

Provisional Translation (as of August 2012)*

Ministerial Ordinance on Good Laboratory Practice for Nonclinical Safety Studies of Medical Devices

Ordinance of the Ministry of Health, Labour and Welfare No.37 of March 23, 2005 (as last amended by the Ordinance of the Ministry of Health, Labour and Welfare No.115 of June 13, 2008)

In accordance with the provisions of Article 14, paragraph (3) of the Pharmaceutical Affairs Act (Act No.145 of 1960) (including cases where it is applied mutatis mutandis pursuant to the same article, paragraph (9) and Article 19-4 of the same Act) and Article 14-4, paragraph (4) and Article 14-6, paragraph (4) of the same Act (including cases where it is applied mutatis mutandis pursuant to Article 19-4 of the same Act), the Ministerial Ordinance on Good Laboratory Practice (GLP) for Nonclinical Safety Studies of Medical Devices shall be established as follows.

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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

(Purpose)

Article 1 In standards prescribed by the Minister of Health, Labour and Welfare pursuant to the provision of Article 14, paragraph (3) of the Pharmaceutical Affairs Act (Act No.145 of 1960; hereinafter referred to as “the Act”) (including cases where it is applied mutatis mutandis pursuant to the same Article, paragraph (9) and Article 19-2, paragraph (5) of the Act; the same hereinafter), and Article 14-4, paragraph (4) and Article 14-6, paragraph (4) of the Act (including cases where it is applied mutatis mutandis pursuant to Article 19-4; the same hereinafter), this Ordinance shall provide for matters concerning standard for conduct of nonclinical safety studies of medical devices [limited to the generation and collection of data on biological safety studies conducted at test facilities or test sites using test systems (hereinafter referred to as “study”), in data prescribed in Article 40, paragraph (1), item (v), (b) and (d) (including cases where it is applied mutatis mutandis pursuant to Article 102, paragraph (2)) and Article 59, paragraph (1) (including cases where it is applied mutatis mutandis pursuant to Article 111) of the Ordinance for Enforcement of the Pharmaceutical Affairs Act (Ordinance of Ministry of Health and Welfare No.1 of 1961), and Article 14-6, paragraph (4) of the Act (including cases where it is applied mutatis mutandis pursuant to Article 19-4 of the Act)].

(Definitions)

Article 2 (1) The term “test article” as used in this Ordinance means any medical device or its material (including any chemical or biological substance used as the material) thereof for which the safety is to be evaluated in studies.

(2) The term “control article” as used in this Ordinance means any medical device, chemical or biological substance thereof to be used for the purpose of comparison with the test article in studies.

(3) The term “test system” as used in this Ordinance means any animal, plant, microorganism, or constituent parts to which a test article is applied, or used as control thereof.

(4) The term “specimen” as used in this Ordinance means any material collected from a test system for examination or analysis.

(5) The term “raw data” as used in this Ordinance means the results of observation obtained in studies and records thereof.

(6) The term “test site” as used in this Ordinance means any site where the commissioned part of the study is conducted (excluding test facility) when a person responsible for the management and administration of test facility (hereinafter referred to as the “test facility management”) commissions the part of the study.

(Standards for conduct of study)

Article 3 Generation and collection of data prescribed in Article 14, paragraph (3), Article 14-4, paragraph (4) and Article 14-6, paragraph (4) of the Act pertaining to conduct of study by those who are intended to obtain or have obtained approval pursuant to the provision of Article 14, paragraph (1) or Article 19-2, paragraph (1) of the Act shall be as prescribed in the following Articles to Article 19.

(Sponsor’s responsibilities)

Article 4 (1) An entity who commissions a study shall notify a contractor in advance that the

study must be conducted in compliance with the provisions of this Ordinance.

- (2) In the case referred to in the preceding paragraph, an entity who commissioned a study or an entity who takes over the position (hereinafter referred to as the “sponsor”) shall confirm that the study is or was conducted in compliance with this Ordinance.
- (3) The notification in paragraph (1) and the confirmation in the preceding paragraph shall be documented and shall be retained.

Chapter II Personnel and Organization

(Personnel)

Article 5 (1) Each individual engaged in a study or belonging to the quality assurance unit prescribed in the following Article, item (ii), (including cases where it is applied mutatis mutandis pursuant to Article 19, item (ii)) shall have the education, training or experience necessary to perform their assigned functions properly and efficiently, and be capable of performing them.

- (2) Personnel engaged in a study shall take sanitation and health precautions necessary to avoid contamination of test and control articles and test systems.

