Guidelines to Clinical Study Authorization for Drugs

Guidelines to Clinical Study Authorization for Drugs shall be enacted as follows:

Chapter 1. General Provisions

Article 1. Purpose

This guidelines is intended to assist appropriate performance of the process for Clinical Study Authorization for drugs by providing matters regarding the scope of products subject to the Clinical Study Authorization for drugs, preparation of data to be submitted, the scope of data to be submitted, the requirements for and exemption from each data, the procedures for approval, and the criteria for approval, in accordance with Clause 7, Article 26-4 of the Pharmaceutical Affairs Law, Articles 28, and Article 29 of the Enforcement Regulation under the same Law and No 4, Clause 1, Article 32 of the Enforcement Regulation of the Narcotics Control Law.

Article 2. Definitions

① The definitions of terms used herein shall be as follows:

1. "Prior Consultation” means the process of consultation between the sponsor intending to conduct a clinical trial and the Commissioner of Korea Food and Drug Administration (KFDA) in regard to the scientific appropriateness in respect of the clinical trial before filing an application for Clinical Study Authorization or conducting the therapeutic confirmatory clinical trial directly associated with licensing of drugs.

2. "Application for Clinical Study Authorization (Investigational New Drug Application)” means the process of applying for Clinical Study Authorization by the Commissioner of KFDA under which the applicant intends to conduct the clinical trial on humans using the subject drug for the purpose of collecting the data on safety and efficacy.
3. "Investigator-Initiated Trial (Sponsor-Investigator Trials)" means the clinical trial conducted independently in respect of drugs of which safety and efficacy are not verified by any clinical study institution or investigator without any request from the outside sponsor.

4. "Treatment Use of an Investigational New Drug" means the compassionate use of an investigational drug or a drug of which marketing is not permitted, in order to treat a patient with a serious life-threatening disease.


② The definition of the terms, which is used herein but not designated herein, shall conform with the provisions of Pharmaceutical Affairs Law, the Enforcement Regulation under the same Law, "Regulation on the Review of an Application (Report) for the Manufacture and Import License of a Drug and Quasi-drug", "Regulation on Evaluation of Safety and Efficacy of Drugs, etc.", "Korean Good Clinical Practice for Pharmaceuticals", "Guidelines on License and Good Clinical Practice for a Gene Remedial Agent" or "Standards for a Toxicity Test of Drugs, etc.".

Chapter 2. Data to be submitted, etc.

Article 3. Preparation of Data to be Submitted

① Anyone intending to conduct the clinical trial shall submit the information as provided in Article 4 to 5 hereof when filing an application for Clinical Study Authorization (amendment) for drugs.

② The submitted information shall have indications of the list, index number by data and page thereon in the order set forth in Article 4, and further shall be in conformity with the requirements as provided in Article 5 hereof. Provided, however, that in case any data submission is waived in accordance with the provision of each Article, the reason shall be specifically described.

③ As for any foreign data, in principle, a Korean summary (excerpts of major matters) and the original literature shall be submitted, and only when necessary, the Commissioner of KFDA may have a complete translation version be submitted.
Article 4. Scope of Data to be Submitted

Anyone intending to conduct the clinical trial shall submit the following data for Clinical Study Authorization for drugs, and the scope of those data to be submitted depending upon the characteristics of each clinical trial protocol is as provided in Attached Table. Provided, however, that in case of applying for approval of amending the clinical trial protocol, only the data required for respective amendments shall be submitted.

