Provisional Translation (as of March 2013)[*]

Ministerial Ordinance on Good Clinical Practice for Drugs

Ordinance of the Ministry of Health and Welfare No. 28 of March 27, 1997
(As last amended by the Ordinance of Ministry of Health, Labour and Welfare No. 161 of December 28, 2012)

The Ministerial Ordinance on Good Clinical Practice (GCP) for Drugs shall be established as stated below in accordance with the following provisions of the Pharmaceutical Affairs Act (Act No. 145 of 1960): Article 14, Paragraph 3 (including cases where it shall apply *mutatis mutandis* in Article 14, Paragraph 6; Article 19-2, Paragraph 4; and Article 23 of the same Act), Article 14-4, Paragraph 4, and Article 14-5, Paragraph 4 (including cases where these provisions shall apply *mutatis mutandis* in Article 19-4 and Article 23 of the same Act); Article 80-2, Paragraphs 1, 4 and 5; and Article 82.

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[*] This English version of the Japanese Ministerial Ordinance is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

Chapter I General Provisions

Article 1. Objectives

This Ministerial Ordinance is intended to provide the standards, which serve as the GCP for Drugs, specified by the Minister of Health, Labour and Welfare pursuant to Article 14, Paragraph 3 of the Pharmaceutical Affairs Act (hereinafter referred to as "PAA") (including cases where it shall apply *mutatis mutandis* in Paragraph 9 of the same article; and Article 19-2, Paragraph 5 of PAA; the same shall apply hereinafter) and Article 14-4, Paragraph 4; and Article 14-6, Paragraph 4 of PAA (including cases where these provisions shall apply *mutatis mutandis* in Article 19-4 of PAA; the same shall apply hereinafter), and the standards specified by MHLW Ordinance pursuant to Articles 80-2, Paragraphs 1, 4 and 5 of PAA so as to ensure the scientific quality of clinical trials and the reliability of clinical trial data while the rights, safety and welfare of human subjects are protected and promoted.

Article 2. Definitions

1. The term "post-marketing clinical study" as used in this Ministerial Ordinance means post-marketing clinical studies specified in Article 2, Paragraph 4 of Good Post-marketing Study Practice (GPSP) for Drugs (MHLW Ordinance No. 171 of 2004).

2. The term "medical institution" as used in this Ministerial Ordinance means medical sites where a clinical trial or post-marketing clinical study is conducted.

3. The term "investigator" as used in this Ministerial Ordinance means a physician or dentist who supervises activities related to a clinical trial conducted at a medical institution.

4. The term "post-marketing clinical study investigator" as used in this Ministerial Ordinance means a physician or dentist who supervises activities related to a post-marketing clinical study conducted at the medical institution.

5. The term "test drug" as used in this Ministerial Ordinance means a drug that is tested in a clinical trial or a drug product that is tested in a post-marketing clinical study.

6. The term "comparator" as used in this Ministerial Ordinance means a drug or other substances, used as a reference in a clinical trial or a post-marketing clinical study for the purpose of comparison with a test drug.

7. The term "investigational products" as used in this Ministerial Ordinance means a test drug and a comparator (limited to the drugs that are used for the clinical trial).

8. The term "post-marketing clinical study drug" as used in this Ministerial Ordinance means a test drug and a comparator (limited to the drug products that are used for the post-marketing clinical study).

9. The term "subject/trial subject" as used in this Ministerial Ordinance means an individual who receives an investigational product or a post-marketing clinical study drug, or an individual who participates in the clinical trial as a control.

10. The term "source documents" as used in this Ministerial Ordinance means data and other records obtained by the administration of investigational products or post-marketing clinical study drug to subjects and the medical treatment of the subjects in the clinical trial.

11. The term "subinvestigator" as used in this Ministerial Ordinance means a physician or a dentist who takes charge of part of the activities related to a clinical trial under the supervision of the investigator at a medical institution.

12. The term "post-marketing clinical study subinvestigator" as used in this Ministerial Ordinance means a physician or a dentist who takes charge of part of the activities related to a post-marketing clinical study under the supervision of the post-marketing clinical study investigator at a medical institution.

13. The term "case report form (CRF)" as used in this Ministerial Ordinance means a document containing source data on each trial subject and evaluation of those data by the investigator or subinvestigator, or by the post-marketing clinical study investigator or post-marketing clinical study subinvestigator.

14. The term "clinical research coordinators" as used in this Ministerial Ordinance means pharmacists, nurses, or other healthcare professionals who collaborate in activities related to a clinical trial under the supervision of either the investigator or the subinvestigator at a medical institution.

15. The term "post-marketing clinical research coordinators" as used in this Ministerial Ordinance means pharmacists, nurses, or other healthcare professionals who collaborate in activities related to a post-marketing clinical study under the supervision of either the post-marketing clinical study investigator or the post-marketing clinical study subinvestigator at a medical institution.

16. The term "coordinating investigator" as used in this Ministerial Ordinance means a physician or dentist to whom the duties of coordinating clinical trial-related issues, including interpretation of the protocol at the relevant medical institutions, (hereinafter referred to as the “duties of coordination”) are assigned by the sponsor (which refers to the one specified in Article 2, Paragraph 18 (the same shall apply in the next paragraph) or sponsor-investigator if the clinical trial is conducted according to a single protocol but at more than one medical institution.

17. The term "coordinating committee" as used in this Ministerial Ordinance means a committee (composed of multiple physicians or dentists) to which the duties of coordination are assigned by the sponsor or sponsor-investigator if the clinical trial is conducted according to a single protocol but at more than one medical institution.

18. The term "monitoring" as used in this Ministerial Ordinance means the act of overseeing the progress of a clinical trial or post-marketing clinical study, and of determining whether the clinical trial or post-marketing clinical study is being conducted in compliance with this Ministerial Ordinance and the protocol of the clinical trial (hereinafter referred to as "protocol") or the protocol of the post-marketing clinical study (hereinafter referred to as "post-marketing protocol"), in order to ensure that the clinical trial or post-marketing clinical study is properly conducted. Such act is performed at the medical institutions by a person sponsoring a clinical trial (hereinafter referred to as "sponsor") or a person sponsoring a post-marketing clinical study (hereinafter referred to as "post-marketing clinical study sponsor"), or by an individual appointed by a sponsor-investigator.

19. The term "audit" as used in this Ministerial Ordinance means an examination of trial-related activities to determine whether the clinical trial or post-marketing clinical study has been conducted in compliance with this Ministerial Ordinance and the protocol or the post-marketing protocol, in order to assure the reliability of data collected in the clinical trial or post-marketing clinical study. Such examination is performed by a sponsor or a post-marketing clinical study sponsor, or by an individual appointed by a sponsor-investigator.

20. The term "adverse event" as used in this Ministerial Ordinance means any disease or its clinical signs occurring in a subject who has been treated with an investigational product or post-marketing clinical study drug.

21. The term "legally acceptable representative" as used in this Ministerial Ordinance means an individual who exercises parental rights over a subject, the subject’s spouse or guardian, or any other person who is considered to be such a representative.

22. The term "person who intends to be a sponsor-investigator" as used in this Ministerial Ordinance means a physician or dentist as a prospective investigator who intends to submit a clinical trial notification pursuant to Article 80-2, Paragraph 2 of PAA in order to conduct a clinical trial at the medical institution etc. to which the physician or dentist belongs (including a physician or dentist as a prospective coordinating investigator who intends to submit a clinical trial notification pursuant to Article 80-2, Paragraph 2 of PAA, on behalf of all participating investigators, for a clinical trial conducted according to a single protocol but at more than one medical institution).

23. The term "sponsor-investigator" as used in this Ministerial Ordinance means an investigator who has submitted a clinical trial notification pursuant to Article 80-2, Paragraph 2 of PAA in order to conduct a clinical trial at the medical institution etc. to which the sponsor-investigator belongs (including a coordinating investigator who has submitted a clinical trial notification pursuant to Article 80-2, Paragraph 2 of PAA, on behalf of all participating investigators, for a clinical trial conducted according to a single protocol but at more than one medical institution).

24. The term "investigational product provider" as used in this Ministerial Ordinance means an individual who provides investigational products to a sponsor-investigator.

Article 3. Standards for Documents Submitted in Product Application

1. With regard to the documents as stipulated in Article 14, Paragraph 3 of PAA concerning a drug clinical trial conducted by a person who intends to obtain approval as stipulated in Article 14 or Article 19-2 of PAA, the relevant data shall be collected and generated in compliance with the provisions of Chapter II, Section 1; Chapter III, Section 1; and Chapter IV (excluding Article 29, Paragraph 1, Item (2); Article 31, Paragraph 4; Article 32, Paragraphs 4 and 7; Article 33, Paragraph 3; and Article 48, Paragraph 3).

2. With regard to the documents as stipulated in Article 14, Paragraph 3 of PAA concerning a drug clinical trial conducted by a sponsor-investigator, the relevant data shall be collected and generated in compliance with the provisions of Chapter II, Section 2; Chapter III, Section 2; and Chapter IV (excluding Article 29, Paragraph 1, Item (1); Article 32, Paragraphs 6 and 8; and Article 48, Paragraph 2).

Chapter II. Standards for Preparing Clinical Trials

Section 1. Standards for Preparing Clinical Trials by Persons Who Intend to Sponsor Clinical Trials

Article 4. Operating Procedures, etc.

1. A person who intends to sponsor a clinical trial shall prepare written operating procedures for the duties related to sponsoring and managing the clinical trial such as preparation of the protocol, selection of medical institutions and investigators, control/accountability of investigational products, collection of information on adverse drug reactions, record keeping.

2. The person who intends to sponsor a clinical trial shall secure professionals with adequate expertise to fulfill the duties related to sponsoring and managing the clinical trial, such as physicians, dentists, and pharmacists.

Article 5. Conduct of Toxicity Studies etc.

The person who intends to sponsor a clinical trial shall have completed studies on the quality, toxicity and pharmacological effects of the test drug and other studies required for sponsoring the clinical trial.

Article 6. Selection of Medical Institution

The person who intends to sponsor a clinical trial shall select a medical institution that meets the qualifications specified in Article 35 and an investigator who meets the qualifications specified in Article 42.

Article 7. Protocol

1. The person who intends to sponsor a clinical trial shall prepare a protocol that should include the following information:

   (1) Name and address of the person who intends to sponsor a clinical trial (or, in the case of a corporation, company name [the same shall apply in this item, the following item, Article 13, Paragraph 1, Items (2) and (3); Article 15-4, Paragraph 1, Items (2), (3) and (7); and Article 16, Paragraph 1, Item (2)] and address of its principal office [the same shall apply in this item; the following item; Article 13, Paragraph 1, Items (2) and (3); Article 15; Article 15-4, Paragraph 1, Items (2), (3) and (7); Article 16, Paragraph 1, Item (2); and Article 26, Paragraph 2]) (or, if the person resides outside Japan, then his or her name and name of the country where the person is located, and name and address of the clinical trial in-country representative pursuant to Article 15; the same shall apply in Article 13, Paragraph 1, Item (2))

   (2) When all or any of the duties related to the clinical trial are outsourced to another person or organization (hereinafter referred to as "contractor" in this chapter), name and address of the contractor and the scope of the duties outsourced

   (3) Name(s) and address(es) of medical institution(s)

   (4) Name(s) and title(s) of the person(s) to be appointed as the investigator(s)

   (5) Objectives of the clinical trial

   (6) Summary of the test drug

   (7) Clinical trial design

   (8) Description of subject selection

   (9) Description of direct access to source documents

   (10) Description of record (including data) keeping

   (11) Name(s) and title(s) of coordinating investigator(s) to whom the responsibilities for coordination are assigned, if applicable

   (12) Names and titles of physicians or dentists constituting a coordinating committee to which the responsibilities for coordination are assigned, if applicable

   (13) If an Efficacy and Safety Assessment Committee is established pursuant to Article 19, then a note to that effect.

2. The person who intends to sponsor a clinical trial shall state in the protocol, if applicable, that the investigational product affords no intended clinical benefit to the subject, and that some subjects are to be enrolled in the clinical trial although it would be difficult to obtain their own consent under Article 50, Paragraph 1. The protocol should also include the following information:

   (1) Reasons why some subjects are to be enrolled in the clinical trial although it would be difficult to obtain their own consent under Article 50, Paragraph 1

(2) Explanation that the potential disadvantages which the subject may incur in the clinical trial are minimized

3. The person who intends to sponsor a clinical trial shall state in the protocol that, if applicable, some subjects are to be enrolled in the clinical trial although it would be difficult to obtain their own consent under Article 50, Paragraphs 1 and 2. The protocol should also include the following information:

(1) Explanation that an application for marketing approval of the test drug is intended to be submitted so that the drug will be used for emergency treatment to save lives of patients in a life-threatening condition

(2) Explanation that currently available treatments are unlikely to achieve sufficient therapeutic effects in the prospective subject

(3) Explanation that there is a sufficient possibility of saving the life of the prospective subject by using the test drug

(4) A note that an Efficacy and Safety Assessment Committee under Article 19 has been established for the clinical trial

4. When preparing a protocol pursuant to Paragraph 1, the person who intends to sponsor a clinical trial shall gain agreement with a person to be appointed as an investigator on the content of the protocol and that the clinical trial be conducted in compliance with the protocol.

