Republic of the Philippines
Department of Health
FOOD AND DRUG ADMINISTRATION

FDA CIRCULAR
No. 2023-004

17 FEB 2023

SUBJECT : Guidelines on Regulatory Reliance on the Conduct of Clinical Trials

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I. BACKGROUND

Republic Act (RA) 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 2020, the FDA worked on a streamlined regulation for the conduct of clinical trials in the Philippines. This effort resulted in the publication of Administrative Order (AO) No. 2020-0010, entitled "Regulations on the Conduct of Clinical Trials for Investigational Products," approved on 06 March 2020 and implemented on 06 August 2020.

The World Health Organization (WHO) supports the implementation of reliance on other regulators' work as a general principle in order to make the best use of available resources and expertise (*WHO Technical Report Series, No.1033, 2021 (Annex 10, Good reliance practices in the regulation of medical products: high level principles and considerations)*[1]. This principle enables leveraging the output of other regulatory agencies whenever possible while placing a greater focus at the national level on value-added regulatory activities that cannot be undertaken by other authorities, such as in-country vigilance and clinical trial activities. Reliance approaches can facilitate timely access to safe, effective, and quality-assured drug products and can help in regulatory preparedness and response, particularly during public health emergencies.

Good Reliance Practices[1] are anchored in the overarching Good Regulatory Practices (GRP) which provide a means for establishing sound, affordable and effective regulation of medical products as an important part of health system strengthening. Effective implementation of GRP can lead to consistent regulatory processes, sound regulatory decision-making, increased efficiency of regulatory systems and better public health outcomes.

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1. *WHO Technical Report Series, No.1033, 2021 (Annex 10, Good reliance practices in the regulation of medical products: high level principles and considerations, https://www.wto.org/english/tratop_e/trips_e/techsymp_290621/gaspar_pres3.pdf*

In relation to these, the FDA, as the National Regulatory Authority (NRA), recognizes that reliance will further streamline its review process and accelerate the conduct of clinical trials in the country especially for addressing public health emergencies, rare diseases, and emerging and re-emerging infectious diseases of public health threats. The existing regulations related to the conduct of clinical trials were streamlined to create a clear, simplified and transparent regulation.

II. OBJECTIVE

This Circular provides guidelines on reliance for approval of clinical trial applications and to promote a more efficient and effective approach to the regulations in the oversight of the conduct of clinical trials in the Philippines. Specifically, this Circular aims to:

A. To facilitate the evaluation of clinical trial applications through regulatory reliance; and

B. 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.

III. SCOPE AND COVERAGE

This Circular shall apply to Sponsors, Contract Research Organizations (CRO), investigators and Research Ethics Committees (RECs) involved in the approval, conduct, monitoring and inspection, in 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.

IV. DEFINITION OF TERMS

To ensure a common understanding of concepts and clarity in the interpretation of the terms used in this Circular, the definitions listed in this section are from *AO No. 2020-0010*[2], *International Council for Harmonization (ICH) Guidelines (E6 & E17)*[3,4], and/or modified from the *WHO Technical Report Series, No.1033, 2021*[1].

A. Abridged Regulatory Pathway refers to regulatory procedures facilitated by reliance, whereby the regulatory decision is solely or partially based on the application of reliance. Clinical trial application under abridged regulatory pathway will undergo facilitated review through reliance.

B. Contract Research Organization (CRO) refers to 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.

2. *Administrative Order No. 2020-0010: Regulations on the Conduct of Clinical Trials for Investigational Products, https://www.fda.gov.ph/wp-content/uploads/2020/05/Administrative-Order-2020-0010.pdf*
3. *ICH Guidelines E6(R2): Guideline for Good Clinical Practice, https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf*
4. *ICH Guidelines E17: General Principles for Planning and Design of Multi-Regional Clinical Trials, https://database.ich.org/sites/default/files/E17EWG_Step4_2017_1116.pdf*

C. **Emerging or re-emerging infectious diseases** refer to diseases that: (1) have not occurred in humans before; (2) have occurred previously but affected only small numbers of people in isolated areas; (3) have occurred throughout human history but have only recently been recognized as a distant disease due to an infectious agent; (4) are caused by previously undetected or unknown infectious agents; (5) are due to mutant or resistant strains of a causative organism; and (6) once were major health problems in the country, and then declined dramatically, but are again becoming health problems for a significant proportion of the population, as defined in RA No. 11332[5] also known as Mandatory Reporting of Notifiable Diseases and Health Events of Public Health Concern Act and as declared by the President.

