

To: Prefectural Governors

From: Pharmaceutical and Food Safety Bureau,  
Ministry of Health, Labour and Welfare

**Guidance on the Implementation of the Ministerial Ordinance on the Good Laboratory Practice for Nonclinical Safety Studies of Medical Devices as Revised by the Ministerial Ordinance for Partial Revision of the Ministerial Ordinance on the Good Laboratory Practice for Nonclinical Safety Studies of Medical Devices**

Nonclinical safety studies to be conducted by those who intend to apply for marketing approval for medical devices have been prescribed in the Ministerial Ordinance on Good Laboratory Practice (GLP) for Nonclinical Safety Studies of Medical Devices (Ordinance of Ministry of Health, Labour and Welfare No. 37 of 2005, hereinafter referred to as “the GLP Ordinance for Medical Devices”).

In recent years, medical device development has been carried out on an international basis and it is now necessary to conduct nonclinical studies efficiently, in cooperation with test facilities in other countries, while still ensuring the quality of those studies. In addition, nonclinical safety studies are often conducted at multiple sites, and various provisions to respond to such cases are set forth in the Organization for Economic Co-operation and Development (OECD) Principles of GLP. In the light of these circumstances, the Ministerial Ordinance for the Partial Revision of the Ministerial Ordinance on Good Laboratory Practice for Nonclinical Safety Studies of Medical Devices (Ordinance of Ministry of Health, Labour and Welfare No. 115 of 2008; hereinafter referred to as “the Ministerial Ordinance for the Partial Revision”) was recently promulgated in order to ensure further quality of nonclinical studies, and will come into effect as from August 15, 2008.

The implementation of the GLP Ordinance for Medical Devices as revised by the Ministerial Ordinance for the Partial Revision is as described below. Please take note of the guidance specified in this Notification and provide all relevant business operators under your jurisdiction with the information.

**1. Each article**

**(1) Article 2**

- (a) “Any chemical or biological substance used as the material” as stated in paragraph (1) should include extracts of the test article prepared for contract laboratories etc. and shaped products processed for implantation tests.
- (b) “Raw data” as stated in paragraph (5) means worksheets, notes, memorandums, or their exact transcripts which are necessary for the reconstruction and evaluation of the final reports, and include photos, microfilms, microfiche, computer records, magnetic records of dictated observation results, study results recorded by automated instruments, etc.

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

**(2) Article 4**

- (a) With regard to “a study conducted at multiple sites” prescribed in Article 19 (hereinafter referred to as “multi-site study”), “an entity who commissions” as stated in paragraph (1) and “an entity who commissioned” as stated in paragraph (2) should include an entity who commissions part of a study and an entity who commissioned part of a study. In the same way, “a contractor” as stated in paragraph (1) should include an entity who will be commissioned to conduct part of a study.
- (b) To “confirm” as stated in paragraph (2), confirmation may be made by any appropriate means for each case, and the sponsor does not necessarily visit the contractor for on-site review.
- (c) “Notification” as stated in paragraph (3) may be documented by incorporating the provisions to that effect into a contract or other documents.

**(3) Article 5**

- (a) Those who are “capable of performing their assigned functions” as stated in paragraph (1) should be knowledgeable in those parts of the GLP Ordinance for Medical Devices which are applicable to their involvement in the study.
- (b) “Sanitation and health precautions” as stated in paragraph (2) should include the use of clothing suitable for conduct of work of personnel engaged in studies. An individual with an illness that may adversely affect the quality and integrity of studies should report this to an appropriate person such as the study director or test facility management, and should be excluded from direct contact with test systems until his/her health condition is corrected.

**(4) Article 6**

- (a) “Study director” as stated in item (i) means the individual responsible for the overall conduct of the study. The test facility management should designate an individual who has sufficient capability and experience to conduct and supervise the study as a study director. In addition, designation of replacement of the study director should be conducted pursuant to the predetermined procedures, and be documented and retained.
- (b) “Quality assurance unit” as stated in item (ii) means any individual or organizational element, which is independent of study conduct, designed to assure test facility management that studies are conducted at the test facility in compliance with the GLP Ordinance for Medical Devices.
- (c) It is not necessary to “ensure” as stated in item (iv) in the cases where the leachables or extracts, which is difficult to be tested for identity, purity, stability and uniformity, are used in accordance with the standard operating procedures immediately after the extraction.
- (d) The provisions of items (v) and (vi) should include ensuring that facilities, equipment, materials and personnel are available for proper conduct of the study.
- (e) “Master schedule” as stated in item (ix) should be prepared so that the assessment of workload and the tracking of studies at the test facility can be understood.
- (f) “Any other functions relating to the management and administration of the test facility” as stated in item (x) should include the following:
  - 1) Prepare and maintain a document that identifies the test facility management at the test facility;

- 2) Ensure that an individual or individuals in the quality assurance unit (hereinafter referred to as the “quality assurance personnel”) has obtained the approved protocol from the study director.

**(5) Article 7**

- (a) “Unforeseen circumstances” as stated in item (iii) should include deviations from the protocol and standard operating procedures. The study director should assess the effects of those circumstances on the quality and integrity of the study, and ensure that the details of “circumstances that may affect the quality and integrity of study” and the corrective actions taken are documented on the basis of actions taken by personnel engaged in the study.
- (b) Measures to “appropriately manage” as stated in item (vi) should include the establishment of measures to prevent loss or falsification, etc. of study-related materials during the study.
- (c) “Any other functions relating to the conduct, recording and reporting of the study” as stated in item (vii) should include the following:
  - 1) Supply a copy of the protocol and any amendments to the quality assurance personnel without delay, and communicate effectively with the quality assurance personnel as required during the conduct of the study;
  - 2) Ensure that the protocols and amendments and the applicable standard operating procedures are available to personnel engaged in the study;
  - 3) Pay attention to prevent equipment, materials, etc. used in the study from having adverse effects on the study;
  - 4) Ensure that the computerized systems used in the study have appropriately been validated.