(Test Facility Management)

Article 6 The test facility management shall:

- (i) for each study, designate, from among the individuals engaged in conduct of the study, an individual responsible for the overall conduct, recording, and reporting etc. of the study (hereinafter referred to as the “study director”);
- (ii) designate a responsible individual (hereinafter referred to as the “quality assurance manager”) for the unit (hereinafter referred to as the “quality assurance unit”) who assures that studies conducted at the test facility are in compliance with this Ordinance;
- (iii) ensure that the quality assurance manager performs his/her functions appropriately;
- (iv) ensure that test and control articles or mixtures thereof have been appropriately tested, where possible, for identity, purity, stability and uniformity;
- (v) ensure that facilities and equipment are used according to the standard operating procedures and protocols;
- (vi) ensure that a sufficient number of personnel are available for the proper conduct of the study according to the protocol;
- (vii) provide the necessary education and training for the personnel engaged in a study or belonging to the quality assurance unit;
- (viii) prepare and maintain documents on education, training and job experience, and job description for personnel engaged in a study or belonging to the quality assurance unit;
- (ix) prepare and maintain documents which were indexed by test article to identify the sponsor (for a corporate body, its name), study director, test system, the type of the study, study initiation date, status of the study, and status of the final report of all studies conducted at the test facility (hereinafter referred to as the “master schedule”);
- (x) perform any other functions relating to the management and administration of the test

facility.

(Study director)

Article 7 The study director shall:

- (i) ensure that each study is conducted in accordance with this Ordinance, the standard operating procedures, and protocol;
- (ii) ensure that the raw data are recorded accurately and appropriate actions are taken;
- (iii) ensure that unforeseen circumstances that may affect the quality and integrity of the study are noted when they occur and corrective action is taken and documented.
- (iv) take corrective actions for the findings as prescribed in the following Article, paragraph (1), item (iii) and the recommended actions prescribed in item (iv) of the same paragraph;
- (v) ensure that test systems are the same as specified in the protocol;
- (vi) appropriately manage the protocol, specimens, raw data and other records, final report, and documents showing any changes or amendments (hereinafter referred to as “study-related materials”), and appropriately transfer them to the locations where the study-related materials are to be retained (hereinafter referred to as “archives”) after completion of the study;
- (vii) manage any other functions relating to the conduct, recording and reporting of the study.

(Quality Assurance Unit)

Article 8 (1) The quality assurance manager shall perform the following functions by him/herself, or shall have them performed by the individual(s) designated by him/her for each study:

- (i) maintain a copy of the master schedule;
- (ii) maintain copies of the protocols and standard operating procedures;
- (iii) inspect each study at intervals adequate to assure the quality and integrity of the study, determine if the study is conducted in compliance with this Ordinance, prepare documents showing the contents of the inspection, findings, corrective actions recommended and taken, and any scheduled date for re-inspection etc., and then retain them either signed or affixed with the name and seal;
- (iv) report to the test facility management and the study director, any findings, which may affect the quality and integrity of the study, identified during the course of an inspection prescribed in the preceding item, and corrective action recommended;
- (v) for each study, prepare a report noting corrective action recommended and taken, and submit it to the test facility management and the study director;
- (vi) assure that the verifications by the study director prescribed in Article 7, item (iii) are performed appropriately;
- (vii) review the final report to assure that it accurately describes the testing method and reflects the raw data of the study, and then report the results of the review to the test facility management and the study director;

- (viii) prepare a document showing that the dates and results of the assurances prescribed in item (iii) and preceding item were reported to the test facility management and the study director, and then submit it either signed or affixed with the name and seal to the study director;
 - (ix) prepare documents describing the methods of indexing the records retained by the quality assurance unit, and maintain them;
 - (x) perform any other functions necessary to assure that studies are conducted at the test facility in compliance with this Ordinance.
- (2) The individual(s) in the quality assurance unit who are designated to be responsible for each study shall not be engaged in the conduct of such study.
- (3) The documents to be retained pursuant to the provision of paragraph (1) shall be retained at the test facility, otherwise at the location designated by the sponsor etc.

Chapter III Test Facility and Equipment

(Test facility)

- Article 9** (1) The test facility shall be of suitable size and construction for proper conduct of studies and shall be designed so that there is an adequate degree of separation that will prevent any function from having an adverse effect on the studies.
- (2) The test facility where animal studies are conducted shall have adequate animal care facilities, animal supply facilities for feed and other supplies and other necessary facilities, to ensure appropriate care and management of animals.
- (3) The test facility shall have separate areas each for handling test articles etc. and for laboratory operations, and any other separate areas necessary for proper conduct of studies.
- (4) The test facility shall have archive(s).