D. **Multi-Regional Clinical Trial (MRCT)** refers to a clinical trial conducted in more than one country/region under a single protocol.

E. **Orphan drug** refers to any drug or medicine used to treat or alleviate the symptoms of persons afflicted with a rare disease and declared as such by the DOH upon recommendation of the National Institutes of Health (NIH), as defined in RA No. 10747[6] also known as Rare Disease Act of the Philippines.

F. **Public health emergency** refers to an occurrence or imminent threat of an illness or health condition that:

1. Is caused by any of the following: (a) Bio terrorism; (b) Appearance of a novel or previously controlled or eradicated infectious agent or biological toxin; (c) A natural disaster; (d) A chemical attack or accidental release; (e) A nuclear attack or accident; or (f) An attack or accidental release of radioactive materials; and
2. Poses a high probability of any of the following: (a) A large number of deaths in the affected population; (b) A large number of serious injuries or long-term disabilities in the affected population; (c) Widespread exposure to an infectious or toxic agent that poses a significant risk of substantial harm to a large number of people in the affected population; (d) International exposure to an infectious or toxic agent that poses a significant risk to the health of citizens of other countries; or (f)Trade and travel restrictions,

as defined in RA No. 11332 and as declared by the President

G. **Public health threat** refers to any situation or factor that may represent a danger to the health of the people.

H. **Rare disease** refers to disorders such as inherited metabolic disorders and other diseases with similar rare occurrence as recognized by the DOH upon recommendation of the NIH but excluding catastrophic (i.e., life threatening, seriously debilitating, or serious and chronic) forms of more frequently occurring diseases, as defined in RA No. 10747.

I. **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. The list of RDRAs is provided under Annex A of this Circular, subject to regular updating.

J. **Regulatory Reviewer** refers to an individual, organization, or institution duly recognized by the FDA to assist in the review of the technical and scientific

5. Republic Act No. *11332: Mandatory Reporting of Notifiable Diseases and Health Events of Public Health Concern Act, https://www.officialgazette.gov.ph/downloads/2019/04apr/20190426-RA-11332-RRD.pdf*
6. *Republic Act No. 10747: Rare Disease Act of the Philippines, https://www.officialgazette.gov.ph/2016/03/03/republic-act-no-10747/*

soundness, merit, and regulatory compliance of a clinical trial application and provide recommendation.

K. **Reliance** refers to the act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority in reaching its own decision.

L. **Scientific Advisory Committee (SAC)** refers to a committee composed of Subject Matter Experts invited by the FDA to assist in the review of scientific and technical aspects of any regulatory applications and provide recommendations.

M. **Sponsor** refers to an individual, company, institution, or organization that takes responsibility for the initiation, management, and or financing of clinical trial.