5. The person who intends to sponsor a clinical trial shall revise the protocol as necessary whenever important new information becomes available that may be relevant to the proper conduct of the clinical trial, such as information on the quality, efficacy and safety of the test drug. In this case, the provisions of the preceding paragraph shall apply *mutatis mutandis*.

Article 8. Investigator's Brochure (IB)

1. The person who intends to sponsor a clinical trial shall prepare an Investigator's Brochure that states the following information, based on the data obtained in the studies specified in Article 5 and the information on the quality, efficacy and safety of the test drug:

(1) Chemical name or identification code of the test drug

(2) Information on the test drug, such as its quality, toxicity, and pharmaceutical effects

(3) Results of clinical studies of the investigational product, if any has been conducted

2. The person who intends to sponsor a clinical trial shall revise the Investigator's Brochure as necessary whenever important new information becomes available that may be relevant to the proper conduct of the clinical trial, such as information on the quality, efficacy and safety of the test drug.

Article 9. Request for Preparation of Written Information

The person who intends to sponsor a clinical trial shall request the prospective investigator to prepare documents for providing the explanation as specified in Article 50, Paragraph 1 (hereinafter referred to as "written information").

Article 10. Prior Submission of Documents to the Head of Medical Institution

1. The person who intends to sponsor a clinical trial shall beforehand submit the following documents to the head of the medical institution:

   (1) Protocol (including its amendments pursuant to Article 7, Paragraph 5)

   (2) Investigator's Brochure (including its amendments pursuant to Article 8, Paragraph 2)

   (3) Sample of the case report form

   (4) Written information

   (5) List of prospective investigators and subinvestigators (hereinafter collectively referred to as "investigators etc").

   (6) Documents on the burden of expenses for the clinical trial

   (7) Document explaining compensation to the subject in the event of trial-related injuries

2. A person who intends to sponsor a clinical trial may, in lieu of submitting the documents as stipulated in the preceding paragraph, send the information that must be submitted in writing as stipulated in the preceding paragraph by using electronic data processing system or other information-communication technologies specified below (hereinafter referred to as "electromagnetic means") pursuant to Paragraph 5, with the consent of the head of the medical institution. In this case, the person who intends to sponsor a clinical trial shall be deemed to have submitted the documents.

   (1) A method of using an electronic data processing system of either (a) or (b):

      (a) A method where the information is transmitted from a computer used by the person who intends to sponsor a clinical trial to a computer used by the head of the medical institution via a telecommunication line connecting the computers, and the information is recorded in a file on the computer used by the recipient.

      (b) A method where the information stipulated in the preceding paragraph that is recorded in a file on a computer used by the person who intends to sponsor a clinical trial is made available for access by the head of the medical institution, and the information as stipulated in the preceding paragraph is recorded in a file on the computer used by the head of the medical institution (if the head of the medical institution notifies the person who intends to sponsor a clinical trial of the decision on whether or not to accept the transmission of documents by electromagnetic means, then including the method of recording the notification in a file on the computer used by the person who intends to sponsor a clinical trial).

(2) A method of delivering the information as stipulated in the preceding paragraph recorded in a file on a magnetic disk, CD-ROM, or other storage media that can securely store the specified information.

3. The method as stipulated in the preceding paragraph must allow the head of the medical institution to prepare the documents by printing out the data recorded in the file.

4. The term "electronic data processing system" used in Paragraph 2, Item (1) refers to an electronic data processing system where a computer used by the person who intends to sponsor a clinical trial is connected via a telecommunication line with a computer used by the head of the medical institution.

5. When the person who intends to sponsor a clinical trial submits the documents as stipulated in Paragraph 1 pursuant to Paragraph 2, he or she shall beforehand inform the head of the medical institution of the type and description of the electromagnetic means shown below and obtain consent from the head of medical institution in writing or by electromagnetic means.

   (1) Among the methods stipulated in Paragraph 2, the method used by the person who intends to sponsor a clinical trial

   (2) File format

6. When notified by the head of the medical institution, either in writing or by electromagnetic means, that notification by electromagnetic means is unacceptable, even if the consent has been obtained once as stipulated in the preceding paragraph, the person who intends to sponsor a clinical trial shall not submit the documents stipulated Paragraph 1 by electromagnetic means to the head of the medical institution, except when the head of the medical institution gives another consent pursuant to the preceding paragraph later.

Article 11. Prohibition of Prior Supply of Investigational Products

The person who intends to sponsor a clinical trial shall not supply medical institutions with investigational products before the clinical trial contract is concluded.

Article 12. Outsourcing Duties

1. The person who intends to sponsor a clinical trial shall conclude a contract with a contractor by means of a document specifying the following information when outsourcing all or any of the duties related to sponsoring and managing the clinical trial:

   (1) Scope of the duties outsourced

   (2) Description of the operating procedures for the duties outsourced

   (3) Statement that the person who intends to sponsor a clinical trial is entitled to ascertain whether the duties outsourced are conducted properly and smoothly in compliance with the operating procedures specified in the preceding item

   (4) Description of instructions to the contractor

(5) Statement that if the instructions specified in the preceding item are given, the person who intends to sponsor a clinical trial is entitled to ascertain whether appropriate measures are taken in response to the instructions

(6) Description of reports to be submitted by the contractor to the person who intends to sponsor a clinical trial

(7) Description of measures specified in Article 14 relating to the duties outsourced

(8) Other necessary matters related to the duties outsourced

2. A person who intends to sponsor a clinical trial may, in lieu of making a written contract as stipulated in the preceding paragraph, conclude a contract specifying the matters as stipulated in the preceding paragraph by using an electronic data processing system or other information-communication technologies specified below (hereinafter referred to as "electromagnetic means" in this Article), pursuant to Paragraph 5, with the consent of the contractor as stipulated in the preceding paragraph (hereinafter referred to as "contractor" in this Article). In this case, the person who intends to sponsor a clinical trial shall be deemed to have concluded a written contract.

(1) A method of using an electronic data processing system of either (a) or (b):

(a) A method where the information is transmitted between a computer used by the person who intends to sponsor a clinical trial and a computer used by the contractor via a telecommunication line connecting the computers, and the information is recorded in a file on the computer used by either party.

(b) A method where the information stipulated in the preceding paragraph that is recorded in a file on a computer used by the person who intends to sponsor a clinical trial is made available for access by the contractor, and the information as stipulated in the preceding paragraph is recorded in a file on the computer used by the contractor (if the contractor notifies the person who intends to sponsor a clinical trial of the decision on whether or not to accept the conclusion of a contract by electromagnetic means, then including the method of recording the notification in a file on the computer used by the person who intends to sponsor a clinical trial).

(2) A method of delivering the information as stipulated in the preceding paragraph is recorded in a file on a magnetic disk, CD-ROM, or other storage media that can securely store the specified information.

3. The method as specified in the preceding paragraph must conform to the technical standards below.

(1) The method must allow the person who intends to sponsor a clinical trial and the contractor to prepare the documents by printing out data recorded in a file.

(2) The method must employ a means by which one can confirm that the information in the documents recorded in the file has not been modified.

4. The term "electronic data processing system" used in Paragraph 2, Item (1) refers to an electronic data processing system where a computer used by the person who intends to

sponsor a clinical trial is connected via a telecommunication line with a computer used by the contractor.

5. When the person who intends to sponsor a clinical trial concludes a contract specifying the matters as stipulated in Paragraph 1 pursuant to Paragraph 2, he or she shall beforehand inform the contractor of the type and description of the electromagnetic means shown below, and obtain consent from the contractor in writing or by electromagnetic means.

   (1) Among the methods stipulated in Paragraph 2, the method used by the person who intends to sponsor a clinical trial

   (2) File format

6. When notified by the contractor, either in writing or by electromagnetic means, that the conclusion of the contract by electromagnetic means is unacceptable, even if the consent has been obtained once as stipulated in the preceding paragraph, the person who intends to sponsor a clinical trial shall not conclude the contract stipulated Paragraph 1 by electromagnetic means with the contractor, except when the contractor gives another consent pursuant to the preceding paragraph later.

Article 13. Clinical Trial Contract

1. A clinical trial contract shall be concluded by means of a document specifying the following information between the person who intends to sponsor a clinical trial and medical institutions (or among the person who intends to sponsor a clinical trial, contractor(s), and medical institution when all or any of the duties are outsourced pursuant to the preceding Article):

   (1) Date of concluding the contract

   (2) Name and address of the person who intends to sponsor a clinical trial

   (3) Name(s) and address(es) of the contractor(s) and the scope of the duties outsourced, if all or any of the duties are outsourced pursuant to the preceding article

   (4) Name(s) and address(es) of the medical institution(s)

   (5) Name(s) and title(s) of the person(s) in charge of the contract from each party

   (6) Name(s) of the investigator(s)

   (7) Duration of the clinical trial

   (8) Description of the control/accountability of investigational products

   (9) Description of record keeping (including data)

   (10) Description of notifications given by the sponsor and the personnel of the medical institution in accordance with this Ministerial Ordinance

   (11) Description of maintenance of the confidentiality of the subjects

   (12) Description of the expense for the clinical trial

(13) Statement that the medical institution conducts the clinical trial in compliance with the protocol

(14) Statement that the medical institution will provide the sponsor with direct access to the records (including documents) specified in Article 41, Paragraph 2, upon request by the sponsor

(15) Statement that the sponsor may cancel the contract if it is found that the medical institution has violated this Ministerial Ordinance, the protocol, or the relevant contract, resulting in interference with the proper conduct of the clinical trial (excluding cases stipulated in Article 46)

(16) Description of compensation to the subject in the event of trial-related injuries

(17) Other matters necessary to ensure that the clinical trial is conducted properly and smoothly

2. The provisions of Article 12, Paragraphs 2 through 6 shall apply *mutatis mutandis* to the written contract as stipulated in the preceding paragraph. In this case, “the contractor as stipulated in the preceding paragraph” in Article 12, Paragraph 2 and "contractor" in Article 12, Paragraph 2, Items (1); Paragraph 3, Item (1); and Paragraphs 4 through 6, shall be read as "the medical institution" (the medical institution and the contractor, if all or any of the duties are outsourced pursuant to this article) (hereinafter referred to as the "medical institutions etc.”) and "medical institutions etc.," respectively.

Article 14. Compensation to Subjects

The person who intends to sponsor a clinical trial shall beforehand take necessary measures such as purchasing insurance in preparation for compensation to the subject in the event of trial-related injuries (including those attributable to the duties performed by the contractor).

Article 15. Clinical Trial In-Country Representative

In order to take the necessary measures to prevent the occurrence or spread of health hazards due to investigational products, the person who intends to sponsor a clinical trial and resides outside Japan shall appoint a person eligible for sponsoring the clinical trial on behalf of the person who intends to sponsor a clinical trial from among persons residing in Japan (including the head of a Japanese business office of a foreign company) to have him or her (hereinafter referred to as "clinical trial in-country representative") conduct the procedures for sponsoring the clinical trial.

Section 2. Standards for Preparing Clinical Trials by Person Who Intends to Be a Sponsor-investigator

Article 15-2. Operating Procedures etc.

1. A person who intends to be a sponsor-investigator shall prepare written operating procedures for the duties related to preparing and managing a clinical trial, such as

preparation of a protocol, control/accountability of investigational products, collection of information on adverse drug reactions etc. and record keeping.

2. The person who intends to be a sponsor-investigator shall secure professionals with adequate expertise to fulfill the duties related to preparing and managing the trial, such as physicians, dentists, and pharmacists.

Article 15-3. Conduct of Toxicity Studies etc.

The person who intends to be a sponsor-investigator shall have completed the studies on the quality, toxicity and pharmacological effects of the test drug and other studies required for the conduct of the clinical trial.

Article 15-4. Protocol

1. The person who intends to be a sponsor-investigator shall prepare a protocol that includes the following information:
   (1) Name, title and address of the person who intends to be a sponsor-investigator
   (2) When all or any of the duties related to preparing or managing the clinical trial are outsourced to a contractor, name and address of the contractor and the scope of the duties outsourced
   (3) When a part of the duties related to conducting the clinical trial is outsourced to a contractor, name and address of the contractor and the scope of the duties outsourced
   (4) Names and addresses of the medical institutions
   (5) Objectives of the clinical trial
   (6) Summary of the test drug
   (7) Name and address of the investigational product provider
   (8) Clinical trial design
   (9) Description of subject selection
   (10) Description of direct access to source documents
   (11) Description of record keeping (including data)
   (12) Name(s) and title(s) of coordinating investigator(s) to whom the responsibilities for coordination are assigned, if applicable
   (13) Names and titles of physicians or dentists constituting a coordinating committee to which the responsibilities for coordination are assigned, if applicable
   (14) If an Efficacy and Safety Assessment Committee is established pursuant to Article 26-5, then a note to that effect

2. The person who intends to be a sponsor-investigator shall state in the protocol, if applicable, that the investigational product affords no intended clinical benefit to the

subject and that some subjects are to be enrolled in the clinical trial although it would be difficult to obtain their own consent under Article 50, Paragraph 1. The protocol should also include the following information:

(1) Reasons why some subjects are to be enrolled in the clinical trial although it would be difficult to obtain their own consent under Article 50, Paragraph 1

(2) Explanation that the potential disadvantages which the subject may incur in the clinical trial are minimized

3. The person who intends to be a sponsor-investigator shall state in the protocol that, if applicable, some subjects are to be enrolled in the clinical trial although it would be difficult to obtain their own consent under Article 50, Paragraphs 1 and 2. The protocol should also include the following information:

(1) Explanation that an application for marketing approval of the test drug is intended to be submitted so that the drug will be used for emergency treatment to save lives of patients in a life-threatening condition

(2) Explanation that currently available treatments are unlikely to achieve sufficient therapeutic effects in the prospective subject

(3) Explanation that there is a sufficient possibility of saving the life of the prospective subject by using the test drug

(4) A note that an Efficacy and Safety Assessment Committee under Article 26-5 has been established for the clinical trial

4. The person who intends to be a sponsor-investigator shall revise the protocol as necessary whenever important new information becomes available that may be relevant to the proper conduct of the clinical trial, such as information on the quality, efficacy and safety of the test drug.

