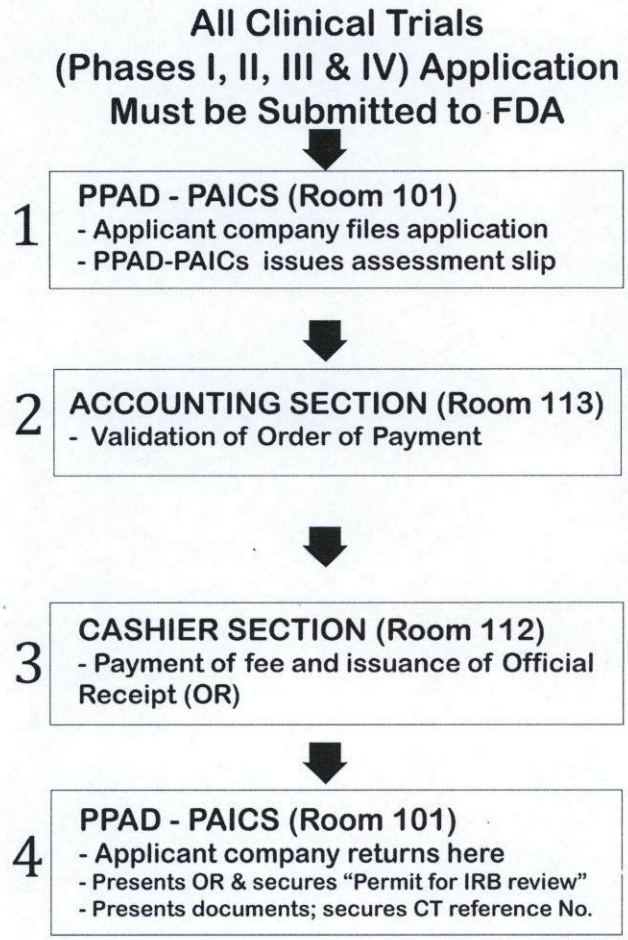
- Non-Clinical Studies
- Pharmacology; PK/PD studies
- Toxicology Studies
- Marketing Experience, Periodic Safety Update Reports (PSUR), product status if marketed abroad
- Risks and ADR anticipated

Efficacy Data

- PK/PD Data in human subjects
- In-house preliminary data
- Summaries of clinical trial studies conducted (Phase I, II, III)
- Published clinical data

4. Submission of documents:
Documents may be submitted as hardcopy or electronic file based on preference of FDA and ERB/ERC.
Figure 2 below shows algorithm of submission of application to the FDA.

Figure2



5. Amendments, notifications and other reports to be submitted to the FDA will be coursed through the same process (Figure 2). Any amendment to the protocol and accompanying documents will have to be approved by the FDA in close coordination with the ERB/ERCs.

B. Ethical/Technical Review of Applications for Clinical Trials by ERB/ERC

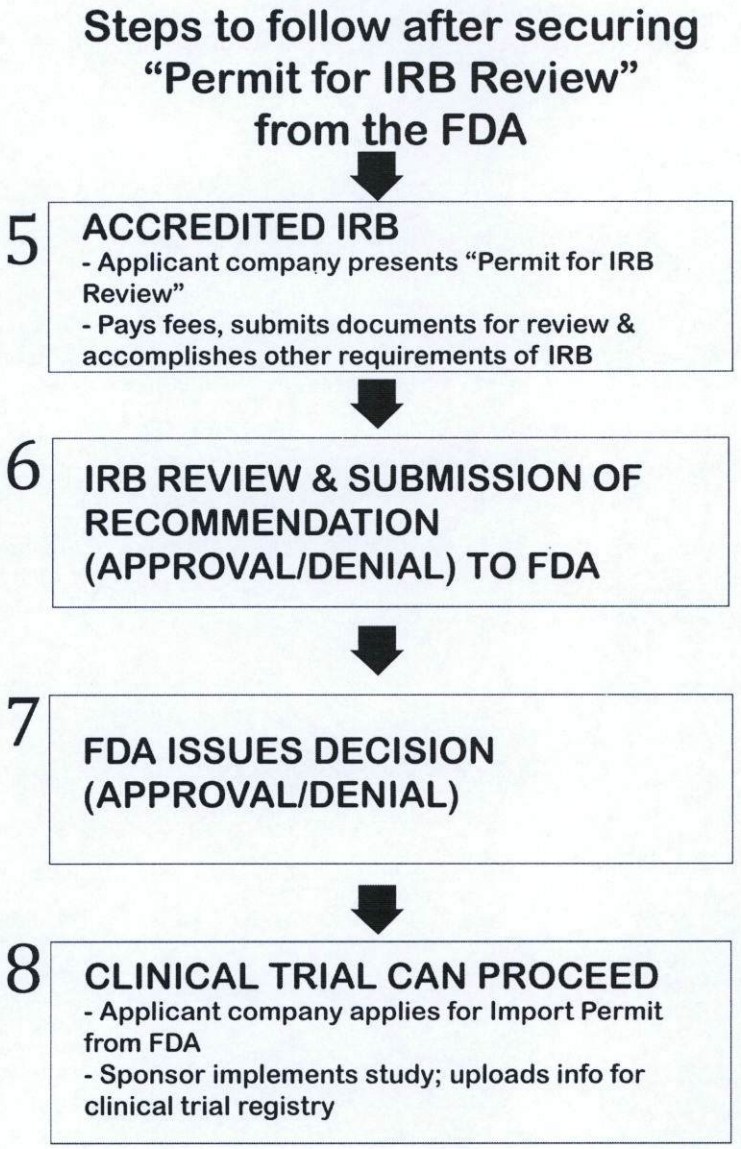
The FDA will accredit the ERB/ERCs of institutions based on the recommendation of the PHREB and the list will be subject to updating based on PHREB's continuing accreditation of institutions. Guideline on the filing, review and approval process must be guided by the following:

1. Approvals of study proposals will be guided by the highest ethical and technical standards.
2. As shown in Figure 2, the initial steps entails the submission of an application to the FDA which will issue the Permit for the ethical and technical review of the clinical trial protocol to be done by an accredited ERB/ERC. Accreditation is based on the recommendation of PHREB which conducts audits to assess the capability of ERB/ERCs all over the Philippines.
3. The accredited ERB/ERCs should be guided by the following conditions:
   a. Fees to be charged per project as fee for technical and ethical review by the ERB/ERC will be standardized at THIRTY THOUSAND PESOS. This amount will be subject to regular review every two years.
   b. The timeline for the review from acceptance to completion should not exceed 60 days
   c. The institutions will ensure that the individuals who will conduct the review process must have established competence in their areas of specializations and properly disclose conflicts of interest. Participation in the review process, by its nature, grants access to privileged information and thus, is subject to exercising confidentiality on the details of the documents submitted for review by the study sponsor. Reviewers and the study sponsor must adhere to a strict code of ethical conduct that ensures independence of reviewers and objectivity as basis for decisions.
4. FDA will be close coordination with the ERB/ERCs during the process and will be provided information on the progress of the review and all pertinent matters of the review.
5. The FDA will give the final decision to approve or deny an application based on the recommendation, submitted in written format, emanating from the ERB/ERC review. A document granting approval for the conduct of a clinical trial based on the completed technical and ethical review by the ERB/ERC will be issued by the FDA to the study sponsor.

C. Mandatory inclusion of clinical trials in the Philippine Clinical Trial Registry

All clinical trials are required to be uploaded in the Philippine Clinical Trial Registry. It is the responsibility of the study sponsor to upload information related to the clinical trial it is conducting to the Registry (http://registry.healthresearch.ph) 30 days after the application to conduct the clinical trial has been granted.

Figure 3



D. Access to medicines for use in clinical trials using the Import Permit

The FDA, as mandated by law, grants approval to all locally manufactured and imported drug products seeking entry into the Philippine market by the issuance of a Certificate of Product Registration (CPR). Only such drug products with CPRs are allowed to be imported and sold in the country. For purposes of clinical trials use, medicines not registered by the FDA can be accessed by an Import Permit. In addition to drug products, the Import Permit allows the inclusion of ancillary supplies such as laboratory kits, reagents, and other materials to be used for the clinical trial concerned to be imported.

The procedure to secure an Import Permit will be defined by FDA based on what capacity is available at its disposal. Specifically, it is currently done under the existing practice of securing permits using a manual system but may, in the futureand

pending ongoing feasibility studies, utilize a computerized online system such as the National Single Window (NSW).

1. The Import Permit authorizes the importation ofdrug products and materials for purposes of clinical trials provided that the clinical trials protocol has been reviewed and ascertained to comply with acceptable ethical and technical standards by a duly-accredited Institutional Review Board and granted the approval to proceed by the FDA.
2. The following can apply for the Import Permit:
   a. Principal investigator
   b. Authorized representative of the Study sponsor (registered pharmaceutical company with permanent address in the Philippines
   c. CRO, with permanent Philippine address, representing the sponsor through a letter of authorization
3. To secure an Import Permit, the application must be supported by the FDA document attesting to the approval of the clinical trials to proceed based on compliance to ethical and technical requirements as ascertained by the ERB/ERC.
4. Under the existing FDA system, the Import Permit will be issued by PSD with the cooperation of the Regulation Division I which has linkage with the Bureau of Customs in this regard.

E. Inspections of clinical trials:

FDA shall conduct random inspections on the clinical trial sites to monitor complianceto the approved study protocol and monitoring plan of the sponsor. It shall specifically look into adherence to the GCP:

F. Safety Reporting

Reporting must be consistent with ICH Topic E2A- Clinical Data Management: Definitions and Standards for Safety Reporting.