V. IMPLEMENTING DETAILS

A. General Guidelines

1. Licensed Sponsor/CRO intending to undertake clinical trials under an abridged pathway shall follow the rules, regulations, and standards provided in AO No. 2020-0010, "Regulations on the Conduct of Clinical Trials for Investigational Products", and the guidelines specified herein.
2. The Sponsor/CRO shall simultaneously submit an application to their respective REC or to the Single Joint Research Ethics Board (SJREB) for multi-site studies with at least one (1) DOH hospital involved. The review shall follow existing ethical guidelines and remains independent with FDA. The decision of REC/SJREB shall be provided to the FDA.
3. Clinical trials shall only commence once the approval from the FDA and SJREB/institutional RECs have been issued.
4. The FDA retains its prerogative on the following, for clinical trials under abridged pathway specially when there is a significant impact on the safety or physical or mental integrity of the subjects and scientific value of the trial:
    a. To assess applications and apply scientific judgements that consider the applicability of the assessment outcomes of the identified RDRA together with its benefits and risks as applicable in the Philippine context. In case of differences, such as in target population, epidemiology, and other features of the disease, concomitantly used medicines and other factors that can substantially affect the benefit–risk profile of an investigational product, appropriate justification should be provided upon filing of application.
    b. To exempt a study from local Good Clinical Practice (GCP) inspection when an RDRA has conducted an inspection of the reliance-related study
    c. To rely on generated information and relevant clinical decisions of RDRA on the reliance-related studies for FDA's own regulatory decision.
5. The FDA remains independent, responsible, and accountable for the following decisions taken, even when it relies on the decisions, assessments and information of others.
6. Only establishments with valid FDA-issued Licenses to Operate (LTOs) as Sponsor and/or CRO can apply for abridged review.
7. The abridged procedures for Clinical Trial applications shall be applied only if all of the following criteria are met:
    a. The investigational product will address any of the following:
        i. Declared public health emergency

ii. Rare diseases
iii. Emerging or re-emerging infectious diseases declared as public health threat

b. All aspects of the clinical trial application, including but not limited to the protocol and investigational product information, 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).

c. The clinical trial protocol and investigational product should have not been rejected, withdrawn, suspended, or pending deferral by any RDRA for any reason.

8. All documents to be submitted shall be written/officially translated into the English language.

B. Application Process and Requirements

1. Initial Clinical Trial and Import License

The applicant company shall submit the clinical trial application to the FDA through email at clinicalresearch@fda.gov.ph.

a. The Center for Drug Regulation and Research (CDRR) shall pre-assess the application by determining the completeness of the dossier submission and if it satisfies the requirements for abridged pathway.

b. The applicant shall submit the documentary requirements cited in AO No. 2020-0010. In addition, the following documents should be submitted:

i. A formal letter written request from the applicant notifying the FDA of its intent to avail of the abridged review, identifying the RDRA

ii. 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

iii. 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

c. The abridged evaluation process and regulatory decisions for clinical trials shall be as follows:

i. Sponsor/CRO shall secure authorization from the FDA for the conduct of clinical trial in the Philippines through the process of approval within 20 working days as illustrated in Annex C.

ii. An application is deemed filed upon submission of the documentary requirements including proof payment of fees.

iii. Upon receipt of the application, the FDA shall review the applicability and veracity of the documentary requirements and shall assign a Regulatory Reviewer for the clinical trial application within two (2) working days.

iv. An application shall be processed by the FDA Regulatory Reviewers within fifteen (15) working days upon receipt of the application and payment of the required fee directly charged to the applicant. If there is a need for any clarification on the application, an electronic

notification shall be sent to the applicant; the processing time or clock stops in this step. The applicant is expected to respond to the query/ies within five (5) working days from sending of e-mail correspondence. If response is not received from the applicant within the required period, the application shall be disapproved.

v. The FDA shall issue a decision within three (3) working days upon receipt of the recommendation from the Regulatory Reviewers.

vi. Disapproved applications can submit re-application and will follow the same process of application.

d. The Clinical Trial Approval (CTA) and the Import License (IL) shall both be issued within 20 working days. The IL shall have a validity of three (3) years and can be used repeatedly within the validity period.

2. Clinical Trial Protocol Amendments

a. Clinical trial protocol amendments, whether for notification or for prior approval, should be submitted following the documentary requirements as stated in the A.O. No. 2020-0010. In addition, the following documents should be submitted:

i. A formal letter written request from the applicant notifying the FDA of its intent to avail of the abridged review, identifying the RDRA

ii. Copy of the clinical trial amendment 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

iii. 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

b. The FDA shall provide a decision on the amendment applications within ten (10) working days from receipt. If there is a need for any clarification on the application, an electronic notification shall be sent to the applicant; the processing time or clock stops in this step. Thereafter, the applicant is expected to respond to the query/ies within three (3) working days from sending of e-mail correspondence. If response is not received from the applicant within the required period, the application shall be disapproved.

c. Substantial amendment such as changes in design and methodology that has a significant impact on its scientific value and changes that may have significant impact on the safety of the participants, or to the risk and benefit assessment of the study, or as deemed necessary by the FDA, may be forwarded to the SAC within 15 working days as illustrated in Annex D.