Article 15-5. Investigator's Brochure (IB)

1. The person who intends to be a sponsor-investigator shall prepare an Investigator's Brochure that states the following information, based on the data obtained in the studies specified in Article 15-3 and the information on the quality, efficacy, and safety of the test drug:

(1) Chemical name or identification code of the test drug

(2) The quality, toxicity, pharmacological effects and other aspects of the test drug

(3) Results of clinical studies of the investigational product, if any has been conducted

2. The person who intends to be a sponsor-investigator shall revise the Investigator's Brochure as necessary whenever important new information becomes available that may be relevant to the proper conduct of the clinical trial, such as information on the quality, efficacy and safety of the test drug.

Article 15-6. Preparation of Written Information

The person who intends to be a sponsor-investigator (limited to a physician or dentist as a prospective investigator; the same shall apply in Article 15-7 and Article 26-4) shall prepare written information.

Article 15-7. Prior Submission of Documents to the Head of Medical Institution

The person who intends to be a sponsor-investigator shall beforehand submit the following documents to the head of the medical institution and obtain his or her approval for the conduct of the clinical trial:

(1) Protocol (including its amendments pursuant to Article 15-4, Paragraph 4)

(2) Investigator's Brochure (including its amendments pursuant to Article 15-5, Paragraph 2)

(3) Sample of the case report form

(4) Written information

(5) Written operating procedures for monitoring

(6) Audit plan and written operating procedures for the related duties

(7) List of prospective subinvestigators

(8) Document explaining the control/accountability of investigational products

(9) Document explaining notifications given by the sponsor-investigator and the personnel of the medical institution in accordance with this Ministerial Ordinance

(10) Documents on the expenses for the clinical trial

(11) Document explaining compensation to the subject in the event of trial-related injuries

(12) Document stating that the medical institution will provide the sponsor-investigator with direct access to the records (including documents) as stipulated in Article 41, Paragraph 2 upon request of the sponsor-investigator

(13) Document stating that the sponsor-investigator may prematurely terminate the clinical trial if it is found that the medical institution has violated this Ministerial Ordinance or the protocol, resulting in interference with the proper conduct of the clinical trial (excluding the cases stipulated in Article 46)

(14) Document stating matters necessary to ensure that the clinical trial is conducted properly and smoothly

Article 15-8. Outsourcing Duties

1. When outsourcing all or any of the duties related to preparing and managing the clinical trial, the person who intends to be a sponsor-investigator or the medical institution shall conclude a contract with a contractor by means of a document specifying the following information:

(1) Scope of the duties outsourced

(2) Description of operating procedures for the duties outsourced

(3) Statement that the person who intends to be a sponsor-investigator or the medical institution is entitled to ascertain whether the duties outsourced are conducted properly and smoothly in compliance with the operating procedures specified in the preceding item

(4) Description of instructions to the contractor

(5) Statement that, if the instructions specified in the preceding item are given, the person who intends to be a sponsor-investigator or the medical institution is entitled to ascertain whether appropriate measures are taken in accordance with the instructions

(6) Description of reports to the person who intends to be a sponsor-investigator or the medical institution from the contractor

(7) Description of measures specified in the following article relating to the duties outsourced

(8) Other necessary matters related to the duties outsourced

2. The provisions of Article 12, Paragraphs 2 through 6 shall apply *mutatis mutandis* to the conclusion of the contract in writing as stipulated in the preceding paragraph. In this case, "person who intends to be a sponsor-investigator" in these provisions shall be read as "person who intends to be a sponsor-investigator or the medical institution."

Article 15-9. Compensation to Subjects

The person who intends to be a sponsor-investigator shall beforehand take necessary measures such as purchasing insurance in preparation for compensation to the subject in the event of trial-related injuries (including those attributable to the duties performed by the contractor).

Chapter III. Standards for Clinical Trial Management

Section 1. Standards for Clinical Trial Management by Sponsor

Article 16. Investigational Product Control/Accountability

1. A sponsor shall indicate the following information in the Japanese language on the container or package of the investigational products:

(1) Statement of “For clinical trial use only”

(2) Name and address of the sponsor (if the sponsor resides outside Japan, name of the sponsor and name of the country where the sponsor is located, and name and address of the clinical trial in-country representative)

(3) Chemical name or identification code

(4) Manufacturing number or manufacturing code

(5) Information on storage method, expiration date, etc., if necessary

2. The sponsor shall not indicate the following information in the documents attached to the investigational products, on the investigational products, or on their containers or packages (including the inner packages):

(1) Proposed brand name

(2) Proposed indications

(3) Proposed administration and dosage

3. When investigational products are supplied to medical institutions in such a state that the subject, investigators etc., and clinical research coordinators cannot distinguish the test drug from the comparator, the sponsor shall take necessary measures so that the investigators etc. can readily identify the test drug from the comparator in the event of an emergency.

4. The sponsor shall supply medical institutions with the investigational products so packaged as to prevent contamination and deterioration during transport and storage.

5. The sponsor shall retain the following records concerning the investigational products:

(1) Records concerning the manufacture of the investigational products, such as the manufacturing date, manufacturing method and manufactured quantity, and the results of the tests on the drug's quality, such as its stability

(2) Records of the supply or retrieval of the investigational products, including the quantity and date, for each medical institution

(3) Records of disposal of the investigational products

6. After concluding the clinical trial contract, the sponsor shall prepare written operating procedures for investigational products control/accountability at the medical institutions, and deliver the procedures to the medical institutions without delay.

7. The sponsor shall prepare, as necessary, documents explaining the reconstitution procedures and other handling procedures for the investigational products and deliver the documents to the investigators etc., clinical research coordinators and the investigational product storage managers specified in Article 39.

8. The provisions of Article 10, Paragraphs 2 through 6 shall apply *mutatis mutandis* to the delivery of the operating procedures as stipulated in Paragraph 6. In this case, "person who intends to sponsor a clinical trial" in these provisions shall be read as "sponsor."

9. The provisions of Article 10, Paragraphs 2 through 6 shall apply *mutatis mutandis* to the delivery of the documents as stipulated in Paragraph 7. In this case, "person who intends to sponsor a clinical trial" and "head of the medical institution" in these provisions shall be read as "sponsor" and "investigators etc., clinical research coordinators and the investigational product storage managers specified in Article 39," respectively.

Article 17. Supplying Investigational Products

The sponsor shall be responsible for supplying medical institutions with the investigational products that have been manufactured at a manufacturing site which is equipped with adequate buildings and facilities to ensure the quality of the investigational products and which has appropriate manufacturing control and quality control systems in place.

Article 18. Preparing Description of Assignment

When the sponsor assigns the duties of coordination as specified in Article 2, Paragraph 16 to a coordinating investigator or a coordinating committee, the sponsor shall prepare a document describing the scope of the duties, the operating procedures and other necessary information.

Article 19. Establishment of Efficacy and Safety Assessment Committee

1. A sponsor may establish an Efficacy and Safety Assessment Committee that deliberates the appropriateness of continuing an ongoing clinical trial, or the revision of the protocol.

2. The sponsor shall prepare written operating procedures for deliberation by the Efficacy and Safety Assessment Committee specified in the preceding paragraph and have the committee conduct deliberation in compliance with the procedures.

3. The sponsor shall prepare and retain records of deliberation of the committee whenever the deliberation specified in the preceding paragraph is held.

Article 20. Information on Adverse Drug Reactions etc.

1. The sponsor shall collect and examine information necessary to conduct the clinical trial properly, such as information on the quality, efficacy, and safety of the test drug, and provide the heads of the medical institutions with such information.

2. Whenever the sponsor becomes aware of any event concerning the test drug that are specified in Article 80-2, Paragraph 6 of PAA, the sponsor shall notify the investigators and the heads of the medical institutions of such events in a list, etc. for each of the test drugs, annually after the date of submission of the first clinical trial notification etc. within 3 months after the end of each period of 1 year.

3. Whenever the sponsor becomes aware of any event, which is unexpected based on the information provided in the Investigator’s Brochure for the test drug, among those specified in the preceding paragraph, the sponsor shall immediately notify the investigators and the heads of the medical institutions of the fact.

4. Whenever the sponsor becomes aware of any information relevant to the proper conduct of the clinical trial, such as information on the quality, efficacy, and safety of the test

drug, the sponsor shall revise the protocol and the Investigator’s Brochure, as necessary. In such cases, the sponsor shall obtain the consent of the investigators on the revision of the protocol.

Article 21. Monitoring

1. The sponsor shall prepare written operating procedures for monitoring, and conduct monitoring activities in accordance with the procedures.

2. Monitoring pursuant to the preceding paragraph shall be conducted by visiting the medical institutions, except when monitoring is adequately performed by other means.

Article 22. Monitor's Responsibilities

1. If an individual engaged in monitoring (hereinafter referred to as a "monitor") has found, as a result of monitoring, that the clinical trial is not being conducted at a medical institution in compliance with the Ministerial Ordinance or the protocol, the monitor shall immediately notify the investigator of the medical institution of the fact.

2. The monitor shall submit a monitoring report documenting the following information to the sponsor after each visit to or communication with the medical institution:

   (1) Date of monitoring

   (2) Medical institution monitored

   (3) Name of the monitor

   (4) Names of investigators etc. interviewed during the monitoring visit

   (5) Summary of the results of the monitoring

   (6) Description of the facts of which the monitor notified the investigator pursuant to the preceding paragraph

   (7) Actions to be taken concerning the matters specified in the preceding item and the monitor's comments on such actions

Article 23. Audit

1. The sponsor shall prepare an audit plan and written operating procedures for the related duties, and conduct audits in accordance with the audit plan and the operating procedures.

2. An individual engaged in auditing (hereinafter referred to as an "auditor") shall be independent of the divisions responsible for drug development or monitoring.

3. The auditor(s) shall prepare an audit report documenting the findings in the audit and an audit certificate verifying that the audit has been conducted, and submit them to the sponsor.

Article 24. Premature Termination etc. of Clinical Trial

1. If it is found that a medical institution has violated this Ministerial Ordinance, the protocol or the clinical trial contract, resulting in interference with the proper conduct of the clinical trial (excluding the cases specified in Article 46), the sponsor shall cancel the contract and prematurely terminate the clinical trial at the medical institution.

2. If a clinical trial is suspended or prematurely terminated, the sponsor shall promptly notify in writing the head(s) of the medical institution(s) of the suspension or premature termination and the reasons thereof.

3. If the sponsor has decided not to include the clinical data obtained in the clinical trial in the application specified in Article 14, Paragraph 3 of PAA, the sponsor shall notify in writing the head(s) of the medical institution(s) of the fact and the reason thereof.

4. The provisions of Article 10, Paragraphs 2 through 6 shall apply *mutatis mutandis* to the notification in writing as stipulated in Paragraph 2 and the preceding paragraph. In this case, "person who intends to sponsor a clinical trial" in these provisions shall be read as "sponsor."

Article 25. Clinical Trial Reports

The sponsor shall prepare the clinical trial reports (refers to documents that summarize the results etc. of the clinical trial; the same shall apply hereinafter) when the clinical trial is completed or prematurely terminated.

Article 26. Record Keeping etc.

1. The sponsor shall appropriately retain the following records (including documents and data) related to the clinical trial until the day on which marketing approval of the test drug is obtained (or the day 3 years after the date of notification in the case of a notification pursuant to Article 24, Paragraph 3) or the day 3 years after the date of premature termination or completion of the clinical trial, whichever comes later:

   (1) Protocol, contracts, clinical trial reports, and other documents prepared by the sponsor in accordance with this Ministerial Ordinance, or copies thereof.

   (2) Case report forms, the written notification pursuant to Article 32, Paragraph 6, and other records obtained from the heads of medical institutions or investigators etc. in accordance with this Ministerial Ordinance.

   (3) Records of the duties related to sponsoring and managing the clinical trial, such as monitoring and audits (excluding those specified in the preceding two items and Item (5))

   (4) Data generated in conducting the clinical trial

   (5) Records specified in Article 16, Paragraph 5

2. The sponsor who resides outside Japan shall have a clinical trial in-country representative retain the records specified in Article 16, Paragraph 5, during the period specified in the preceding paragraph.