(Equipment)

- Article 10** (1) Equipment used in the generation, measurement or analysis of study data, equipment used for facility environmental control, and other equipment necessary to conduct a study (hereinafter referred to as the “equipment”) shall be of appropriate design, adequate capacity, and suitably located.
- (2) The equipment shall be maintained, inspected, cleaned and repaired appropriately.
- (3) When the maintenance, inspection, cleaning or repair prescribed in the preceding paragraph is conducted, written records of the dates, content and operators shall be prepared and maintained.

Chapter IV Operation at Test Facility

(Standard operating procedures)

- Article 11** (1) The test facility management shall prepare standard operating procedures describing the methods and procedures for the following:
- (i) Management of test and control articles
 - (ii) Maintenance, inspection and repair of facilities and equipment

- (iii) Maintenance of animal care facilities
 - (iv) Care and management of experimental animals
 - (v) Observation of general signs etc. in experimental animals
 - (vi) Operation, measurement, examination and analysis in a study
 - (vii) Handling of moribund or dead animals
 - (viii) Necropsy and postmortem examination of animals
 - (ix) Collection and identification of specimens
 - (x) Histopathological examination
 - (xi) Management of raw data
 - (xii) Functions the quality assurance unit is to perform
 - (xiii) Health care of personnel engaged in a study
 - (xiv) Other necessary matters
- (2) The standard operating procedures shall be located under the responsibility of the test facility management in each area where each activity mentioned in the preceding paragraph is performed.
 - (3) When any revision is made in standard operating procedures, the test facility management shall date the revision and retain a historical file of standard operating procedures in the test facility.
 - (4) Personnel engaged in a study shall obtain approval by the study director for unavoidable deviations from the standard operating procedures.
 - (5) Personnel engaged in a study shall document in the raw data, the deviation(s) from the standard operating procedures prescribed in the preceding paragraph.

(Animal care and management)

- Article 12** (1) Personnel engaged in a study shall house all animals newly received from outside sources in isolated animal facilities, such that contamination of other animals by any disease can be prevented. Animals shall be observed during this period and any abnormalities recorded.
- (2) Personnel engaged in a study shall isolate animals which are found during the observation period prescribed in the preceding paragraph or during the course of the study to have diseases or conditions that might interfere with the conduct of the study. Such affected animals shall not be used in studies.
 - (3) Personnel engaged in a study shall take necessary measures to acclimatize animals used in the study to the test environment.
 - (4) Personnel engaged in a study shall take necessary measures to identify animals individually so as to prevent erroneous housing of animals used in the study.
 - (5) Personnel engaged in a study shall control sanitary conditions of animal care facilities and animal supplies etc.

Chapter V Handling of Test Article etc.

(Handling of test and control articles)

Article 13 (1) Personnel engaged in a study shall appropriately handle the test and control articles by labeling with the proper identification etc. and, where possible, by determining their characteristics and stabilities.

(2) Personnel engaged in a study shall properly prepare and use the mixture of test or control article with a vehicle, where possible, by determining the stability and uniformity of the mixture.

(3) When each test or control article is distributed, received, returned or discarded, personnel engaged in a study shall record the date and quantity involved.

(Reagents and solutions)

Article 14 Personnel engaged in a study shall appropriately label reagents and solutions with storage requirements and expiration date, etc. and use them according to their characteristics and instructions for use etc.

Chapter VI Protocol and Conduct of a Study

(Protocol)

Article 15 (1) The study director shall prepare the protocol for each study specifying the following items. He/she shall acquire approval for the protocol from the test facility management (the sponsor and test facility management in the cases where the entire study is commissioned; hereinafter the same shall apply in this paragraph):

- (i) Title and purpose of the study
 - (ii) Name and address of test facility
 - (iii) Name and address of the sponsor (entity name and location of the main office in the case of a legal entity) in the cases where the study is commissioned
 - (iv) Name of the study director
 - (v) Identification of the test and control articles
 - (vi) Information concerning the test system
 - (vii) Information concerning methods
 - (viii) Statistical methods to be used for analysis of raw data
 - (ix) Records and materials to be retained
 - (x) Signatures or names and seals with dates of the test facility management and study director
 - (xi) Other necessary matters to plan a study
- (2) When the protocol is to be changed, the study director shall document the date, the part and the reason for the change with signature or name and seal, and then maintain this document with the protocol.

(Conduct of study)

Article 16 (1) The study shall be properly conducted according to the protocol and standard operating procedures under the direction and supervision of the study director.

- (2) Personnel engaged in a study shall properly record all raw data with the name of person entering the data and dates.
- (3) When raw data is to be changed, personnel engaged in a study shall appropriately change them, indicating the reason for the change, the name of the person making the change and date of the change.
- (4) When any unexpected or unforeseen circumstances occur during a study, personnel engaged in the study shall promptly report them to the study director, take corrective action, and document them.