3. Reporting and other Regulatory Requirements

The Sponsor or CRO shall comply with the following reporting and other regulatory requirements stated in the AO No. 2020-0010:

a. Quarterly submission of IL notification

b. Reporting of suspected Unexpected Serious Adverse Reaction (SUSAR) reporting following ICH E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting)

c. Submission of annual progress report, except for clinical trials addressing public health emergencies which shall provide monthly progress reports.

d. Submission of early termination or end of trial report

e. Mandatory uploading in the clinical trial registry

f. Shall not promote, distribute and market test the investigational product
g. Allow the conduct of GCP inspection
h. Notification of any clinical trial-related inspection conducted by other NRA.
i. Notification of any regulatory action of other NRA (e.g., termination, suspension, put on hold)

C. Fees

The appropriate fees as prescribed under existing regulations shall apply or any amendment or latest issuance thereafter.

VI. PENALTY CLAUSE

Violation of any of the provisions of this Circular shall be subject to the penalties/sanctions provided for under Book III, Article XI of the Implementing Rules and Regulations of Republic Act No. 9711 or the "Food and Drug Administration Act of 2009", and other penalties provided by other applicable laws.

VII. SEPARABILITY CLAUSE

If any provisions in this Circular, or application of such provision to any circumstances, is held invalid, the remainder in this Circular shall not be affected.

VIII. EFFECTIVITY

This Circular shall take effect fifteen (15) calendar days after publication in one (1) newspaper of general circulation and upon filing with the University of the Philippines, Office of the National Administrative Register (ONAR).

DR. SAMUEL A. ZACATE
Director General

ANNEX A

List of Reference Drug Regulatory Agencies (RDRAs)*

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

Note: The list may be updated at any time as determined by FDA.

* *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.*

Annex B

Sworn Assurance

I, (name of Head of Sponsor/CRO), (legal age), (citizenship), resident of (address), after being sworn according to law, hereby depose and state:

1. I am the Head of the Sponsor/CRO, (Name of Applicant Company), with business address at (address).

2. I am applying for the issuance of a (Approval to Conduct Initial Clical Trial/Amendments) of the (name of investigational product) under Abridged Regulatory Pathway Review addressing any public health emergency, and emergenging or re-emerging infectious diseases considered as public health threat.

3. That all aspects of the clinical trial application, including but not limited to the protocol and investigational product information, are identical to that currently approved by the following identified RDRA at the time of submission, not withstanding changes made in adherence to local regulations or guidelines (e.g. local customization of information consent form or other patient materials):

RDRA	Date of RDRA approval
1. 2. . . .	1. 2. . . .

4. The documents submitted to the RDRA are in accordance with the requirements of ICH GCP, and if not, I hereby submit the necessary technical documents to comply with the dossier requirements and format following existing guidelines.

5. The clinical trial protocol and investigational product has not been rejected, withdrawn, suspended, or pending deferral by any RDRA for any reason.

6. That there is full compliance with the eligibility requirements provided under the FDA Circular on clinical trial regulatory reliance, and all data and information submitted in connection with this application as well as other submissions in the future are true and correct and reflect the total information available.

7. I understand that the Philippine Food and Drug Administration (FDA) may verify through both government and private entities the authenticity of all the information and documents submitted. I fully consent and authorize the Philippine FDA to conduct such verification for purposes of evaluation of my application.

IN WITNESS WHEREOF, I have hereunto set my hand this (date) in (city).

(Name of Head of Sponsor/CRO)
Affiant

SUBSCRIBED AND SWORN to before me this _____ at _____, Philippines.

