Guideline

on

Submission of Application for Drug Import Permit into Thailand for Clinical Trial

International Affairs and Investigational Drug Section

Drug Control Division, Thai Food and Drug Administration

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Guideline on Submission of Application for Drug Import Permit into Thailand for Clinical Trial

1. **Definition: Clinical Trial Drugs** in this Guideline are included Modern Drugs or Traditional Drugs, which are indicated in the application for drug import permit into Thailand for clinical trial

2. **Procedures are as follows:**

2.1 **Screening Process**

2.1.1 Eligible applicant submits an application with attached documents as listed in the Checklist form and attached documents for the application of drug import permit into Thailand for clinical trial according to Nor Yor Mor 1 form (see Annex 3) at the One Stop Service Center(OSSC), Thai Food and Drug Administration

2.1.2 OSSC sends the application package to International Affairs and Investigational Drug Section

2.1.3 Officer of International Affairs and Investigational Drug Section screens documents/evidences as listed in the "Checklist form" and attached documents for the application of drug import permit into Thailand for clinical trial according to Nor Yor Mor 1 form (see Annex 3). Then the officer informs the eligible applicant or its attorney the screening results within 5 working days from the date, when International Affairs and Investigational Drug Section first received the application package

(1) If the screening result is "completed application package", the officer will send the application package to an assigned reviewer to proceed

(2) If the screening result is "uncompleted application package", the officer will send "Screening Result Notification form" (Annex 4) to the applicant or its attorney to correct the application package by submitting additional documents together with "Additional Documents Submission form" (see Annex 5)

If the applicant or its attorney fails to fully correct the package within 5 working days, Thai FDA will send a rejection letter and return all documents to the applicant. However, the applicant can later correct or amend the application package and re-submit it at the OSSC.

If the correction is completed, the officer will send the application package to the assigned reviewer to proceed

2.2 **Assessment Process**

Reviewer receives the application package and performs technical assessment

(1) If the reviewer finds that the package is correct and appropriate in terms of technical evidence, the reviewer will put forward this application to Thai FDA for approval of the Drug Import Permit for clinical trial

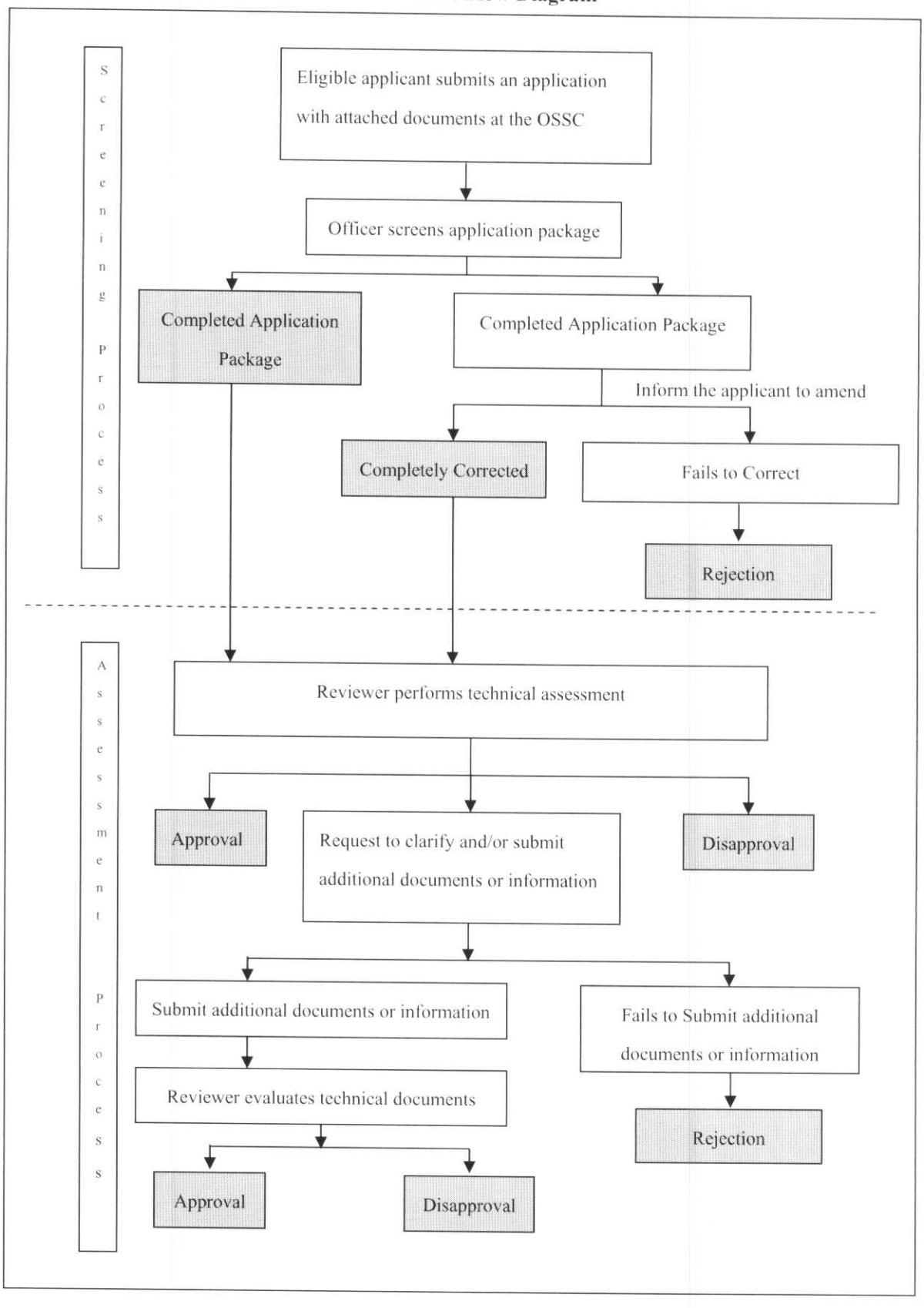
(2) If the reviewer finds that the package is inappropriate in terms of technical evidence, the reviewer will put forward this application to Thai FDA for disapproval