1. Development plan
2. Introduction
3. Information on the evidence of chemical structure and the physicochemical and biological properties (including a placebo)
4. Data on results of non-clinical tests
   a. Data on efficacy and general pharmacology
   b. Data on absorption, distribution, metabolism and excretion
   c. Data on toxicity
      1) Test data on single-dose toxicity
      2) Test data on repeated-dose toxicity,
      3) Test data on genetic toxicity,
      4) Test data on reproductive and developmental toxicity
      5) Test data on carcinogenicity
      6) Test data on other toxicity depending upon characteristics of a test substance (local toxicity, dependency, antigenicity, immunological toxicity, etc.)
5. Data on results of clinical trial (if available)
6. Clinical trial protocol
7. List of References
8. Investigator's Brochure

Article 5. Requirements for Information to be submitted

Requirements for data as provided in Article 4 hereof shall be as follows:

1. Development Plan

A data briefly describing the overall plan to be conducted in the initial year and the subsequent year at least, including theoretical grounds for conducting the clinical trial, indications, the clinical evaluation method and expected serious risk incidental to the
investigational new drug and further a brief information on the format of the clinical trial, the expected number of subjects, etc. according to each clinical trial protocol.

2. Introduction

A data describing detailed information on the investigational new drug (name of the drug, active ingredient, therapeutic class, formulation, administration route, etc.), the purpose and the period of the scheduled clinical trial, the clinical experience and in the case of the drug of which the clinical trial or the sale is suspended, the brief statement thereof.

3. Data on the evidence of chemical structure and the physicochemical and biological properties (including a placebo)

A data describing specifications of drug substances of the investigational new drug (structural formula, physicochemical and biological characteristics, etc.) and in case a new additive is used, explanation thereof, a storage method thereof, the stability data for establishing the shelf-life or the re-examination date, and a data including explanation of the structural similarity to any known substance, specifications of drug substances or the results of conducting the quality control according to the specification and the test method of the investigational new drug.

4. Data on results of non-clinical tests

A data describing a summary of the test results on toxicity, pharmacology, absorption · distribution · metabolism and excretion, but including discussions on the test method, test results and their correlation to clinical aspects, in which the data on the toxicity test includes the data charting the results thereof in details and the information proving that the test has been conducted in accordance with the Good Laboratory Practice.

5. Data on results of the clinical trial

A data including theoretical grounds for the clinical trial and clinical discussions in principle, and describing a summary of available clinical information on pharmacokinetics, pharmacodynamics, dose-response, safety and efficacy, in the case of the drug of which the clinical trial has been already conducted or which is available on the market.
6. Clinical trial protocol

A clinical trial protocol in conformity with the provision of Clause 2, Article 28 of the Enforcement Regulation under the "Pharmaceutical Affairs Law". In the case of the phase 1 clinical trial protocol, the brief outline of the clinical trial including the expected number of subjects, dose regimen, etc. shall be described therein and also the information on the safety shall be included in details therein.

7. Investigator’s Brochure

Data summarizing and arranging the information as provided in Clauses 2 through 5, Article 4 hereof for investigator's conducting the clinical trial.

Chapter 3. Application for Clinical Study Authorization

Article 6. Application for Clinical Study Authorization for a New Drug under Development and Amendment of Permit Items

① Anyone intending to conduct a clinical trial with a new drug under development, or for development of a drug of new composition and of a new formulation, or for amendment of permit items such as indication and usage, posology and method of administration, etc. shall file an application for Clinical Study Authorization as accompanied by the data set forth in Attached Table.

② Anyone intending to obtain a Clinical Study Authorization may request a prior consultation to Commissioner of KFDA before filing an application therefor, as provided in Article 14 hereof.

③ For conducting the therapeutic confirmatory clinical trial directly associated with licensing of the drug, anyone intending to conduct it may request a prior consultation during the development process, and in this case, the provision of Article 14 hereof shall be applied to the procedure thereof and the like.

Article 7. Approval of Investigator-initiated Clinical Trial, etc.

The provision of Article 6 shall be applied to approval of the investigator-initiated clinical trial.
Article 8. Exemption from Submission of Data

① In case any of the following subparagraphs is applicable, the applicant may file an application for Clinical Study Authorization with only the development plan, the clinical trial protocol and the Investigator's Brochure among the data as provided in Article 4 hereof. And, in the case of No. 3 hereof, the applicant may submit only the clinical trial protocol and the Investigator's Brochure.