Section 2. Standards for Clinical Trial Management by Sponsor-Investigators

Article 26-2. Investigational Product Control/Accountability

1. The sponsor-investigator shall indicate the following information on the container or package of the investigational products in the Japanese language:
   (1) Statement of “For clinical trial use only”
   (2) Name, title, and address of the sponsor-investigator
   (3) Chemical name or identification code
   (4) Manufacturing number or manufacturing code
   (5) Information on storage method, expiration date, etc., if necessary

2. The sponsor-investigator shall not indicate the following information in the documents attached to the investigational products, on the investigational products, or on their containers or packages (including the inner packages):
   (1) Proposed brand name
   (2) Proposed indications
   (3) Proposed administration and dosage

3. When investigational products are supplied to the medical institutions in such a state that the subject, subinvestigator, and clinical research coordinators cannot distinguish the test drug from the comparator, the sponsor-investigator shall take necessary measures so that the subinvestigator can readily identify the test drug from the comparator in the event of an emergency.

4. The sponsor-investigator shall take necessary measures to prevent contamination and deterioration of the investigational products during transport and storage.

5. The sponsor-investigator shall prepare or obtain the following records concerning the investigational products:
   (1) Records concerning the manufacture of the investigational products, such as the manufacturing date, manufacturing method and manufactured quantity, and the results of the tests on the product's quality, such as its stability
   (2) Records of the quantity and the date of obtaining or receiving the investigational products when sponsor-investigator obtains the investigational products, or receives them from the investigational product provider
   (3) Records of disposal of the investigational products

6. The sponsor-investigator shall prepare written operating procedures for investigational product control/accountability at the medical institution and deliver the procedures to the medical institution without delay after the conduct of the clinical trial is approved by the head of the medical institution.

7. The sponsor-investigator shall prepare, as necessary, documents explaining the reconstitution procedures and other handling procedures for the investigational products and deliver the documents to the subinvestigator, clinical research coordinators, and the investigational product storage managers specified in Article 39.

Article 26-3. Ensuring Quality of Investigational Products

The sponsor-investigator shall conduct the clinical trial by using investigational products that have been manufactured at a manufacturing site furnished with adequate buildings and facilities to ensure the quality of the investigational products. The manufacturing site shall also have appropriate manufacturing control and quality control systems in place.

Article 26-4. Preparing Description of Assignment

When the sponsor-investigator assigns the duties of coordination as specified in Article 2, Paragraph 16 to a coordinating investigator or a coordinating committee , the sponsor-investigator shall prepare a document describing the scope of the duties, the operating procedures and other necessary details.

Article 26-5. Establishment of Efficacy and Safety Assessment Committee

1. A sponsor-investigator may establish an Efficacy and Safety Assessment Committee that deliberates the appropriateness of continuing an ongoing clinical trial, or the revision of the protocol.

2. The sponsor-investigator shall prepare written operating procedures for the deliberation by the Efficacy and Safety Assessment Committee specified in the preceding paragraph and have the committee conduct deliberation in compliance with the procedures.

3. The sponsor-investigator shall prepare and retain records of the deliberation of the committee whenever the deliberation specified in the preceding paragraph is held.

Article 26-6. Information on Adverse Drug Reactions etc.

1. The sponsor-investigator shall collect and examine information necessary to conduct the clinical trial properly, such as information on the quality, efficacy, and safety of the test drug, and provide the head of the medical institution with such information.

2. Whenever the sponsor-investigator becomes aware of any events concerning the test drug that are specified in Article 80-2, Paragraph 6 of PAA, the sponsor-investigator shall immediately notify the head of the medical institution of the fact (if the clinical

trial is jointly conducted at more than one medical institution according to a single protocol, then including the investigators of the other medical institutions).

3. Whenever the sponsor-investigator becomes aware of any information relevant to the proper conduct of the clinical trial, such as information on the quality, efficacy, and safety of the test drug, the sponsor-investigator shall revise the protocol and the Investigator's Brochure, as necessary.

Article 26-7. Monitoring

1. The sponsor-investigator shall prepare written operating procedures for monitoring, and have the monitor conduct monitoring activities in compliance with the procedures, taking into account the opinions of the IRB as specified in Article 27, Paragraph 1.

2. The monitor shall not engage in the clinical trial at the medical institution to be monitored.

3. Monitoring pursuant to Paragraph 1 shall be conducted by visiting the medical institution, except when monitoring is adequately performed by other means.

Article 26-8. Monitor's Responsibilities

1. If the monitor has found, as a result of monitoring, that the clinical trial is not being conducted at a medical institution in compliance with this Ministerial Ordinance or the protocol, the monitor shall immediately notify the investigator of the medical institution of the fact.

2. The monitor shall submit a monitoring report documenting the following information to the sponsor-investigator and the head of the monitored medical institution after each site visit:

   (1) Date of monitoring

   (2) Name of the monitor

   (3) Name of the investigators etc. interviewed during the monitoring visit

   (4) Summary of the results of the monitoring

   (5) Description of the fact of which the monitor notified the investigator pursuant to the preceding paragraph

   (6) Actions to be taken concerning the matters specified in the preceding item and the monitor's comments on such actions

Article 26-9. Audit

1. The sponsor-investigator shall prepare an audit plan and written operating procedures for the related duties, and have auditors conduct audits in accordance with the audit plan and the operating procedures, taking into account the opinion of the IRB as specified in Article 27, Paragraph 1.

2. The auditors shall not engage in the clinical trial (including its preparation and management) and monitoring at the medical institution to be audited.

3. The auditors shall prepare an audit report documenting the findings in the audit and an audit certificate verifying that the audit has been conducted, and submit them to the sponsor-investigator and the head of the medical institution.

Article 26-10. Premature Termination etc. of Clinical Trial

1. If it is found that a medical institution has violated this Ministerial Ordinance or the protocol, resulting in interference with the proper conduct of the clinical trial (excluding the cases specified in Article 46), the sponsor-investigator shall prematurely terminate the clinical trial at the medical institution.

2. If the clinical trial is suspended or prematurely terminated, the sponsor-investigator shall promptly notify in writing the head(s) of the medical institution(s) of the suspension or premature termination and the reasons thereof.

3. If the sponsor-investigator is informed that the clinical data obtained in the clinical trial will not be submitted in the application specified in Article 14, Paragraph 3 of PAA, the sponsor-investigator shall notify in writing the head(s) of the medical institution(s) of the fact and the reason thereof.

Article 26-11. Clinical Trial Reports

The sponsor-investigator shall prepare the clinical trial reports when the clinical trial is completed or prematurely terminated.

Article 26-12. Record Keeping etc.

The sponsor-investigator shall appropriately retain the following records (including documents and data) related to the clinical trial until the day on which the investigational product provider receives marketing approval of the test drug (or the day 3 years after the date of notification in the case of a notification pursuant to Article 26-10, Paragraph 3) or the day 3 years after the date of premature termination or completion of the clinical trial, whichever comes later:

(1) Protocol, Approval Document, clinical trial reports, and other documents prepared by the sponsor-investigator in accordance with this Ministerial Ordinance, or copies thereof

(2) Case report forms, the written notification pursuant to Article 32, Paragraph 7, and other records obtained from the head of medical institution or subinvestigators

(3) Records of the duties related to the standards for conducting the clinical trial and the management of the clinical trial, such as monitoring and audits (excluding those specified in the preceding two items and Item (5))

(4) Data generated in conducting the clinical trial

(5) Records specified in Article 26-2, Paragraph 5

Chapter IV. Standards for Conducting Clinical Trials

Section 1. Institutional Review Board

Article 27. Establishment of Institutional Review Board (IRB)

1. The head of a medical institution shall have any one of the following IRBs review and deliberate whether it is appropriate to conduct the clinical trial and other issues regarding the clinical trial.

   (1) IRB established by the head of the medical institution

   (2) IRB established by a general incorporated association or general incorporated foundation.

   (3) IRB established by a specified non-profit organization stipulated in Article 2, Paragraph 2 of the Act to Promote Specified Non-Profit Activities (Act No. 7 of 1998)

   (4) IRB established by an academic society composed of healthcare professionals

   (5) IRB established by an incorporated educational institution stipulated in Article 3 of the Private Educational Institutions Act (Act No. 270 of 1949) (limited to one that has a medical institution)

   (6) IRB established by an Incorporated Administrative Agency stipulated in Article 2, Paragraph 1 of the Act on General Rules for Independent Administrative Agencies (Act No.103 of 1999) (limited to one that provides medical care etc. as its main business)

   (7) IRB established by an Incorporated National University stipulated in Article 2, Paragraph 1 of the Incorporated National University Act (Act No. 112 of 2003) (limited to one that has a medical institution)

   (8) IRB established by a Local Incorporated Administrative Agency stipulated in Article 2, Paragraph 1 of the Act on Local Incorporated Administrative Agency (Act No.118 of 2003) (limited to one that has a medical institution)

2. The person or organization that establishes the IRB specified in Items (2) through (4) of the preceding paragraph (hereinafter referred to as the "founder of the IRB") shall meet the following requirements:

   (1) The founder of the IRB shall include any provisions which stipulate the establishment of the IRB in the article of incorporation and other equivalent standing rules.

   (2) The executive directors (regardless of the title, including the one who has the authority or control as well or better; the same shall apply in the following item) of the IRB shall include at least one healthcare professional such as physicians, dentists, pharmacists, nurses.

(3) The following members shall respectively account for not more than one third of all the executive directors:

(a) employees of a certain medical institution or other persons who have a close relationship with the medical institution

(b) executives or employees of a certain juridical person or other persons who have a close relationship with the juridical person

(4) The founder of the IRB shall have a sufficient financial basis to establish and operate the IRB adequately.

(5) The founder of the IRB shall retain its financial documents, such as the inventory of assets, the balance sheet, the profit and loss statement, and the business report in its office, and provide the public with access to those documents.

(6) There shall be no risk of impairment of fair and proper execution of the duties of the IRB.

Article 28. Composition etc. of Institutional Review Board

1. The IRB shall meet the following qualifications:

(1) Being capable of fully reviewing the proposed clinical trial from ethical and scientific viewpoints

(2) Being composed of at least five members

(3) Having, as its member(s), a person or persons other than those who have expertise of medicine, dentistry, pharmaceutical science, health care, or clinical trials (besides the member(s) described in the following item and Item (5))

(4) Having, as its member(s), among others, a person or persons independent of the medical institution

(5) Having, as its member(s), among others, a person or persons independent of the founder of the IRB

2. The founder of the IRB shall prepare written operating procedures specifying the following information, the list of members of the IRB, and records and summaries of IRB meetings, and have the board perform its functions in compliance with the operating procedures:

(1) Method of appointing a chairperson

(2) Conditions for a regular IRB meeting

(3) Description of operation of the meeting

(4) Description of the timing of the reviews stipulated in Article 31, Paragraph 1

(5) Description of records of IRB meetings

(6) Description of record keeping

(7) Other necessary details

3. The founder of the IRB shall disclose the written operating procedures, the list of members of the IRB, and the summaries of IRB meeting records specified in the preceding paragraph.

4. The founder of the IRB shall appoint a person(s) who performs clerical work of the IRB.

Article 29. Institutional Review Board Meetings

1. The following members of the IRB shall not participate in the deliberation or voting regarding a clinical trial to be reviewed:

   (1) Persons who have a close relationship with the sponsor, such as executives or employees of the sponsor

   (2) The sponsor-investigator or persons who have a close relationship with the sponsor-investigator

   (3) The head(s) of the medical institution(s), investigators etc. or clinical research coordinators

2. Members who have not participated in the IRB deliberation shall not vote.

Article 30. Review by Institutional Review Board

1. The head of the medical institution shall beforehand seek the opinion of the IRB stipulated in Article 27, Paragraph 1, with respect to the appropriateness of conducting the clinical trial at the medical institution.

2. The head of the medical institution shall conclude a written contract specifying the following matters beforehand with the founder of the IRB if reviews/deliberations are to be performed by the IRB as described in the preceding paragraph (excluding an IRB established by the head of the medical institution as stipulated in Article 27, Paragraph 1, Item (1) and IRBs listed in Items (5) to (8) of the same paragraph that are established by a corporation owning the medical institution concerned):

   (1) Date of concluding the contract

   (2) Names and addresses of the medical institution and the founder of the IRB

   (3) Procedures for operations related to the contract

   (4) Due date when the IRB should give its opinion

   (5) Description of maintaining the confidentiality of the subject

   (6) Other necessary details

3. The provisions of Article 12, Paragraphs 2 to 6 shall apply *mutatis mutandis* to the conclusion of the contract specified in the preceding paragraph. In such case, the "person who intends to sponsor a clinical trial" in these provisions shall be read as the "head of the medical institution," and the "contractor" shall be read as the "the founder of the IRB as specified in Article 27, Paragraph 1 (excluding the IRB established by the head of the medical institution stipulated in Item (1) of the same paragraph and IRBs

listed in Items (5) to (8) of the same paragraph that are established by a corporation owning the medical institution concerned)."

4. In seeking the opinion of the IRB stipulated in Article 27, Paragraph 1, pursuant to Paragraph 1 of this article, the head of the medical institution may seek the opinion of another IRB (limited to those specified in the items of Article 27, Paragraph 1 [for IRBs listed in Items (2) to (4) of Paragraph 1, those meeting the requirements stipulated in the items of Article 27, Paragraph 2]) other than the IRB concerned regarding specialized matters necessary for determining the appropriateness of the conduct of the clinical trial, with the agreement of the IRB concerned, if the head of the medical institution finds it necessary that the specialized matters should be reviewed/deliberated.