1. Suspected Unexpected Serious Adverse Drugs Reactions (SUSARs)
   a. Fatal or Life-Threatening Unexpected ADRs

      All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting. Fatal (deaths) or life-threatening, serious unexpected ADRs occurring in clinical trials, onsite or offsite (for multi-site studies) should be reported. The FDA should be notified (landline/mobile phone, facsimile transmission, email or written letter) as soon as possible **but no later than 7 calendar days** after first knowledge by the sponsor that a case qualifies, followed by a complete report as soon as possible **within 8 additional calendar days**. The CIOMS-I form has been a widely accepted standard for expedited adverse event reporting

   b. All Other Unexpected Serious ADRs

      Serious, unexpected reactions (ADRs) that are not fatal or life-threatening, whether onsite or offsite, must 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.

2. ExpectedAdverse Drug Reactions

   a. Serious adverse drug reactions which are expected based on information from Investigator's Brochure will be reported in the regular progress report and final report.

   b. Adverse drug reactions which are not serious will also be reported in the regular progress report and final report.

G. Termination of Clinical Trial and Sanctions

For the effective implementation of this Circular, this Office shall order the termination of an on-going clinical trial without need of a hearing should the result of random trial sites inspections reveal any major violation(s), notifying only the concerned establishment of such termination. Other sanction(s) to concerned entities shall be imposed respectively under the following instances of violations and the table below:

1. The result of the random clinical trial sites inspections shall have the following categories:
   a. No violation - No objectionable conditions or practices were found during the inspection, or the significance of the documented objectionable conditions found does not justify further FDA action (from USFDA). Compliant to GCP rules and approved protocol
   b. Minor violations - Regulatory violations uncovered during the inspection are few and do not seriously impact subject safety or data integrity.
   c. Major violations-The regulatory violation(s) uncovered is/are significant/serious and/or numerous, and the scope, severity, or pattern of violation(s) support a finding that:
      1) Subjects under the care of the investigator would be or have been exposed to an unreasonable and significant risk of illness or injury.
      2) Subjects' rights would be or have been seriously compromised. OR
      3) Data integrity or reliability is or has been compromised.
      4) Non disclosure of conflict of interest by the investigator and other members of the trial team
      5) Failure to get an informed consent is a major violation

Any pharmaceutical product the clinical trial of which has been ordered terminated by FDA shall be a ground for the invalidation of data for drug registration purposes and accordingly disapproval of subsequent application for product registration pursuant to Paragraphs (1) or (6), Item B, Section 4, Article I, Book II of the Implementing Rules and Regulations of Republic Act No. 9711 on ground that application requirements does not meet the required technical requirements or appropriate standards, or such other analogous grounds or causes as determined by the FDA.

2. Disciplinary actions shall be imposed on the following after finalizing the Inspection Report by the Legal Division of the FDA.

Entity/Individual	Minor Violation(s)	Major Violation(s)
Researcher	Warning, re-inspection	Suspension from conduct of researches from (range in months or years) depending on the type and degree of violation
Sponsor	Warning, re-inspection	Termination of trial, invalidation of data for drug registration purposes
Ethics Review Committee The FDA shall recommend appropriate action to the PHREB based on inspection findings.	Warning, re-inspection	Suspension from the conduct of reviews for (range in months/years) depending on the type and degree of violation

H. Archiving and Database Management

All original and latest approved versions of CT protocols, IB, Informed Consent, ERC proof of approval, summary of amendments, and final CT report including summary of safety reports shall be recorded, filed and archived by the clinical unit of the FDA.

Stored files shall be accessed only by duly authorized personsand shall be stored and disposed thereafter in a manner as may be provided by existing laws, rules and regulations. Disposal of files shall be in coordination with the Records Section of the Administrative Division which shall seek approval from the National Archives of the Philippines.

VI. SUPERVISION AND OVERSIGHT

The Policy Planning and Advocacy Division (PPAD) shall supervise and provide technical guidance in the implementation of this Circular. The Clinical Trial Management staff shall prepare and submit quarterly reports to the Chief of the PPAD on the status of implementation, issues and problems and proposed solutions.

Likewise, the PPAD shall provide the FDA MANCOM an annual report on the implementation of this Circular.

In pursuit of good governance and transparency the PPAD shall organize and convene regular meetings with concerned partners and networks to provide updates and reports on the implementation or any matter concerning this Circular.

VII. SEPARABILITY AND REPEALING CLAUSE

In the event that a rule, section, paragraph, sentence, clause or words of this Circular is declared invalid for any reason, the other provisionsnot affected/ or without material significance shall remain in force and effect.

All provisions of previous issuances and other related issuances inconsistent or contrary with the provisions of this Circular are hereby revised, modified, repealed or rescinded accordingly. All other relevant provisions of existing issuances supporting this Circular shall remain valid and in effect.

VIII. EFFECTIVITY

This Circular shall take effect immediately. A Task Force to facilitate the transition has been set up under the supervision of PHREB to coordinate the smooth transitioning into the new system that will involve the technical and ethical evaluation to be carried out by the institutional ERB/ERCs.

SUZETTE H. LAZO, MD
Acting Director IV, FDA