1. A drug to which any of the followings is not applicable.
   A. A drug under development in Korea for the first time in the world
   B. A drug under development in any foreign country

2. In case the applicant had prior consultation with the Commissioner of KFDA on the appropriateness of conducting the clinical trial as provided in Article 14 hereof before filing an application for Clinical Study Authorization and the appropriateness thereof is acknowledged.

3. In the case of the clinical trial to be conducted for meeting the permit conditions after the license of the drug is issued.

② Notwithstanding the provision of No. 1, Clause ①, Article 8 hereof, in case any of the followings is applicable, the applicant may only the clinical trial protocol and the Investigator's Brochure.

1. An orphan drug

2. A drug with sufficient clinical grounds in Korea and foreign countries, in case the applicant intends to commence a therapeutic confirmatory clinical trial directly/indirectly associated with licensing the drug (including any amendment).

3. A new drug of natural substance(s) (excluding a case that any characteristic component is separated and extracted).

4. A drug containing a component(s) that has ever been used in Korea that is different from an existing drug(s) containing it in indication and usage, posology and method of administration, composition, formulation and/or the administration route thereof and having no particular problem in safety.

5. Other drugs acknowledged separately by the Commissioner of KFDA.

③ Notwithstanding the provisions of clauses ① and ② hereof, in case the Commissioner of KFDA acknowledges that it is necessary to have any specific data, he/she may require the applicant to submit it.
Irrespective of the provision of Article 4, when it is impossible to conduct any test itself theoretically and technically or when, even if it is possible to conduct it, it is acknowledged that the conduct of the test is meaningless, the applicant may be exempted from submission of the applicable data.

In case the applicant intends to conduct a comparative clinical trial for obtaining the license of the drug according to the provision of No 1-C, Clause 1, Article 23 of the Enforcement Regulation under the Pharmaceutical Affairs Law, the applicant may be exempted from submission of data as provided in Clauses 4, 5, and 7, Article 4.

Chapter 4. Amendment of Clinical Trial Protocol

Article 9. Scope of Data to be submitted for Amendment of Clinical Trial Protocol

1. In case the applicant intends to conduct a new clinical trial belonging to the category of the approved clinical trial protocol;
   A. Clinical trial protocol
   B. Investigator's Brochure, including any updated information on safety and efficacy.
      (in case no amendment is available, the applicant shall be exempted from submission of this data)

2. In case the manufacturer (importer) of the investigational new drug to be used is amended;
   A. A data proving that the drug is in conformity with No. 2, Clause 1, Article 28 of the Enforcement Regulation under the Pharmaceutical Affairs Law.

3. In case the applicant intends to amend the development plan in order to include a new indication based on a new action mechanism additionally;
   A. Clinical trial protocol
   B. A data enabling the new action mechanism to be pharmacologically proved.

4. In case the applicant intends to conduct a new clinical trial by amending the formulation of the investigational new drug or the composition;
   A. Clinical trial protocol
B. In-house Specifications and Test Methods (if necessary)
C. Data as provided in Clauses 3 to 4, Article 4 hereof (if necessary)
D. Other data describing a summary of the result of the toxicity test (if necessary)

② In case the applicant intends to amend the clinical trial protocol under the provision of No. 3 and 4, Clause ① hereof, the applicant shall file an application for approval of the amendment of the clinical trial protocol with the development plan reflecting the amendment items being attached thereto.

Article 10. Amendment of Clinical Trial Protocol

① In case the applicant intends to amend details of the clinical trial protocol not affecting directly the evaluation of safety and efficacy of the drug in addition to any of the following subparagraphs, the applicant may conduct the clinical trial upon getting an approval from the Institutional Review Board of the competent institution without a separate approval of the Commissioner of KFDA. In this case, the amendments shall be reflected in the result of the clinical trial. However, in the case of the amendment of principal investigator or of the clinical trial institution, when the applicant submits the amendment to the Commissioner of KFDA, it shall be regarded as being approved by the Commissioner of KFDA.