5. The head of the medical institution shall promptly report any opinion of another IRB which the head of the medical institution consults pursuant to the preceding paragraph (hereinafter referred to as the "expert IRB") to the IRB whose opinion has been sought pursuant to Paragraph 1 of this article.

6. The head of the medical institution shall conclude a written contract specifying the following matters beforehand with the founder of the expert IRB if reviews/deliberations are to be performed by the expert IRB pursuant to the Paragraph 4 of this article (excluding an IRB established by the head of the medical institution stipulated in Article 27, Paragraph 1, Item (1) and IRBs listed in Items (5) to (8) of the same paragraph that are established by a corporation owning the medical institution concerned):

   (1) Date of concluding the contract

   (2) Names and addresses of the medical institution and the founder of the expert IRB

   (3) Procedures for operations related to the contract

   (4) Scope of the specialized matters which the expert IRB reviews/deliberates, and the due date when the expert IRB should give its opinion

   (5) Description of maintaining the confidentiality of the subject

   (6) Other necessary details

7. The provisions of Article 12, Paragraphs 2 to 6 shall apply *mutatis mutandis* to the conclusion of the contract specified in the preceding paragraph. In such case, the "person who intends to sponsor a clinical trial" in these provisions shall be read as the "head of the medical institution," and the "contractor" shall be read as the "founder of the expert IRB as stipulated in Article 30, Paragraph 5 (excluding the IRB organized by the head of the medical institution stipulated in Article 27, Paragraph 1, Item (1) and IRBs listed in Items (5) to (8) of the same paragraph that are established by a corporation owning the medical institution concerned)."

8. The head of the medical institution shall obtain the written operating procedures and the list of members of the IRB specified in Article 28, Paragraph 2 when seeking an opinion of the IRB as described in Article 27, Paragraph 1 (excluding the IRB established by the

head of the medical institution stipulated in Item (1) of the same paragraph) pursuant to Paragraphs 1 or 4 of this article.

Article 31. Continuing Review etc.

1. The head of the medical institution shall seek the opinion of the IRB whose opinion has been sought pursuant to Paragraph 1 of the preceding article, with respect to the appropriateness of continuing the clinical trial at the medical institution, and if applicable, the opinion of the expert IRB whose opinion has been sought pursuant to Paragraph 4 of the preceding article regarding specialized matters necessary for determining the appropriateness of continuing the clinical trial, at least once a year when the duration of the clinical trial exceeds one year.

2. When notified pursuant to Article 20, Paragraphs 2 and 3, Article 26-6, Paragraph 2, and Article 48, Paragraphs 2 and 3; when reported pursuant to Article 54, Paragraph 3; and when finding it necessary, the head of the medical institution shall seek the opinion of the IRB whose opinion has been sought pursuant to Paragraph 1 of the preceding article, with respect to the appropriateness of continuing the clinical trial at the medical institution, and if applicable, the opinion of the expert IRB whose opinion has been sought pursuant to Paragraph 4 of the preceding article regarding specialized matters necessary for determining the appropriateness of continuing the clinical trial.

3. The provision of Paragraph 5 of the preceding article shall apply *mutatis mutandis* to cases where the head of the medical institution has sought the opinion of the expert IRB pursuant to the preceding two paragraphs of this article.

4. When the head of the medical institution receives a monitoring report as stipulated in Article 26-8, Paragraph 2 or an audit report as stipulated in Article 26-9, Paragraph 3, the head of the medical institution shall seek the opinion of the IRB whose opinion has been sought pursuant to Paragraph 1 of the preceding article, with respect to whether the clinical trial is being conducted or has been conducted properly at the medical institution.

Article 32. Responsibilities of Institutional Review Board

1. When consulted by the head of the medical institution pursuant to Article 30, Paragraph 1, the IRB stipulated in Article 27, Paragraph 1 (hereinafter “the IRB” in this article), shall review the ethical and scientific appropriateness of the clinical trial and whether it is appropriate to conduct the clinical trial at the medical institution on the basis of the following documents, and give its opinion in writing:

   (1) Documents specified in the Article 10, Paragraph 1 or Article 15-7

   (2) Documents concerning subject recruitment procedures

   (3) Documents describing information specified in Article 7, Paragraph 5 and Article 15-4, Paragraph 4, and other information relevant to the proper conduct of the clinical trial.

   (4) *Curriculum vitae* of each prospective investigator etc.

(5) Other documents that the IRB considers necessary

2. When consulted by the head of the medical institution pursuant to Article 30, Paragraph 4, the expert IRB shall review the specialized matters to be reviewed on the basis of the documents specified in the preceding paragraph (limited to those documents that the expert IRB considers necessary) and give its opinion in writing.

3. When consulted by the head of the medical institution pursuant to Paragraph 1 or 2 of the preceding article, the IRB shall review the appropriateness of continuing the clinical trial at the medical institution upon examining whether the clinical trial is being conducted properly at the medical institution, and give its opinion in writing, and the expert IRB shall review specialized matters necessary for determining the appropriateness of continuing the clinical trial upon examining the specialized matters consulted, and give its opinion in writing. Each IRB shall provide its opinions promptly according to the urgency of the matters consulted.

4. When consulted by the head of the medical institution pursuant to Paragraph 4 of the preceding article, the IRB shall review whether the clinical trial is being conducted or has been conducted properly at the medical institution, and give its opinion in writing.

5. When the head of the medical institution seeks the opinion of an expert IRB pursuant to Article 30, Paragraph 4, the IRB shall provide its opinion pursuant to Paragraph 1 or 3 of this article in consideration of the opinion of the expert IRB reported pursuant to Article 30, Paragraph 5 (including the application *mutatis mutandis* in Paragraph 3 of the preceding article).

6. The head of the medical institution shall notify in writing the person who intends to sponsor a clinical trial or the sponsor and the prospective investigator or the investigator of the opinion of the IRB specified in the Paragraph 1 or 3 of this article.

7. The head of the medical institution shall notify in writing the person who intends to be a sponsor-investigator or the sponsor-investigator of the opinion of the IRB specified in Paragraph 1, 3 or 4 of this article.

8. The provisions of Article 10, Paragraphs 2 through 6 shall apply *mutatis mutandis* to the notification in writing as stipulated in Paragraph 6 of this article. In this case, "person who intends to sponsor a clinical trial" and "head of the medical institution" in these provisions shall be read as "head of the medical institution" and "person who intends to sponsor a clinical trial or sponsor," respectively.

Article 33. Opinion of the Institutional Review Board

1. The medical institution shall not undertake a sponsored clinical trial nor approve the conduct of a clinical trial when the IRB whose opinion has been sought pursuant to Article 30, Paragraph 1, offers its opinion that it is inappropriate to conduct the clinical trial.

2. The medical institution shall cancel the clinical trial contract or prematurely terminate the clinical trial when the IRB whose opinion has been sought pursuant to Article 31, Paragraph 1 or 2, offers its opinion that it is inappropriate to continue the clinical trial.

3. The head of the medical institution shall take appropriate measures when the IRB whose opinion has been sought pursuant to Article 31, Paragraph 4, offers its opinion that the clinical trial is not being conducted or has not been conducted properly.

Article 34. Record Keeping

The founder of the IRB shall retain the written operating procedures, the list of members of the IRB and the record of the meetings and its summary that are specified in Article 28, Paragraph 2; documents regarding the contract pursuant to Article 30, Paragraphs 2 and 6; the documents listed in Article 32, Paragraph 1; documents specified in Article 32, Paragraph 2; and the notifications submitted to the IRB and the expert IRB pursuant to Article 40, Paragraphs 1 through 4 ,until the day on which marketing approval of the test drug is obtained (or the date of notification in the case of a notification pursuant to Article 24, Paragraph 3; or Article 26-10, Paragraph 3) or the day 3 years after the date of premature termination or completion of the clinical trial, whichever comes later.

Section 2. Medical Institution

Article 35. Qualifications for Medical Institution

The medical institution shall meet the following qualifications:

(1) Being well equipped with facilities and having sufficient personnel to conduct the necessary clinical observations and laboratory tests.

(2) Being capable of taking necessary measures for the subject in the event of an emergency.

(3) Having investigators etc., pharmacists, nurses and other adequate personnel for the proper and smooth conduct of the clinical trial.

Article 36. Head of Medical Institution

1. The head of the medical institution shall prepare written operating procedures for the duties related to the clinical trial.

2. The head of the medical institution shall take necessary measures to ensure that the clinical trial is conducted properly and smoothly at the medical institution in compliance with this Ministerial Ordinance, the protocol, and the clinical trial contract in the case of a sponsor-initiated clinical trial, or the documents stipulated in Article 15-7, Items (5) though (11), in the case of an investigator-initiated clinical trial, as well as the procedures as stipulated in the preceding paragraph.

3. The head of the medical institution shall take necessary measures to ensure that confidentiality of subjects is protected.

Article 37. Cooperation for Monitoring

1. The head of the medical institution shall cooperate for the monitoring and audit conducted by the sponsor or outsourced by the sponsor-investigator, as well as the reviews by the IRB stipulated in Article 27, Paragraph 1 and the expert IRB (the expert IRB becomes involved in the reviews only when the head of the medical institution seeks the opinion of the expert IRB pursuant to Article 30, Paragraph 4; hereinafter collectively referred to as "IRB etc").

2. When the monitoring, audit, or review as stipulated in the preceding paragraph is conducted, the head of the medical institution shall provide direct access to the records of the clinical trial as stipulated in Article 41, Paragraph 2, upon the request of the monitor, auditor, or the IRB etc.

Article 38. Clinical Trial Office

The head of the medical institution shall appoint a person or persons who perform clerical work concerning trial-related duties.

Article 39. Investigational Product Control/Accountability

The investigational product storage manager (which refers to the person who is responsible for investigational product control/accountability) shall properly conduct the duties of investigational product control/accountability in compliance with the operating procedures as stipulated in Article 16, Paragraph 6 or Article 26-2, Paragraph 6.

Article 39-2. Outsourcing Duties

The medical institution (the investigator or the medical institution, in the case of a investigator-initiated clinical trial; the same applies in this article) shall conclude a contract with a contractor by means of a document specifying the following information when outsourcing any of the duties related to the conduct of the clinical trial:

(1) Scope of the duties outsourced

(2) Description of the operating procedures for the duties outsourced

(3) Statement that the medical institution can ascertain whether the duties outsourced are conducted properly and smoothly in compliance with the operating procedures specified in the preceding item

(4) Description of the instructions to the contractor

(5) Statement that if the instructions specified in the preceding item are given, the medical institution is entitled to ascertain whether appropriate measures are taken in response to the instructions

(6) Description of the reports to be submitted by the contractor to the medical institution

(7) Other necessary matters related to the duties outsourced

Article 40. Premature Termination etc. of Clinical Trial

1. When notified by the sponsor pursuant to Article 20, Paragraphs 2 and 3 or by the sponsor-investigator pursuant to Article 26-6, Paragraph 2, the head of the medical institution shall immediately notify in writing the IRB etc. of the fact.

2. When notified by the sponsor pursuant to Article 24, Paragraph 2 or by the sponsor-investigator pursuant to Article 26-10, Paragraph 2, of suspension or premature termination of the clinical trial; when notified by the sponsor, pursuant to Article 24, Paragraph 3, that the sponsor has decided not to include the clinical trial data in the application; or when notified by the sponsor-investigator, pursuant to Article 26-10, Paragraph 3, that the sponsor-investigator has been informed that the clinical trial data will not be included in the application, the head of the medical institution shall promptly notify in writing the investigator and the IRB etc. of the fact and the reason thereof.

3. When reported by the investigator that the clinical trial will be suspended or prematurely terminated by the investigator pursuant to Article 49, Paragraph 2, the head of the medical institution shall promptly notify in writing the IRB etc. and the sponsor of the fact and the reason thereof.

4. When reported by the investigator that the clinical trial has been completed pursuant to Article 49, Paragraph 3, the head of the medical institution shall notify the IRB etc. and the sponsor of the fact and a summary of the trial's outcome.

5. The provisions of Article 10, Paragraphs 2 through 6 shall apply *mutatis mutandis* to the notification in writing as stipulated in Paragraph 3 of this article. In this case, "person who intends to sponsor a clinical trial" and "head of the medical institution" in these provisions shall be read as "head of the medical institution" and "sponsor," respectively.

Article 41. Record Keeping

1. The head of the medical institution shall appoint a record keeping manager.

2. The record keeping manager specified in the preceding paragraph shall retain the following records (including documents) until the day on which marketing approval of the test drug is obtained (or the day 3 years after the date of notification in the case of a notification pursuant to Article 24, Paragraph 3 or Article 26-10, Paragraph 3) or the day 3 years after the date of premature termination or completion of the clinical trial, whichever comes later:

   (1) Source documents

   (2) The contract or Approval Document, informed consent forms, written information and other documents prepared by persons engaged in the clinical trial at the medical institution in accordance with this Ministerial Ordinance, or their copies

(3) The protocol, documents obtained from the IRB etc. pursuant to Article 32, Paragraphs 1 through 3, and other documents obtained in accordance with this Ministerial Ordinance

(4) Records of trial-related duties such as control/accountability of investigational products

Section 3. Investigator

Article 42. Qualifications for Investigator

An investigator shall meet the following qualifications:

(1) Being fully qualified by education, training, and adequate clinical experience to assume responsibility for the proper conduct of the clinical trial.