(3) If the reviewer considers and finds that the technical information is incomplete, the reviewer will inform the result to the applicant or its attorney to clarify and/or submit additional documents or information.

If the applicant or its attorney fails to submit additional documents or cannot amend the application package with in 5 working days, Thai FDA will issue a rejection letter and return the package to the applicant. However, the applicant can later correct or amend the application package and re-submit it at the OSSC.

If the applicant can completely correct the application package, the officer will forward the package to the assigned reviewer for re-assessment

3.3 Process Flow Diagram



3. Documents/ Evidences for Application to Import Permit of Medicinal Drugs into Thailand for Clinical Trials

The application for Drug Import Permit into Thailand for clinical trial requires 2 copies of documents listed below

1. Cover letter
2. Checklists and Attached Documents for Application Import Permit of Medicinal Drugs into Thailand for Clinical Trial according to Nor Yor Mor 1
3. Nor Yor Mor 1 form
4. Drug Labels of every container (Thai or AEnglish)
5. Package Insert (for Registered Drugs)
6. Investigator's Brochure (for Unregistered Drugs)
7. Patient Information Sheet (Thai)
8. Protocol Synopsis (Thai)
9. Completed Version of Study Protocol (Thai or English)
10. Chemistry, Manufacturing, and Control Information (CMC)
11. Approval to Conduct Clinical Trial From Institutional Review Board(IRB) or Independent Ethics Committee(IEC) that Food And Drug Administration Recognizes

4. Requirements for Cover Letter

To be in accordance with Annex 6

5. Requirements for Checklist and Attached Documents for Application Import Permit of Medicinal Drugs into Thailand for Clinical Trial according to Nor Yor Mor 1

To be in accordance with Annex 3

6. Requirements for Eligible Applicant

6.1 The eligible applicant must be Drug Manufacturing License Holder, Drug Import License Holder, Ministry/ Department responsible for disease protection or treatment, Thai Red Cross, or Government Pharmaceutical Organization

6.2 The first time applicant must attach

6.2.1 certified copies of Drug Import License, or

6.2.2 certified copies of Order of Department in case of person acting for Director-General, or

6.2.3 certified copies of Order of University in case of person acting for President

Thai FDA's officer will keep this document in a separated binder for verification for every time that the same applicant files application. And this document must be re-submitted every end of year and/or every time that it has been updated

6.3 The applicant who signed in Nor Yor Mor 1 form must be the highest executive of that organization, i.e.

6.3.1 *Drug Manufacturing License Holder* must the license holder or entrepreneur as indicated in the license

6.3.2 *Drug Import Lidense Holder* must be the license holder or entrepreneur as indicated in the license