1. A composition for the investigational new drug
2. A disease in respect of which the clinical trial is conducted
3. Criteria for including and excluding subjects
4. A method for administering the investigational new drug and an administration period
5. Criteria for evaluating safety and efficacy, important laboratory tests directly related to the safety of subjects, an observation method and a test method
6. Other cases as acknowledged separately by the Commissioner of KFDA

② In case the applicant intends to amend the clinical trial protocol under the provision of Clause ① hereof, the applicant shall submit appropriate data.

Chapter 5. Treatment Use of an Investigation New Drug

Article 11. Treatment Use of an Investigation New Drug, etc.

① In case the applicant intends to use the investigational new drug or the drug not licensed for marketing in order to provide a treatment opportunity to patients with any serious life-
threatening disease, the applicant shall submit a protocol including the followings and further obtain an approval for the use thereof from the Commissioner of KFDA:

1. Purpose and reason of using the investigational new drug.
2. Criteria for selecting patients to use the drug
3. A method for administering the investigational new drug and an administration dose
4. A method for collecting data related to safety and efficacy in connection with using the drug
5. The updated Investigator's Brochure, or a data on safety and efficacy equivalent thereto or better.

② The approval provided in Clause ① hereof shall be applicable to any of the following subparagraphs, provided that it shall be limited to the case that the clinical effect of the drug on the relevant disease in question has been objectively observed:

1. A case to treat patients with any serious life-threatening disease
2. A case of a disease for which any existing treatment is not expected to have a satisfactory efficacy due to lack of any alternative drug or treatment
3. A case that the chairperson of Korea Orphan Drug Center acknowledges that it is necessary for treatment of patients

③ In case the applicant gets an approval under the provision of Clause ① hereof, the applicant shall conduct the treatment use upon getting an approval from the Institutional Review Board of the clinical trial institution as designated by the Commissioner of KFDA.

**Article 12. Emergency Use of an Investigational New Drug**

① Notwithstanding the provision of Article 11 hereof, in case any doctor thinks that a patient is in an emergency condition threatening his/her life seriously or imminently and intends to use an investigational new drug or a drug not licensed for marketing under doctor's responsibility upon getting an agreement to use thereof from the patient, he/she shall submit the following data and further get an approval for the use thereof from the Commissioner of KFDA.

1. Medical record of the patient and a summary of a specialist’s findings
2. A medical certificate
3. An agreement executed by the patient
4. A letter of intent for supplying the drug by the developer
② The doctor as provided in Clause ① hereof shall have a specialized knowledge on the relevant disease and moral attainments, and further belongs to the clinical trial institution as designated by the Commissioner of KFDA.

③ The Commissioner of KFDA may recommend the developer to apply for Clinical Study Authorization for the investigational new drug of which the use has been approved under the provision of Clause ① hereof, as provided in Clause ①, Article 28 of the Enforcement Regulation under the Pharmaceutical Affairs Law.

Article 13. Case Report, etc.

In case the approval of the use of the investigational new drug or the drug not licensed for marketing is obtained under the provision of Article 11 or 12 hereof, after completion of the use thereof, the investigator shall fill the case report form provided by the developer, including the collected information such as the follow-up results in respect of adverse events having taken place with each patient, the treatment effect on each patient and the safety thereof, and further submit it to the developer. In case any unexpected serious adverse event takes place, the developer shall immediately report it to the Commissioner of KFDA in accordance with Korean Good Clinical Practice for Pharmaceuticals (However, if the developer is a foreign company, the doctor in charge shall report so).


Article 14. Prior Consultation

① Anyone intending to get a Clinical Study Authorization for conducting the clinical trial smoothly, may request the Commissioner of KFDA to provide a prior consultation on whether there is a possibility to commence the clinical trial, kinds of additional data to be required for filing an application for Clinical Study Authorization in the future, whether the clinical trial protocol is appropriate, advice on the development plan, association with a license for marketing through the results of the final safety and efficacy confirmatory clinical trial, and the like by submitting the data as provided in Article 4 hereof to the Commissioner of KFDA.