(2) Being well versed in the appropriate administration of the investigational products specified in the protocol, the Investigator's Brochure, and the document specified in Article 16, Paragraph 7 or Article 26-2, Paragraph 7.

(3) Having sufficient time to conduct the clinical trial.

Article 43. Subinvestigators etc.

1. When the clinical trial is conducted with involvement of subinvestigators or clinical research coordinators, the investigator shall prepare a list of the duties assigned to them.

2. The investigator shall fully explain the duties of the clinical trial to the subinvestigators and clinical research coordinators and provide them with the information notified pursuant to Article 20, Paragraphs 2 and 3, the information notified pursuant to Article 26-6, Paragraph 2, and other information necessary for the proper and smooth conduct of the assigned duties.

Article 44. Selection of Subjects

The investigators etc. shall select prospective subjects, taking into account the following principles:

(1) The prospective subject's health condition, symptoms, age, ability to give consent, etc. shall be carefully considered, in line with the objectives of the clinical trial, from ethical and scientific viewpoints.

(2) Any prospective subject who is incapable of giving consent shall not be selected unless it is inevitable to enroll him or her in the clinical trial.

(3) In selecting a subject who may unduly incur any disadvantage if the subject refuses to participate in the clinical trial, careful considerations shall be given so that he or she can voluntarily give consent to his or her participation.

Article 45. Responsibilities for Medical Care of Subjects

1. The investigators etc. shall explain the appropriate use of the investigational products to each subject and, as necessary, check whether each subject is properly using the investigational products.

2. If a subject is receiving treatment by another primary physician, the investigators etc. shall inform the primary physician, with prior consent of the subject, that the subject will participate in the clinical trial.

3. The head of the medical institution and the investigators etc. shall beforehand take necessary measures to ensure that adequate medical care is provided to a subject for any adverse event.

4. The investigators etc. shall inform a subject of the fact that medical care is needed for adverse event(s) of which the investigator becomes aware, if applicable.

Article 46. Deviations from Protocol

1. When the investigator has failed to comply with the protocol in order to eliminate immediate hazards to subjects or for other inevitable medical reasons, the investigator shall document all such deviations, and immediately submit the document describing those deviations and the reasons thereof to the sponsor and the head of the medical institution in the case of a sponsor-initiated clinical trial, or submit to the head of the medical institution in the case of a investigator-initiated clinical trial.

2. The provisions of Article 10, Paragraphs 2 through 6 shall apply *mutatis mutandis* to the submission of documents as stipulated in the preceding paragraph in the case of a sponsor-initiated clinical trial. In this case, "person who intends to sponsor a clinical trial" and "head of the medical institution" in these provisions shall be read as "investigator" and "sponsor," respectively.

Article 47. Case Report Form (CRF) etc.

1. The investigators etc. shall prepare CRFs accurately in compliance with the protocol, and shall affix the name(s) and seal, or sign the forms.

2. Any changes or corrections made to a CRF shall be dated and affixed with the seal, or signed by the investigators etc.

3. The investigator shall inspect the CRFs prepared by the subinvestigator(s) and confirm the content thereof to affix the name and seal, or sign the forms.

Article 48. Reporting of Adverse Drug Reactions that Occurred during Clinical Trial

1. The investigator shall submit a written summary of the clinical trial status to the head of the medical institution, as appropriate.

2. In the case of a sponsor-initiated clinical trial, if the investigator becomes aware of death or any serious adverse event suspected to be attributable to adverse reactions to the

investigational product, the investigator shall immediately report the fact to the head of the medical institution and notify the sponsor of the fact. In such cases, the investigator shall provide additional relevant information upon the request of the sponsor, the head of the medical institution, or the IRB etc.

3. In the case of an investigator-initiated clinical trial, if the investigator becomes aware of death or any serious adverse event suspected to be attributable to adverse reactions to the investigational product, the investigator shall immediately report the fact to the head of the medical institution (if the clinical trial is conducted jointly at more than one medical institution according to a single protocol, then including the investigators of the other medical institutions) and notify the investigational product provider of the fact. In such cases, the investigator shall provide additional relevant information upon the request of the investigational product provider, the head(s) of the medical institution(s), or the IRB etc.

Article 49. Premature Termination etc. of Clinical Trial

1. If the clinical trial is suspended or prematurely terminated in accordance with the notification pursuant to Article 40, Paragraph 2, the investigator shall promptly notify the subjects of the fact, and shall provide appropriate medical care to the subjects and take other necessary measures.

2. If the investigator suspends or prematurely terminates a clinical trial at his or her discretion, the investigator shall promptly report the fact and the reason thereof in writing to the head of the medical institution.

3. Upon completion of a clinical trial, the investigator shall report the completion in writing and submit a written summary of the trial's outcome to the head of the medical institution.

Section 4. Informed Consent of Subjects

Article 50. Providing Written Information for Explanation and Obtaining Written Informed Consent

1. Prior to a subject's participation in the clinical trial, the investigators etc. shall obtain written informed consent from the subject by appropriately explaining in writing the trial-related information, such as the content of the clinical trial, to the subject so that he or she will understand the information.

2. Notwithstanding the provisions of the preceding paragraph, a subject who is incapable of giving consent may be enrolled in a trial on the consent given by the subject's legally acceptable representative.

3. When the consent of the subject's legally acceptable representative is obtained pursuant to the preceding paragraph, the investigators etc. shall prepare records of the consent and the relationship of the legally acceptable representative to the subject.

4. Notwithstanding the provisions of Paragraph 2, the investigator etc. shall not enroll any subject who is incapable of giving consent to participation in a clinical trial in which no clinical benefit of the investigational product to the subject is anticipated, excluding the cases stated in Article 7, Paragraph 2 or Article 15-4, Paragraph 2.

5. The investigators etc. shall give the prospective subject (or the legally acceptable representative if applicable; the same shall apply in Articles 51 though 53) the opportunity to make inquiries about the content of the written information and other trial-related matters. All inquiries should be answered to the satisfaction of the subject.

Article 51. Written Information

1. When providing written information as specified in Paragraph 1 of the preceding article, the investigators etc. shall give each subject the written information that should include the following information:

   (1) That the clinical trial involves research

   (2) The objectives of the clinical trial

   (3) The name, title and contact information of the investigator

   (4) Clinical trial design

   (5) The expected benefits to the subject's physical and mental health from using the investigational product (or that there is no intended clinical benefit to the subject, if applicable), and the potential disadvantages to the subject

   (6) Description of alternative procedure(s) or course(s) of treatment

   (7) Duration of the subject's participation in the clinical trial

   (8) That the subject may withdraw from the clinical trial at any time

   (9) That the subject's refusal of or withdrawal from participation in the trial does not cause any disadvantage to the subject

   (10) That the monitors, auditors, and IRB etc. are given direct access to the source documents on the condition that confidentiality of the subject is fully secured

   (11) That the subject's identity will be kept confidential

   (12) The contact information of the medical institution in the event of trial-related injury

   (13) That necessary treatment is available to the subject in the event of trial-related injury

   (14) Description of compensation in the event of any trial-related injury

   (15) Type of the IRB reviewing/deliberating the appropriateness of the clinical trial, etc., matters reviewed/deliberated by each IRB, and other matters concerning the IRB involved in the clinical trial

   (16) Other necessary matters concerning the clinical trial

2. The written information shall not include any language that causes the prospective subject to waive or to appear to waive any legal rights, or any language that eliminates or reduces, or appears to eliminate or reduce, the liabilities of the sponsor, the sponsor-investigator, the medical institution or investigators etc.

3. Wording and expressions in the written information shall be as plain as possible.

Article 52. Signing Informed Consent Forms etc.

1. The informed consent specified in Article 50, Paragraph 1 or 2, shall not become valid unless both the investigators etc. who have given the explanation and the prospective subject (or if a witness is present as specified in Paragraph 3, then the prospective subject and the witness; the same shall apply in the following article) date, affix the name and seal, or sign the consent form in which the prospective subject has specified that he or she gives consent to participation in the clinical trial upon fully understanding the content of the clinical trial that are provided in the written information (hereinafter referred to as "informed consent form").

2. The informed consent specified in Article 50, Paragraph 1 or 2, shall not be obtained such a way that the investigators etc. coerce or unduly influence a subject or the subject’s legally acceptable representative to give consent.

3. The provision of written information to and the obtainment of written informed consent from a prospective subject, as specified in Article 50, Paragraph 1, who is incapable of reading the written information (excluding the prospective subjects specified in Article 50, Paragraph 2), shall be performed in the presence of a witness.

4. The witness specified in the preceding paragraph shall neither be the investigators etc. nor the clinical research coordinator.

Article 53. Delivery of Informed Consent Form

Investigators etc. shall give the subject (or the subject’s legally acceptable representative, if applicable; the same shall apply in the following article) a copy of the informed consent form affixed with the names and seals, or signed by the investigators etc. and the prospective subject.

Article 54. Cases Where Information Influencing the Subject's Willingness Is Obtained

1. When any information that might influence the subject's willingness to continue to participate in the ongoing trial is obtained, the investigators etc. shall immediately provide the subject with such information, document the communication of the information and ascertain whether the subject is willing to continue his or her participation in the ongoing trial. In such cases, the provisions of Article 50, Paragraph 5 and Article 52, Paragraph 2 shall apply *mutatis mutandis*.

2. In the cases specified in the preceding paragraph, the investigator shall revise the written information promptly whenever it is deemed necessary.

3. When the written information is revised pursuant to the preceding paragraph, the investigator shall report the fact to the head of the medical institution and obtain the subject's consent to continue his or her participation in the clinical trial. In such cases, the provisions of Articles 51 through 53 shall apply *mutatis mutandis*.

Article 55. Life-Saving Clinical Trial in Case of Emergency

1. In the clinical trials specified in Article 7, Paragraph 3 or Article 15-4, Paragraph 3, the investigators etc. may enroll a subject without obtaining the consent of the subject or the subject's legally acceptable representative only when the subject fulfills all the following conditions:

   (1) The prospective subject is in an emergency and obviously at life-threatening risk.

   (2) Currently available treatments are unlikely to achieve sufficient therapeutic effects in the prospective subject.

   (3) There is a sufficient possibility of saving the life of the prospective subject in a life-threatening condition by using the test drug.

   (4) The potential disadvantages which the subject may incur in the clinical trial are minimized.

   (5) The prospective legally acceptable representative cannot immediately be contacted for consent.

2. In the case specified in the preceding paragraph, the investigators etc. shall appropriately provide the subject or the prospective legally acceptable representative with the trial-related information promptly and obtain the written informed consent to participation in the clinical trial.

Chapter V. Standards for Documents Submitted in Reexamination etc.

Article 56. Standards for Documents Submitted in Reexamination etc.

The provisions of Articles 4 through 6; Article 7 (excluding Item (1) of Paragraph 3); Article 9; Article 10 (excluding Item (2) of Paragraph 1); Articles 11 through 15; Articles 16 through 23; Article 24, Paragraphs 1 and 2; Article 25; Article 26; and Articles 27 through 55 of this Ministerial Ordinance shall apply *mutatis mutandis* to the data collection and generation for the documents specified in Article 14-4, Paragraph 4 and Article 14-6, Paragraph 4 of PAA concerning clinical trials on drugs conducted by the person who has been granted approval as specified in Article 14 or Article 19-2 of PAA (including cases where these provisions shall apply *mutatis mutandis* in Article 19-4 of PAA). In such cases, the following references in the above-mentioned provisions (including their headings) shall be read as follows: "clinical trial" shall be read as "post-marketing clinical study," "protocol" shall be read as "post-marketing

protocol," "investigator" shall be read as "post-marketing clinical study investigator," "clinical trial in-country representative" shall be read as "post-marketing clinical study in-country representative," "coordinating investigator" shall be read as "post-marketing clinical study coordinating investigator," "coordinating committee" shall be read as "post-marketing clinical study coordinating committee," "subinvestigator" shall be read as "post-marketing clinical study subinvestigator," "investigators etc." shall be read as "post-marketing clinical study investigators etc," "sponsor" shall be read as "post-marketing clinical study sponsor," "investigational product storage manager" shall be read as "post-marketing clinical study drug storage manager," "clinical research coordinator" shall be read as “post-marketing clinical research coordinator," and "IRB" shall be read as "post-marketing clinical study IRB," “expert IRB” shall be read as “post-marketing clinical study expert IRB,” “IRB etc.” shall be read as “post-marketing clinical study IRB etc.” Also, in those provisions (including their headings, but excluding Article 11; Article 16, Paragraphs 1, 2, and 5 through 7; Article 17; and Article 39), "investigational products" shall be read as "post-marketing clinical study drugs," “all or any of” in Article 7, Paragraph 1, Item (2), shall be read as “any of,” “investigational products" in Article 11 shall be read as "post-marketing clinical study drugs supplied in such a state that the subject, post-marketing clinical study investigators etc., or post-marketing clinical research coordinators cannot distinguish the test drug from the comparator (hereinafter referred to as "blinded")," “all or any of” in Article 12, Paragraph 1, and Article 13, Paragraph 1, shall be read as “any of,” "For clinical trial use only" in Article 16, Paragraph 1, Item (1), shall be read as "For post-marketing clinical study use only," "investigational products" in Paragraphs 1, 2 and 5 through 7 of the same article shall be read as "blinded post-marketing clinical study drugs," “Proposed” in Article 16, Paragraph 2, Item (1), shall be read as “Approved,” “investigational product” in Article 17 shall be read as “blinded post-marketing clinical study drug,” "any event […]specified in Article 80-2, Paragraph 6 of PAA" in Article 20, Paragraphs 2, shall be read as "any event specified in Article 77-4-2 of PAA [limited to those which occurred during the post-marketing clinical study and which have been specified in Article 253, Paragraph 1, Items (1) and (2), of the Ordinance for Enforcement of the PAA (MHW Ordinance No. 1 of 1961)]," “the date of submission of the first clinical trial notification etc.” shall be read as “the date which the Minister of Health, Labour and Welfare designated when marketing approval is granted to the test drug,” "the Investigator’s Brochure" and "immediately notify the investigator" in Article 20, Paragraphs 3, shall be read as "the package insert" and "immediately notify the post-marketing clinical study investigator," respectively, “the protocol and the Investigator’s Brochure” in Article 20, Paragraph 4, shall be read as “the post-marketing protocol,” "until the day on which marketing approval of the test drug is obtained (or the day 3 years after the date of notification in the case of a notification pursuant to Article 24, Paragraph 3) or the day 3 years after the date of premature termination or completion of the clinical trial, whichever comes later" in Article 26, Paragraph 1, shall be read as "for 5 years after completion of the reexamination or reevaluation of," “until the day on which marketing approval of the test drug is obtained (or the day of notification in the case of a notification pursuant to Article 24, Paragraph 3 or Article 26-10, Paragraph 3) or the day 3 years after the date of premature termination or completion of the clinical trial, whichever comes later” in