Chapter VII Report and Storage**(Final report)**

Article 17 (1) The study director shall prepare a final report for each study including the following items:

- (i) Title and purpose of the study
 - (ii) Name and address of test facility
 - (iii) Study initiation and completion dates
 - (iv) Name of the study director and names of other personnel engaged in the study
 - (v) Information concerning the test and control articles
 - (vi) Information concerning the test system
 - (vii) Unforeseen circumstances that may affect the quality or integrity of the study and deviations from the protocol
 - (viii) Information concerning methods
 - (ix) Statistical methods used for analysis of raw data
 - (x) Study results, discussions and summary
 - (xi) The locations where raw data and specimens are to be archived
 - (xii) Signature or name and seal with date of the study director
 - (xiii) The documents prepared by the quality assurance manager with signature or name and seal pursuant to the provision of Article 8, paragraph (1), item (viii)
 - (xiv) Other necessary matters
- (2) When a final report is to be amended, the study director shall document the date, the part of and the reason for the amendment, sign or affix the name and seal, and retain this document with the final report.

(Storage of study-related materials)

Article 18 (1) The test facility management shall properly retain study-related materials in archives.

(2) The test facility management shall designate an individual responsible for the archives (hereinafter referred to as the “archivist”).

(3) Nobody but those authorized by the archivist shall enter the archives.

(4) When the business of the test facilities is discontinued or suspended, the test facility management shall transfer the study-related materials to the successor or the sponsor etc. (hereinafter referred to as the “material successor”).

(5) The provisions of paragraphs (1) to (3) shall apply mutatis mutandis to the material successor.

Chapter VIII Multi-site Study

(Compliance matters)

Article 19 A study conducted at multiple sites shall, in addition to what is provided in Articles 4 to 18, be as prescribed in the following items:

(i) The test facility management shall take necessary measures, including ensuring lines of communication between the test facility and test sites, to ensure the quality and integrity of the study data generated at test sites.

(ii) The provisions of Article 6, Article 11, paragraphs (1) to (3) and Article 18, paragraphs (1), (2) and (4) shall apply mutatis mutandis to a person responsible for the management and administration of a test site (hereinafter referred to as the “test site management”). In this case, the term “an individual responsible for the conduct, recording, and reporting etc. of the study (hereinafter referred to as the “study director”)” in Article 6, item (i) shall be deemed to be replaced with “an individual responsible for the conduct, recording, and reporting etc. of the commissioned part of the study (hereinafter referred to as the “principal investigator”)”; the term “test facility” in items (ii), (ix) and (x) of the same Article and Article 11, paragraph (3) shall be deemed to be replaced with “test site”; and “study director” in Article 6, item (ix) shall be deemed to be replaced with “study director and principal investigator”.

(iii) The provisions of Article 7 shall apply mutatis mutandis to the principal investigator. In this case, the terms “the following Article, paragraph (1), item (iii)” and “item (iv) of the same paragraph” in Article 7, item (iv) shall be deemed to be replaced respectively with “the following Article, paragraph (1), item (iii), as applied mutatis mutandis pursuant to Article 19, item (iv)” and “the following Article, paragraph (1), item (iv), as applied mutatis mutandis pursuant to Article 19, item (iv)”.

(iv) The provisions of Article 8 shall apply mutatis mutandis to the quality assurance manager pursuant to the provision of Article 6, item (ii), as applied mutatis mutandis pursuant to item (ii). In this case, “the test facility management and the study director” in Article 8, paragraph (1), items (iv), (v), (vii) and (viii) shall be deemed to be replaced with “the test facility management, the study director, the test site management and the principal investigator”; “the study director prescribed in Article 7, paragraph (3)” in item (vi) of the same paragraph shall be deemed to be replaced with “the principal investigator prescribed in Article 7, paragraph (3), as applied mutatis mutandis pursuant to Article 19, item (iii)”; and “test facility” in item (x) of the same paragraph and

paragraph (3) of the same Article shall be deemed to be replaced with “test site”.

- (v) The provisions of Article 9 shall apply mutatis mutandis to test sites.
- (vi) With regard to personnel engaged in a study at a test site, “the study director” in Article 11, paragraph (4) and Article 16, paragraphs (1) and (4) shall be deemed to be replaced with “the study director and the principal investigator.”

Supplementary Provisions (Excerpt)

(Effective date)

Article 1 This Ordinance shall come into force as from the date of enforcement (April 1, 2005) of the Act for the Partial Revision of the Pharmaceutical Affairs Act and the Blood Collection and Donation Services Control Act (Act No. 96 of 2002).

Supplementary Provisions [Ordinance of Ministry of Health, Labour and Welfare No.115 of June 13, 2008]

This Ordinance shall come into force as from August 15, 2008.