② The applicant shall request the Commissioner of KFDA in writing to provide a prior consultation with a consultation data being attached to the written request by 40 days before the date when he/she wants to have the consultation.
③ In case the Commissioner of KFDA is requested to provide a prior consultation, he/she shall have consultations with various specialists on toxicity, pharmacology and clinic, specialists belonging to National Institute of Toxicological Research, the persons concerned with the application for Clinical Study Authorization and the like, and further inform the applicant of the consultation results in writing within 50 days from the request date for the prior consultation.

④ The Commissioner of KFDA shall have an interview with the applicant from time to time before the date of the prior consultation to examine the required data sufficiently, and further in principle, approve the clinical trial protocol within 30 days from the date when an application for Clinical Study Authorization is filed according to consultation result, unless there is any special reason. In this case, the data as provided in No 2 through 5, Clause ① may be substituted for the Investigator's Brochure.

⑤ In the case of a new drug, the applicant for the prior consultation shall bear 5,000,000 Won for the Commissioner of KFDA, and in the case of other drug than a new drug, he/she shall bear 4,250,000 Won. The Commissioner of KFDA may have the applicant bear the actual cost required for other services.

Article 15. Advisory Consultation, etc.

The Commissioner of KFDA may, if necessary, have an advisory consultation from Central Pharmaceutical Affairs Council when examining the application for Clinical Study Authorization.

Article 16. Complement of Data

① In case any of the subparagraphs is applicable to the data of the application for Clinical Study Authorization, the Commissioner of KFDA shall require the applicant to complement it by pointing out the required matters specifically.

1. In case any kind and scope of or requirement for the submitted data is not in conformity with the provision of Article 4 and 5 hereof;
2. In case it is acknowledged that in addition to the data provided in No.1 hereof, any additional data is specially required for the appropriateness of the clinical trial;

② Complement of the data under the provision of Clause ① hereof shall be made one time, and the complement period shall be within 30 days. If the complementary data is not submitted within 30 days, the Commissioner of KFDA may urge the applicant to
complement it within additional 7 days. However, in case the applicant requests the Commissioner of KFDA to extend the complement period by any given date, he/she may determine the extended period in consideration of the reason for such request.

③ In case the Commissioner of KFDA thinks during examination of the data that any of the following subparagraphs is applicable, he/she may return the application to the applicant with the reason for such return being specified.

1. In case the complementary data is not submitted within the time limit as provided in Clause ② hereof;
2. In case the clinical trial protocol is not in conformity with the criteria for examination so that its appropriateness is not acknowledged;

Article 17. Application mutatis mutandis

"Pharmaceutical Affairs Law", "Enforcement Regulation under the same Law", "Korean Good Clinical Practice for Pharmaceuticals", and "Regulation on Designation of a Clinical Trial Institution" shall apply to any matters relating to Clinical Study Authorization as not provided herein.

Addenda

Article 1. Date of Enforcement

This notification shall be enforced from the date when this notification is made. However, the provision of Article 14 hereof shall be enforced from January 1, 2003.

Article 2. Transitional Measures

① Anyone conducting continuously a clinical trial which was not subject to approval under the prior regulation before this notification is enforced shall obtain a Clinical Study Authorization from the Commissioner of KFDA in accordance with this notification.

② In case anyone having obtained a license for an investigational new drug and a Clinical Study Authorization in accordance with the prior regulation before the date when this notification is enforced wants to receive a Clinical Study Authorization to be issued under the current provision, the Commissioner of KFDA shall issue the Clinical Study Authorization.
### Scope of Data to be submitted for Clinical Study Authorization