Article 34 shall be read as “until the day of completion of reexamination or reevaluation,” "Clinical Trial Office" in the heading of Article 38 shall be read as "Post-marketing Clinical Study Office," "investigational products" in Article 39 shall be read as "blinded post-marketing clinical study drugs," "notified, or notified by sponsor, pursuant to Article 24, Paragraph 3, that the sponsor has decided not to include the clinical trial data in the application, or notified by the sponsor-investigator, pursuant to Article 26-10, Paragraph 3, that the sponsor-investigator has been informed that the clinical trial data will not be submitted in the application" in Article 40, Paragraph 2, shall be read as "notified," "until the day on which marketing approval of the test drug is obtained (or the day 3 years after the date of notification in the case of a notification pursuant to Article 24, Paragraph 3 or Article 26-10, Paragraph 3) or the day 3 years after the date of premature termination or completion of the clinical trial, whichever comes later" in Article 41, Paragraph 2, shall be read as "until the day of completion of the reexamination or reevaluation of," and "the protocol and the Investigator’s Brochure" in Article 42, Item (2), shall be read as "the post-marketing protocol."

Chapter Ⅵ. Standards for Sponsoring Clinical Trials etc.

Article 57. Standards Specified in MHLW Ordinance under the Article 80-2, Paragraph 1 of PAA

The provisions of Article 4, Paragraph 1; Article 5; Article 7, Paragraph 1 (excluding Items (9) and (11) through (13)); Article 8, Paragraph 1; Article 11; Article 13 (excluding Article 13, Paragraph 1, Items (10), (12) through (15), and (17)); Article 14 and Article 15 shall apply *mutatis mutandis* to sponsoring clinical trials as stipulated in Article 80-2, Paragraph 1 of PAA. In this case, "related to sponsoring and managing the clinical trial, such as […] selection of medical institutions and investigators, control/accountability of investigational products, collection of information on adverse drug reactions, record keeping, etc.” in Article 4, Paragraph 1, shall be read as "of […] control/accountability of investigational products and record keeping," "studies on the quality, toxicity, and pharmacological effects of the test drug and other studies required for sponsoring the clinical trial" in Article 5 shall be read as "studies on the quality, toxicity, and pharmacological effects of the test drug," and "pursuant to the preceding article" in Article 13, Paragraph 1, shall be read as "related to sponsoring and managing the clinical trial."

Article 58. Standards Specified in MHLW Ordinance under the Article 80-2, Paragraph 4 of PAA

1. In the case of a sponsor-initiated clinical trial, the provisions of Articles 27 through 55 (excluding Article 29, Paragraph 1, Item (2); Article 31, Paragraph 4; Article 32, Paragraphs 4 and 7; Article 33, Paragraph 3; and Article 48, Paragraph 3) shall apply *mutatis mutandis* to the conduct of the clinical trial specified in Article 80-2, Paragraph 4 of PAA.

2. In the case of an investigator-initiated clinical trial, the provisions of Article 15-2, Paragraph 1; Article 15-3; Article 15-4, Paragraph 1 (excluding Items (10) and (12) through (14)); Article 15-5, Paragraph 1; Article 15-7 (excluding Items (9), (10), and (12) through (14)); Article 15-9; Article 26-2 (excluding Paragraph 1, Item (5) and Paragraph 7); Article 26-7, Paragraphs 1 and 3; Article 26-12, Item (5); Articles 27 through 55 (excluding Article 29, Paragraph 1, Item (1); Article 32, Paragraphs 6 and 8; and Article 48, Paragraph 2) shall apply *mutatis mutandis* to the conduct of the clinical trial specified in Article 80-2, Paragraph 4 of PAA. In this case, "related to preparing and managing the clinical trial, such as preparation of a protocol, control/accountability of investigational products, collection of information on adverse drug reactions, record keeping, etc." in Article 15-2, Paragraph 1, shall be read as "of control/accountability of investigational products and record keeping," "studies on the quality, toxicity and pharmacological effects of the test drug and other studies required for the conduct of the clinical trial" in Article 15-3 shall be read as "studies on the quality, toxicity and pharmacological effects of the test drug," "manufacture of […] manufactured quantity" and "quality, such as its stability" in Article 26-2, Paragraph 5, shall be read as "manufactured quantity" and "quality," respectively, and "appropriately retain" in Article 26-12 shall be read as "retain."

Article 59. Standards Specified in MHLW Ordinance under the Article 80-2, Paragraph 5 of PAA

The provisions of Article 16 (excluding Paragraph 1, Item (5) and Paragraph 7), Article 21, Paragraph 1; Article 26, Paragraph 1 (excluding Items (1) through (4)) and Paragraph 2, shall apply *mutatis mutandis* to the management of clinical trials as stipulated in Article 80-2, Paragraph 5 of PAA. In this case, "manufacture of […] manufactured quantity" and "quality, such as its stability" in Article 16, Paragraph 5 shall be read as "manufactured quantity" and "quality," respectively, and "appropriately retain" in Article 26, Paragraph 1, shall be read as "retain."

Supplementary Provisions

Article 1. Effective Date

This Ministerial Ordinance shall come into effect as from April 1, 1997.

Article 2. Interim Measures Concerning Standards for Documents Submitted in Product Application

1. With regard to the documents stipulated in Article 14, Paragraph 3 of PAA, when the relevant data have already been collected or generated, or are being collected or generated, at the time of the implementation of this Ministerial Ordinance, "the provisions of the following article through Article 55" in Article 3 shall be read as "the provisions of Article 30, Paragraph 1; Article 35; Article 44; Article 47, Paragraph 1; Article 50, Paragraphs 1 and 2, and the provisions of Article 67 of the Ordinance for Enforcement of the Pharmaceutical Affairs Act (MHW Ordinance No. 1 of 1961) prior

to revision by Article 1 of the Ministerial Ordinance to Partially Revise the Ordinance for Enforcement of the Pharmaceutical Affairs Act (MHW Ordinance No. 29 of 1997), etc.," and "obtain written informed consent from the subject appropriately" in Article 50, Paragraph 1, shall be read as "obtain informed consent from the subject appropriately."

2. With regard to the documents stipulated in Article 14, Paragraph 3 of PAA, when the relevant data were collected or generated in sponsor-initiated clinical trials under Article 80-2, Paragraph 1 of PAA, for which the request was submitted by June 30, 1997, or in clinical trials whose protocols were submitted pursuant to Paragraph 2 of the same article by the same day (excluding the data specified in the preceding paragraph), "the next article" in Article 3 shall be read as "the next article through Article 6, Article 7 (excluding Paragraph 1, Item (9)), Articles 8 through 12, Article 13 (excluding Items (9) to (13) and Item (15)), Article 14, Article 15, Article 16 (excluding Paragraph 6), Articles 17 through 20, Articles 24 through 27, Article 28, Paragraphs 2 and 3, Articles 29 through 35, Article 38, Articles 40 through 50, Article 51 (excluding Paragraph 1, Item (10)) and Article 52."

3. With regard to the documents stipulated in Article 14, Paragraph 3 of PAA, when the relevant data were collected or generated in sponsor-initiated clinical trials under Article 80-2, Paragraph 1 of PAA, for which the request was submitted by March 31, 1998, or in clinical trials whose protocols were submitted pursuant to Paragraph 2 of the same article by the same day (excluding the data specified in Paragraph 1 and the preceding paragraph), "the next article" in Article 3 shall be read as "the next article to Article 6, Article 7 (excluding Paragraph 1, Item (9)), Articles 8 through 12, Article 13 (excluding Items (12) and (15)), Articles 14 through 20, Articles 24 through 27, Article 28, Paragraphs 2 and 3, Articles 29 through 35, Articles 38 through 50, Article 51 (excluding Paragraph 1, Item (10)) and Article 52."

Article 3. Interim Measures Concerning Standards for Documents Submitted in Reexamination, etc.

1. With regard to the documents stipulated in Article 14-4, Paragraph 4 and Article 14-5, Paragraph 4 of PAA, when the relevant data were collected or generated in post-marketing clinical studies, for which the request was submitted by June 30, 1997, the following references in Article 56 shall be read as follows: “Paragraph 3, Item (1)" shall be read as "Paragraph 1, Item (9) and Paragraph 3, Item (1)," "Articles 11 through 16" shall be read as "Article 12, Article 13 (excluding Items (9) through (13) and Item (15)), Article 14, Article 15 and Article 16 (excluding Paragraph 6)," "Article 23" shall be read as "Article 20," "Article 25" shall be read as "Articles 25 through 27; Article 28, Paragraphs 2 and 3; Articles 29 through 35; Article 38; Articles 40 through 50; Article 51 (excluding Paragraph 1, Item (10)); and Article 52."

2. With regard to the documents stipulated in Article 14-4, Paragraph 4 and Article 14-5, Paragraph 4 of PAA, when the relevant data were collected or generated in post-marketing clinical studies, for which the request was submitted by March 31, 1998 (excluding the post-marketing clinical studies specified in the preceding paragraph), the following references in Article 56 shall be read as follows: “Paragraph 3, Item (1)" shall

be read as "Paragraph 1, Item (9), and Paragraph 3, Item (1)," "Article 11" shall be read as "Articles 11 and 12, Article 13 (excluding Items (12) and (15)) and Article 14," "Article 23" shall be read as "Article 20," "Article 25" shall be read as "Articles 25 through 27; Article 28, Paragraphs 2 and 3; Articles 29 through 35; Articles 38 through 50; Article 51 (excluding Paragraph 1, Item (10)); and Article 52."

Article 4. Interim Measures Concerning Standards Specified in MHW Ordinance under Article 80-2, Paragraph 1 of PAA

1. When clinical trial protocols conforming to the provisions of Article 7, Paragraph 1 (excluding Items (2) to (4) and Items (9) through (13)) have already been prepared at the time of implementation of this Ministerial Ordinance, notwithstanding the provisions of Article 57, the provisions of Article 67 (excluding Items (7) to (11)) of the Ordinance for Enforcement of Pharmaceutical Affairs Act (MHW Ordinance No.1, 1961; referred to as "the former Ordinance for Enforcement" in Article 6 of the Supplementary Provisions) prior to revision by Article 1 of the Ministerial Ordinance to Partially Revise the Ordinance for Enforcement of the Pharmaceutical Affairs Act (MHW Ordinance No. 29 of 1997) shall apply to sponsoring clinical trials under Article 80-2, Paragraph 1 of PAA.

2. When the provisions of Article 57 apply to clinical trials whose protocols were submitted pursuant to Article 80-2, Paragraph 2 of PAA between April 1 and June 30, 1997 (excluding the clinical trials specified in the preceding paragraph), "Items (11) and (13)" in Article 57 shall be read as "Item (9)."

3. When the provisions of Article 57 apply to clinical trials whose protocols were submitted pursuant to Article 80-2, Paragraph 2 of PAA between July 1, 1997 and March 31, 1998 (excluding the clinical trials specified in Paragraph 1), "Items (11) and (13)" in Article 57 shall be read as "Item 11)."

Article 5. Interim Measures Concerning Standards Specified in MHW Ordinance under Article 80-2, Paragraph 4 of PAA

1. When clinical trial protocols conforming to the provisions of Article 7, Paragraph 1 (excluding Items (2) through (4) and Items (9) through (13)) have already been prepared at the time of implementation of this Ministerial Ordinance, the provisions of Article 30, Paragraph 1; Article 35; Article 44; Article 47, Paragraph 1; and Article 50, Paragraphs 1 and 2, shall apply to persons conducting the sponsor-initiated clinical trials under Article 80-2, Paragraph 4 of PAA, notwithstanding the provisions of Article 58. In such cases, "written informed consent from the subject by appropriately explaining in writing" in Article 50, Paragraph 1 shall be read as "informed consent from the subject by appropriately explaining."