6.3.3 *Ministry* must be Permanent Secretary or person who is officially assigned to act for him/her

6.3.4 *Department* must be Director General or person who is officially assigned to act for him/her

6.3.5 *Thai Red Cross* must be Secretary General of Thai Red Cross or person who is officially assigned to act for him/her

6.3.6 *Government Pharmaceutical Organization* must be Director of Government Pharmaceutical Organization or person who is officially assigned to act for him/her

6.4 Unless the applicant submits the application by him/herself, the applicant must assign authority to his/her attorney stated in the letter of attorney and attached certified copies of representative's and attorney's identification cards with signatures and dates

6.5 If clinical trial's sponsor is the eligible applicant, it could submit applications for every study site. However, each study site must be approved by ethic committees that Thai FDA recognizes

6.6 If study site is the eligible applicant, it could submit applications for its own site only

7. Requirements for Nor Yor Mor 1 form

7.1 Must submit 2 copies of fully filled Nor Yor Mor 1 Form according to the Ministerial Notification

7.2 Fill in the form only by type without correction marks

7.3 Applicant must sign in Nor Yor Mor 1 form in both original and its copy

7.4 The signing in Nor Yor Mor 1 form is only by the eligible applicant only

8. Requirements for Drug Labels

Drug Labels attached to the container must present

8.1 Non-proprietary or Common Name of Drug Product and Strength(s)

8.2 Trial Number and/or Trial Title

8.3 Batch Number

8.4 Name and Address of sponsor(s)

8.5 Expiry date or Retest date

8.6 Storage Conditions

8.7 "ใช้เพื่อการวิจัยเท่านั้น" indicated

9. Requirements for Package Inserts (for Registered Drug)

If Drug Product is registered in Thailand, a certified copy of a certificate(s) of drug registration by Thai Food and Drug Administration must be submitted.

10. Requirements for Investigator's Brochure (for Non-Registered Drugs)

The Investigator's Brochure must include explanations of the followings, which each part should be supported by sufficient references.

10.1 Table of content

10.2 Summary

10.3 Introduction

10.4 Physical, Chemical, and Pharmaceutical Properties and Formulation

10.5 Nonclinical Studies (Animal Study)

10.5.1 Pharmacology

10.5.2 Pharmacokinetics and Product Metabolism in Animals

10.5.3 Toxicology

10.6 Clinical Study

10.6.1 Pharmacokinetics and Product Metabolism in Humans

10.6.2 Safety and Efficacy

10.6.3 Marketing Experience

10.7 Summary of Data and Guidance for the Investigator

11. Requirements for Patient Information Sheet (Thai language)

Patient information sheet used to give subject(s) information and description during inform consent process and inform consent form including additional information should include explanations of the following:

(1) That the trial involves research.

(2) The purpose of the trial.

(3) The trial treatment(s) and the probability for random assignment to each treatment.

(4) The trial procedures to be followed, including all invasive procedures.

(5) The subject's responsibilities.

(6) Those aspects of the trial are experimental.

(7) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

(8) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject must be made aware of this.

(9) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

(10) The compensation and/or treatment available to the subject in the event of trial-related injury.

(11) The anticipated prorated payment, if any, to the subject for participating in the trial.

(12) The anticipated expenses, if any, to the subject for participating in the trial.

(13) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

(14) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

(15) Those records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

(16) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

(17) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

(18) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

(19) The expected duration of the subject's participation in the trial.

(20) The approximate total and Thailand numbers of subjects involved in the trial

12. Requirements for Protocol Synopsis (Thai language)

The following information must be included in the Protocol Synopsis

12.1 Title and Protocol Number/Code

12.2 Background and Rationale

12.3 The goal(s) of the trial

12.4 Study Design and Duration

12.5 Total Number of Sites and Number of Thailand Sites

12.6 List of Investigators

12.7 Sample Size and Patient Population (including statistic calculation)

12.8 Inclusion Criteria

12.9 Exclusion Criteria

12.10 Study drug

12.11 Dosage Regimen

12.12 Washout Period (if any)

12.13 Pre-study Screening and Baseline Evaluation

12.14 Treatment / Assessment Visits

12.15 Concomitant Medication

12.16 Rescue Medication and Risk Management

12.17 Premature Withdrawal / Discontinuation Criteria

12.18 Efficacy Variables and Analysis

12.19 Safety Variables and Analysis

12.20 Statistical Analysis

13. Requirements for Completed Version of Study Protocol (Thai or English languages)

The contents of a trial protocol must generally include the following topics:

13.1 General Information

13.2 Background Information

13.3 Trial Objectives and Purpose

13.4 Trial Design

13.5 Selection and Withdrawal of Subjects

13.6 Treatment of Subjects

13.7 Assessment of Efficacy

13.8 Assessment of Safety

13.9 Statistics

13.10 Direct Access to Source Data/Documents

13.11 Quality Control and Quality Assurance

13.12 Description of ethical considerations relating to the trial

13.13 Data Handling and Record Keeping

13.14 Financing and Insurance

13.15 Publication Policy

13.16 Supplements

14. Requirements for Chemistry, Manufacturing, and Control Information (CMC)

Chemistry, Manufacturing, and Control Information for Nor Mor Yor 1 filing must comply with the following requirements:

14.1 For New Chemical Entity

Depending on the phase of the clinical trial, the completed Chemistry, Manufacturing, and Control Information (CMC) template, as well as additional Quality information as outlined in the template, must be submitted;

(1) Clinical Trial Applications - Phase I : Quality Overall Summary should include all information indicated in Appendix 8.

(2) Clinical Trial Applications – Phase II : Quality Overall Summary should include all information indicated in Appendix 9.

(3) Clinical Trial Applications – Phase II : Quality Overall Summary should include all information indicated in Appendix 10.

14.2 For registered drug product

(1) In the case that the product approved for marketing authorization in Thailand, a copy of certificate of drug registration and the evidence supports that the imported drug and the registered drug are produced by the same manufacturer.

(2) In the case that the product not approved for market authorization in Thailand but in foreign country, a Certificate of Free Sale must be submitted. See appendix 11.

15. Requirements for Approval to Conduct Clinical Trial From Institutional Review Board(IRB) or Independent Ethics Committee(IEC) that Food And Drug Administration Recognizes

Approval to Conduct Clinical Trial from Institutional Review Board (IRB) or Independent Ethics Committee (IEC) recognized by Food And Drug Administration should include the following topics:

15.1 Protocol Title

15.2 List of Principal Investigator(s)

15.3 Place of proposed study

15.4 List of documents reviewed and approved by IRB or IEC including version of the documents.

15.5 Period of the approval and/or Date of Expired of the approval

16. Processing after Receipt of Drug Import Permit for Clinical Trial

After the import permit is granted, eligible applicant must inform or request permission from Food and Drug Administration (depending on cases) as the following:

16.1 Cases that must be approved by Food And Drug Administration before Processing

(1) changes to clinical trial drug supplies

(2) changes to an approved protocol (Protocol Amendment) or changes related to or affect to safety of subjects

(3) If the sponsor is required to immediately make one or more of the amendments because the clinical trial or the use of the drug for the purposes of the clinical trial endangers the health of a clinical trial subject or other person, the applicant may immediately make the amendment without prior review by Food and Drug Administration. A corresponding notification which clearly identifies the change and the rationale for immediate implementation of the change must be filed within 15 working days after the date of implementation of the amendment.

A corresponding notification letter referred to the related approved import permit (Nor Yor Mor1) along with supplement documents as in appendix 12 is needed.

16.2 Cases that must be informed Food and Drug Administration for Acknowledgement

(1) Changes to the protocol that do not affect the safety of the trial subjects

(2) When the Clinical Trial has been discontinued in its entirety or at any clinical trial site for reasons not related to the safety of clinical trial participants

(3) Changes to Investigator's Brochure

(4) Changes to Quality (Chemistry and Manufacturing) information that do not affect the quality or safety of the drug

(5) In the event of the premature discontinuation of a trial, Food and Drug Administration must be notified no later than 30 working days after the date of discontinuance

A corresponding notification letter referred to the related approved import permit (Nor Yor Mor 1) along with supplement documents as in appendix 13 is needed.

In the event of the premature discontinuation of a trial, a corresponding notification letter along with supplement documents as in appendix 14 is needed.

16.3 Reporting of Adverse Drug Reactions (ADRs)

Adverse drug reactions are subject to reporting to Food and Drug Administration in accordance with the regulations of Food and Drug Administration.

13 Conditions of Approval

Conditions of Approval will be in accordance with the regulations determined by Food and Drug Administration.