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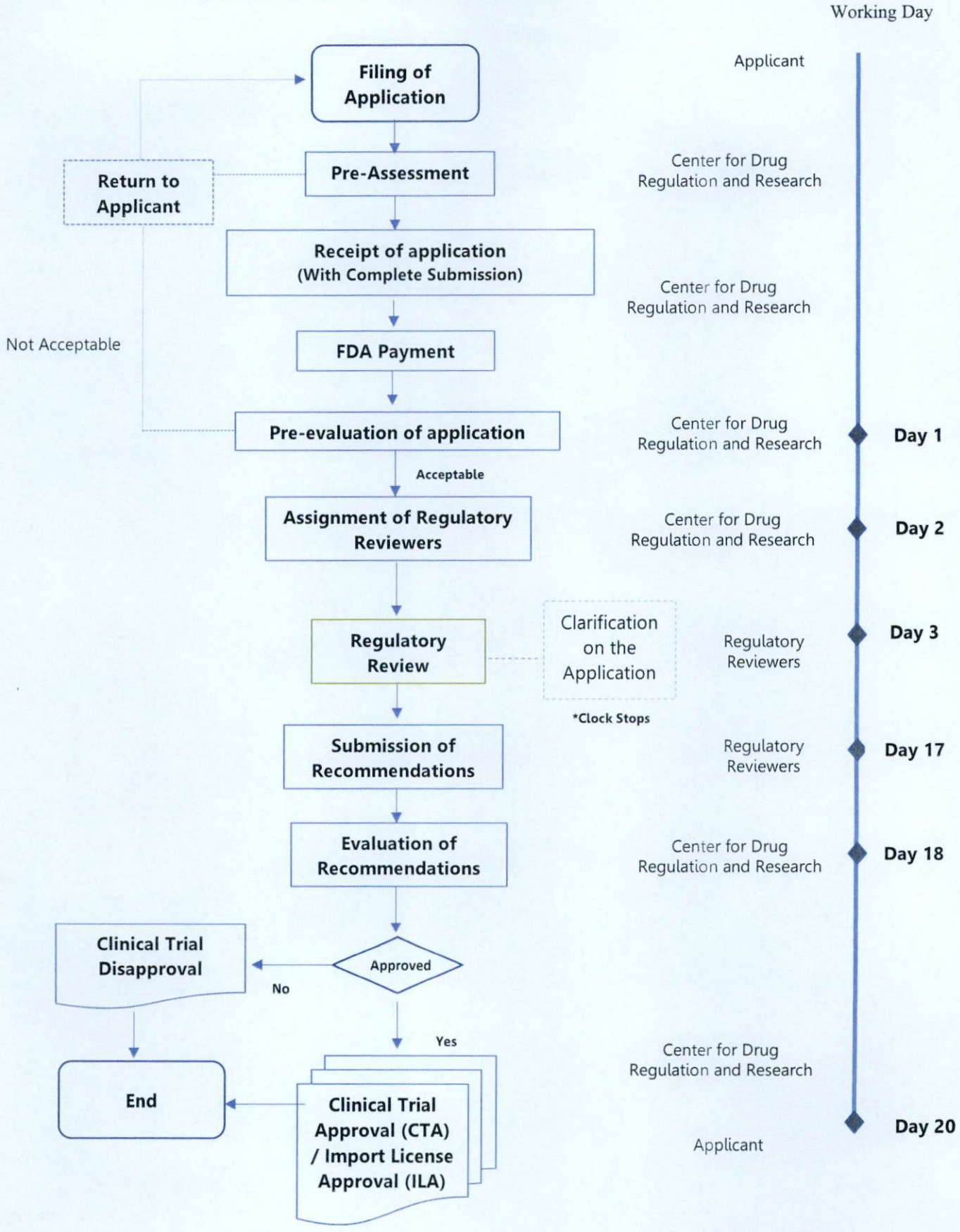
Annex C