(related to Article 4)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Development Plan</th>
<th>Data to be submitted</th>
<th>Pharmacological properties</th>
<th>Toxicity</th>
<th>Data on Non-Clinical Test Results</th>
<th>Data on the result of a clinical trial</th>
<th>List of references</th>
<th>Investigators' Brochure</th>
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<tbody>
<tr>
<td>1. New drug under development</td>
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<td>2. Drug with new salt(isomer)</td>
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<td>3. Drug with new composition</td>
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<td>4. Drug with new administration route</td>
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<td>5. Drug with new indication</td>
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<td>6. Drug with new dosage</td>
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<td>7. Biological agent, gene recombination drug, cell culture drug, genetic remedial agent, cell remedial agent and other drug on which a clinical trial is acknowledged to be necessary by Commissioner of Korea Food and Drug Administration</td>
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<td>The scope of data to be submitted is to be determined depending upon individual characteristics of respective drugs.</td>
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O : Data shall be submitted
△ : Data submission shall be determined depending upon individual characteristics of each drug.
× : Data shall be exempted

※ Data on physical properties: Data on the evidence of chemical structure, physicochemical and biological properties.

**Note:** 1. In case of drug with new administration route, if the systemic exposure does not increase as comparison with drug with previous administration, the repeated-dose toxicity, reproductive and developmental toxicity and carcinogenicity data may be exempted. Also in case the dosage duration of the drug with new administration route is long, the repeated-dose toxicity, carcinogenicity data depending on the duration of treatment shall be submitted.

2. Repeated dose toxicity data shall be what is applicable to the minimum treatment duration depending upon the clinical trial phase, as provided in "Standards of a Toxicity Test on Drugs, etc." stipulated by Commissioner of Korea Food and Drug Administration.
3. In case a male reproductive organ has been examined in the repeated dose toxicity study, phase 1 and phase 2 clinical trials on males may be conducted before the test data on the male reproductive toxicity is submitted, but the test data on the male reproductive toxicity shall be submitted before the phase 3 clinical trial is started.

4. In case a female reproductive organ has been properly examined and evaluated in the repeated dose toxicity study, the clinical trial may be conducted on women under life-long birth control or incapable of pregnancy after menopause without reproductive toxicity data, but the test data on the female reproductive toxicity shall be submitted before the phase 3 clinical trial is started.

5. Among the genetic toxicity studies, the test data on in vitro mutation and chromosomal aberration shall be submitted before the phase 1 clinical trial, and in case the test result appears to be quasi-positive or positive, the in vivo assay on micronucleus shall be submitted before the phase 1 clinical trial. However, in case the test result appears to be negative, the data on in vivo micronucleus assay shall be submitted before the phase 2 clinical trail.

6. If the special concern on subject dose not exist, the clinical trial may be conducted without carcinogenecity data.

7. Data on other toxicity tests
   1) Local toxicity study: The local toxicity data shall be submitted for in case that a drug is directly applied to a skin or mucosa, or may easily be contacted without direct application. However, the mucosa irritation study may be conducted as a part of other toxicity studies
   2) Dependency study: The dependency data shall be submitted for drugs having pharmacological actions on the central nervous system, or drugs acting primarily on the peripheral but having side effects on the central nervous system. However, compounds belonging to the following groups of drug, which are known to be free from inducing dependency may be exempted from the test if they are deemed homogeneous to the group with regard to their chemical structure, pharmacology an purpose of use.
      a) Chlorpromazine, Haloperidol, Reserpine
      b) Imipramine, Amitriptyline
      c) Aspirin, Aminophylline
      d) Indomethacin, Flufenamic acid
      e) Camphor, Picrotoxin, Pentylenetetrazole, Strychnine
   3) Antigenicity: The antigenicity data shall be submitted in case the drug with high-molecular weight substance or the proteinic drug is systemically distributed, and in case the drug with low-molecular weight substance has the possible activity of heptane(eg; penicillin,
sulfonamides). The skin sensitization test (Maximization test) result shall be submitted in case of the skin external preparation.

4) Immune toxicity data: may not be submitted in case that any abnormality in immune system is not observed in repeated dose toxicity studies

8. As for a new drug of natural substance(s), a crude drug and a herbal medicine, even if “o” is applicable, in case it is acknowledged that it is impossible or meaningless to conduct the test, or in case a reference literature(s) is available, the applicant may be exempted from submission of a part or the whole of the data on the applicable non-clinical test.