2. When the provisions of Article 58 apply to persons conducting the sponsor-initiated clinical trials under Article 80-2, Paragraph 1 of PAA between April 1 and June 30, 1997, or to persons conducting the sponsor-initiated clinical trials whose protocols were submitted pursuant to Paragraph 2 of the same article by the same day (excluding

persons specified in the preceding paragraph), "Article 27" in Article 58 shall be read as "Article 27; Article 28, Paragraphs 2 and 3; Articles 29 through 35; Article 38; Articles 40 through 50 ; Article 51 (excluding Paragraph 1, Item (10)) and Article 52."

3. When the provisions of Article 58 apply to persons conducting the sponsor-initiated clinical trials under Article 80-2, Paragraph 1 of PAA between July 1, 1997 and March 31, 1998 (excluding persons conducting the sponsor-initiated clinical trials specified in Paragraph 1 and the preceding paragraph), "Article 27" in Article 58 shall be read as "Article 27; Article 28, Paragraphs 2 and 3; Articles 29 through 35; Articles 38 through 50; Article 51 (excluding Paragraph 1, Item (10)) and Article 52."

Article 6. Interim Measures for the Standards Specified in MHW Ordinance under Article 80-2, Paragraph 5 of PAA

1. When clinical trial protocols conforming to the provisions of Article 7, Paragraph 1 (excluding Items (2) through (4) and (9) through (13)) have already been prepared at the time of implementation of this Ministerial Ordinance, the provisions of Article 67, Items (7), (8) and (10) of the former Ordinance for Enforcement shall apply to the clinical trial management under Article 80-2, Paragraph 5 of PAA to be performed by persons sponsoring the clinical trials, notwithstanding the provisions of Article 59.

2. When the provisions of Article 59 apply to persons sponsoring the clinical trials under Article 80-2, Paragraph 1 of PAA between April 1 and June 30, 1997, or to persons sponsoring clinical trials whose protocols were submitted pursuant to Paragraph 2 of the same article by the same day (excluding the persons specified in the preceding paragraph), "Paragraph 7" in Article 59 shall be read as "Paragraphs 6 and 7" and "Article 21, Paragraph 1 and" in Article 59 shall be read as "and."

3. When the provisions of Article 59 apply to persons sponsoring the clinical trials under Article 80-2, Paragraph 1 of PAA between July 1, 1997 and March 31, 1998 (excluding the persons specified in Paragraph 1 and the preceding paragraph), "Article 21, Paragraph 1 and" shall be read as "and."

Supplementary Provisions (MHW Ordinance No. 127 of October 20, 2000) (excerpt)

(Effective Date)

1. This Ministerial Ordinance shall come into effect as from the date of implementation of the Act for Partial Revision of the Cabinet Act (Act No. 88 of 1999) (January 6, 2001).

Supplementary Provisions (MHLW Ordinance No. 36 of March 26, 2001) (excerpt)

(Effective Date)

1. This Ministerial Ordinance shall come into effect as from the date of implementation of the Act on the Arrangement of Acts related to the Use of Information and Communication Technology for the Issuance of Documents (April 1, 2001).

Supplementary Provisions (MHLW Ordinance No. 14 of February 22, 2002) (excerpt)

1. This Ministerial Ordinance shall come into effect as from the date of implementation of the Act for Partial Revision of the Act on Public Health Nurses, Midwives and Nurses (March 1, 2002).

2. Forms as prescribed prior to revision by this Ministerial Ordinance, which exist at the time of implementation of this Ministerial Ordinance, may be, for the time being, used after necessary modification.

Supplementary Provisions (MHLW Ordinance No. 106 of June 12, 2003)

1. This Ministerial Ordinance shall come into effect as from the date of implementation of the provisions of Article 1, Items (1) of the supplementary provisions to the Act for Partial Revision of the Pharmaceutical Affairs Act and the Blood Collection and Donation Services Control Act (July 30, 2003).

2. The provisions then in force shall remain applicable to clinical trials that are being conducted, in accordance with a contract concluded pursuant to Article 12, Paragraph 1 and Article 13, Paragraph 1 of Ministerial Ordinance on Good Clinical Practice for Drugs prior to revision by this Ministerial Ordinance, at the time of implementation of this Ministerial Ordinance.

Supplementary Provisions (MHLW Ordinance No. 172 of December 21, 2004)

Article 1. Effective Date

This Ministerial Ordinance shall come into effect as from the date of implementation of the provisions of Article 2 of the Act for Partial Revision of the Pharmaceutical Affairs Act and the Blood Collection and Donation Services Control Act (April 1, 2005).

Article 2. Interim Measure

Notwithstanding the provisions of Ministerial Ordinance on Good Clinical Practice for Drugs as revised by this Ministerial Ordinance, the provisions then in force shall remain applicable to clinical studies on drugs that have already been conducted or that are ongoing at the time of implementation of this Ministerial Ordinance.

Supplementary Provisions (MHLW Ordinance No. 72 of March 31, 2006) (excerpt)

Article 1. Effective Date

This Ministerial Ordinance shall come into effect as from April 1, 2006.

Article 2. Interim Measure

Notwithstanding the provisions of the Ministerial Ordinance on Good Clinical Practice for Drugs as revised by this Ministerial Ordinance (hereinafter referred to as the "New Ordinance" in the next article), the provisions then in force shall remain applicable to clinical studies on drugs that have already been conducted or that are ongoing at the time of implementation of this Ministerial Ordinance.

Article 3.

Notwithstanding the provisions of the New Ordinance, the provisions then in force shall remain applicable to clinical studies on drugs (excluding those falling within the scope of the preceding paragraph), for which protocols (limited to those meeting the provisions of Article 7, Paragraphs 1 through 3 or Article 15-4, Paragraphs 1 through 3 of the Ministerial Ordinance on Good Clinical Practice for Drugs) or post-marketing clinical study protocols (limited to those meeting the provisions of Article 7, Paragraphs 1 through 3 [excluding Paragraph 3, Item (1)] applied *mutatis mutandis* in Article 56 of the Ministerial Ordinance on Good Clinical Practice for Drugs prior to revision by this Ministerial Ordinance) have already been prepared at the time of implementation of this Ministerial Ordinance.

Supplementary Provisions (MHLW Ordinance No. 24 of February 29, 2008) (excerpt)

Article 1. Effective Date

This Ministerial Ordinance shall come into effect as from April 1, 2008. However, the revised provisions of Article 20, Paragraphs 2 and 3, the revised provisions of Article 28, Paragraph 3, the revised provisions of Article 31, Paragraph 2 and Article 40, Paragraph 1 (limited to the part adding "and Paragraph 3" after "Article 20, Paragraph 2"), the revised provisions of Article 43, Paragraph 2 and the revised provisions of Article 56, Paragraph 1 (limited to the part adding "and Paragraph 3" after "Article 20, Paragraph 2") shall come into effect as from April 1, 2009.

Article 2. Interim Measure

Notwithstanding the provisions of the Ministerial Ordinance on Good Clinical Practice for Drugs as revised by this Ministerial Ordinance (hereinafter referred to as the "New Ordinance" in the following article), the provisions then in force shall remain applicable to clinical studies on drugs that have already been conducted or that are ongoing at the time of implementation of this Ministerial Ordinance.

Article 3.

Notwithstanding the provisions of the New Ordinance, the provisions then in force shall remain applicable to clinical studies on drugs (excluding those falling within the scope of the preceding article), for which protocols (limited to those meeting the provisions of Article 7, Paragraphs 1 to 3 or Article 15-4, Paragraphs 1 to 3 of the Ministerial

Ordinance on Good Clinical Practice for Drugs) or post-marketing protocols (limited to those meeting the provisions of Article 7, Paragraphs 1 to 3 [excluding Paragraph 3, Item 1] applied *mutatis mutandis* in Article 56 of the Ministerial Ordinance on Good Clinical Practice for Drugs prior to revision by this Ministerial Ordinance) have already been prepared at the time of implementation of this Ministerial Ordinance.

Supplementary Provisions (MHLW Ordinance No. 163 of November 28, 2008) (excerpt)

Article 1. Effective Date

This Ministerial Ordinance shall come into effect as from the date of implementation of the Act on General Incorporated Associations and General Incorporated Foundations (December 1, 2008).

Supplementary Provisions (MHLW Ordinance No. 68 of March 31, 2009)

Article 1. Effective Date

This Ministerial Ordinance shall come into effect as from April 1, 2009.

Supplementary Provisions (MHLW Ordinance No. 161 of December 28, 2012) (excerpt)

Article 1. Effective Date

This Ministerial Ordinance shall come into effect as from the date of promulgation.

Article 2. Interim Measure

1. The provisions then in force shall remain applicable, until June 30, 2014, to the reporting (which refers to the reporting as specified in Article 273, Paragraph 3 of the Ordinance for Enforcement of the Pharmaceutical Affairs Act [hereinafter referred to as the "Ordinance for Enforcement"]; the same shall apply hereinafter) by a person sponsoring a clinical trial (hereinafter referred to as "sponsor") for which the protocol (limited to that which meets the requirements as specified in Article 7, Paragraphs 1 to 3 of the Ministerial Ordinance on Good Clinical Practice for Drugs [hereinafter referred to as the “GCP Ordinance”]) has already been prepared before the implementation of this Ministerial Ordinance.

2. Notwithstanding the provisions of the preceding paragraph, where the reporting by the sponsor under the same paragraph is made by June 30, 2014, the provisions of Article 273, Paragraph 3 of the Ordinance for Enforcement of the Pharmaceutical Affairs Act, as revised by Article 1, (hereinafter referred to as the "New Ordinance for Enforcement") may be applied to such reporting at the discretion of the sponsor.

3. The provisions of Article 273, Paragraph 3 of the New Ordinance for Enforcement shall apply to the reporting by the sponsor under Paragraph 1 as from July 1, 2014.

4. The provisions of Article 273, Paragraph 3 of the New Ordinance for Enforcement shall apply, as from July 1, 2014, to the reporting by the sponsor or sponsor-investigator (which refers to the sponsor-investigator as specified in Article 273, Paragraph 3 of the New Ordinance for Enforcement; the same shall apply hereinafter) of a clinical trial for which the protocol is prepared after the implementation of this Ministerial Ordinance,.

5. The reporting by the sponsor or sponsor-investigator under the preceding paragraph that is made by June 30, 2014 shall be deemed as the one specified in Article 273, Paragraph 3 of the Ordinance for Enforcement prior to the revision by Article 1, and the provisions of the same paragraph shall apply to such reporting.

6. Notwithstanding the provisions of the preceding paragraph, the provisions of Article 273, Paragraph 3 of the New Ordinance for Enforcement may be applied to the reporting under the same paragraph at the discretion of the sponsor or sponsor-investigator.

Article 3.

1. The provisions then in force shall remain applicable, until June 30, 2014, to the notification (which refers to the notification under Article 20, Paragraph 2 of GCP Ordinance; the same shall apply hereinafter) by the sponsor of a clinical trial for which the protocol has already been prepared before the implementation of this Ministerial Ordinance.

2. Notwithstanding the provisions of the preceding paragraph, where the notification by the sponsor under the same paragraph is made by June 30, 2014, the provisions of Article 20, Paragraph 2 of the GCP Ordinance, as revised by Article 2, (hereinafter referred to as the “New GCP Ordinance”) may be applied to such notification at the discretion of the sponsor.

3. The provisions of Article 20, Paragraph 2 of the New GCP Ordinance shall apply to the notification by the sponsor under Paragraph 1 as from July 1, 2014.

4. The provisions of Article 20, Paragraph 2 of the New GCP Ordinance shall apply, as from July 1, 2014, to the notification by the sponsor of a clinical trial for which the protocol is prepared after the implementation of this Ministerial Ordinance.

5. The notification by the sponsor under the preceding paragraph that is made by June 30, 2014 shall be deemed as the one specified in Article 20, Paragraph 2 of the GCP Ordinance prior to the revision by Article 2, and the provisions of the same paragraph shall apply to such notification.

6. Notwithstanding the provisions of the preceding paragraph, the provisions of Article 20, Paragraph 2 of the New GCP Ordinance may be applied to the notification under the same paragraph at the discretion of the sponsor under the same paragraph.

Article 4. (Partial Revision of the Ministerial Ordinance on Use of Information and Communication Technology for Document Retention, etc. Conducted by Private Entities, etc. in Accordance with Laws and Regulations under the Jurisdiction of the Ministry of Health, Labour and Welfare)

The Ministerial Ordinance on Use of Information and Communication Technology for Document Retention, etc. Conducted by Private Entities, etc. in Accordance with Laws and Regulations under the Jurisdiction of the Ministry of Health, Labour and Welfare (MHLW Ordinance No. 44, 2005) shall be partially revised as follows.

Under the section of the Ministerial Ordinance on Good Clinical Practice for Drugs as shown in the Appendix 2, “Article 18, Paragraph 2” shall be revised as “Article 18” and “Article 26-4, Paragraph 2” shall be revised as “Article 26-4.” Under the section of the Ministerial Ordinance on Good Clinical Practice for Medical Devices as shown in the Appendix 2, “Article 26, Paragraph 2” shall be revised as “Article 26” and “Article 37, Paragraph 2” shall be revised as “Article 37.”