Abridged Clinical Trial Approval Process Flow Chart

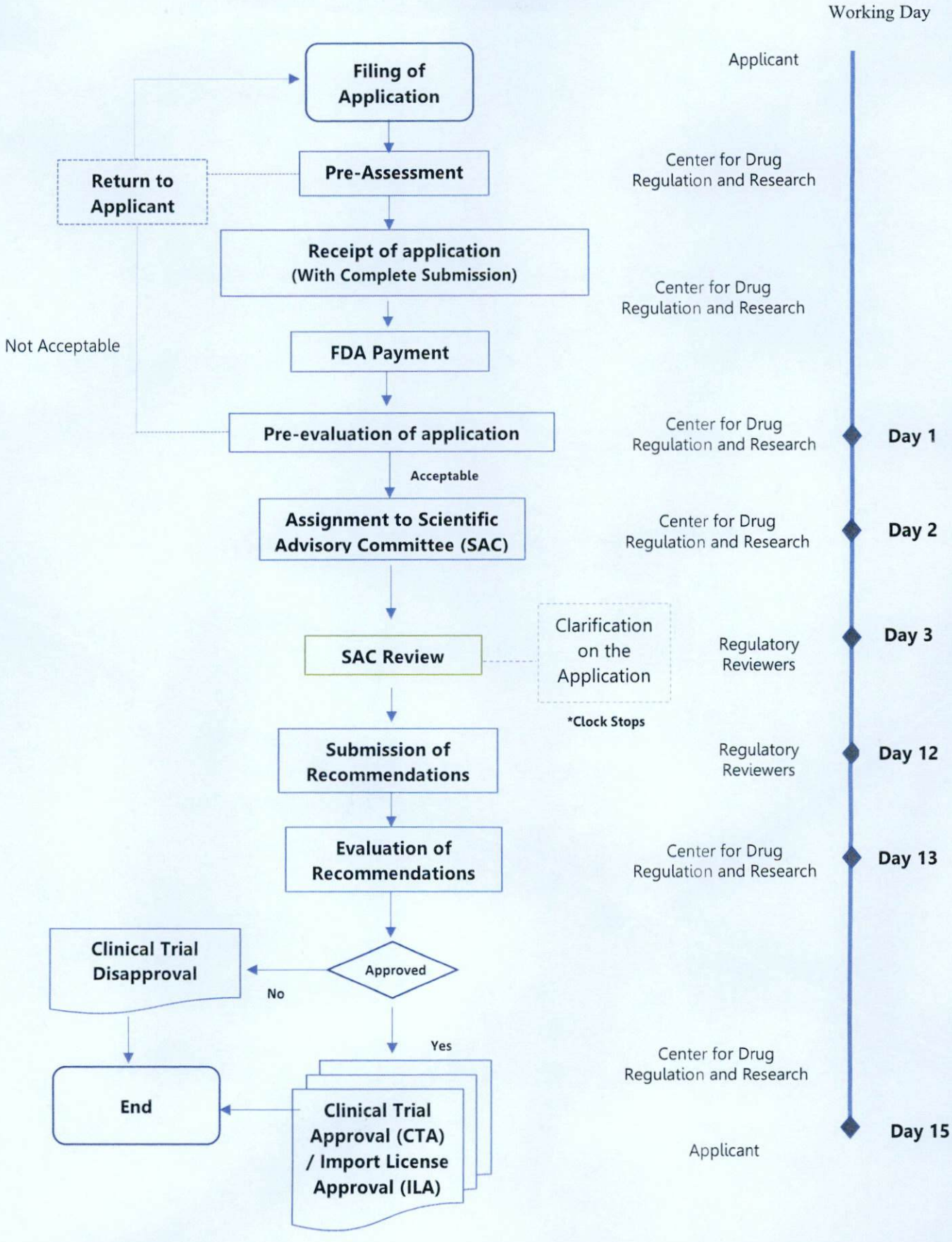


**If the Regulatory Reviewers request for supplementary information from the applicant, the clock stops on the day the request is sent via email. Review will commence on the day the response is received.*

Annex D

Abridged Clinical Trial Amendment Approval Process Flow Chart

[Amendments with Scientific Advisory Committee Review]



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