**(6) Article 8**

- (a) “A copy of the master schedules” as stated in item (i) and “copies of the protocols and standard operating procedures” as stated in item (ii) may be maintained on a computerized system of which the quality has been assured. In such cases, maintaining a paper copy is not necessarily required.
- (b) Inspections “to assure the quality and integrity of the study” as stated in item (iii) are classified into three categories: study-based inspection, facility-based inspection and process-based inspection. Process-based inspection means an inspection conducted by means of assuring the process of a study based on the results of inspection of another study. For process-based inspection, such requirements as inspection items, scope and permissible frequency of inspections should be defined in the standard operating procedures. In addition, it is necessary to provide clear evidence that a process-based inspection can be substituted for performance of individual study-based inspections.
- (c) “A document showing that the dates and results of assurances prescribed in item (iii) and the preceding item were reported to the test facility management and the study director” (hereinafter referred to as “QA statement”) as stated in item (viii) should also clearly specify the phase(s) inspected and the date of inspections, and the types of inspections in the case where multiple types of inspections were conducted for the study.
- (d) “Any other functions necessary to assure that studies conducted at the test facility are in

compliance with this Ordinance” as stated in item (x) should include the following:

- 1) Verify that the protocol contains the information required for compliance with the GLP Ordinance for Medical Devices, and the verification results should be documented;
  - 2) Verify that personnel engaged in the study use and follow the protocol and applicable standard operating procedures.
- (e) “The documents to be retained pursuant to the provision of paragraph (1)” as stated in paragraph (3) means records of inspections conducted by the quality assurance unit, and such documents should be transferred to the archives at an appropriate time after storage at the quality assurance unit, etc.

**(7) Article 9**

(a) “Animal care facilities” as stated in paragraph (2) should have the functions specified below, where necessary:

- 1) Separate housing by species or test system;
- 2) Separate housing by protocol;
- 3) Quarantine of animals;
- 4) Animal care in normal or specialized housing.

(b) “Facilities to store feed and other supplies” as stated in paragraph (2) should have the function of storage areas for feed, bedding, supplies, and equipment, where necessary.

(c) “Other necessary facilities” as stated in paragraph (2) should include the following:

- 1) Animal rooms or areas where studies using volatile substances, radioactive substances, infectious agents, etc. can be conducted in isolation from other animal care facilities;
- 2) Facilities for isolation and treatment of diseased animals;
- 3) Facilities for collection and hygienic disposal of waste from the test system, or for safe and sanitary storage of waste before removal from the test facility.

(d) “Areas for handling test articles, etc.” as stated in paragraph (3) should have the functions specified below in order to preclude contamination or mix-up of these articles and should be designed to maintain the quality of the test and control articles:

- 1) Receipt and storage of the test and control articles;
- 2) Mixing of the test or control article with a vehicle;
- 3) Storage of the mixture of the test or control article with a vehicle.

(e) “Areas for laboratory operations” as stated in paragraph (3) should be separated, where necessary, for the performance of periodical measurements, such as biochemical and histopathological examinations, and other laboratory operations.

(f) “Any other separated areas necessary for proper conduct of studies” as stated in paragraph (3) should include the following:

- 1) Isolated areas where any constituent parts of animals or microorganisms which may

be potential biohazards are used;

- 2) Separated areas for cleaning, sterilizing, and storing supplies and equipment used during a study.
- (g) “Archive(s)” as stated in paragraph (4) means designated areas, facilities or equipment (cabinets, rooms, buildings, or computer systems, etc.) that enable secure storage and retrieval of study-related materials and protection of contents from untimely deterioration. Study-related materials should be retained in principle in the archive(s) of the test facility. However, this does not preclude the use of contract archive facilities. In the case of using contract archive facilities, the facilities must be in compliance with the provisions of the GLP Ordinance for Medical Devices, etc., and the test facility management should be responsible for ensuring the GLP compliance status thereof.

**(8) Article 10**

Procedures for equipment to be “maintained and inspected” as stated in paragraph (2) should include tests, calibration, standardization, etc. that are regularly conducted according to the standard operating procedures.

**(9) Article 11**

- (a) “Standard operating procedures” as stated in paragraph (1) should be represented by documented procedures which describe how to perform tests and activities, etc. that are normally not specified in detail in the protocols.
- (b) Standard operating procedures should be prepared under the responsibility of the test facility management.
- (c) Published literature, etc. may be used as a supplement to standard operating procedures.
- (d) “Management” as stated in paragraph (1), item (i) should include receipt, labeling, storage, handling, mixing with a vehicle, sampling, etc. in each division.
- (e) “Maintenance, inspection and repair of equipment” as stated in item (ii) of the same paragraph should include the procedures and implementation plans (schedules) of inspection, cleaning, maintenance, testing, calibration and standardization of equipment, and the procedures for repairs in the case of equipment failure or malfunction.
- (f) “Management of raw data” as stated in item (xi) of the same paragraph should include maintenance, storage and retrieval of records.
- (g) “Functions the quality assurance unit is to perform” as stated in item (xii) of the same paragraph should include planning, performing, documenting and reporting inspections by the quality assurance unit.
- (h) “Other necessary matters” as stated in item (xiv) of the same paragraph should include the following:
- 1) Matters relating to preparation, storage, labeling, etc. of reagents;
  - 2) Preparation of reports, etc.;
  - 3) Validation, operation, maintenance, security, change control and back-up of computerized systems;
  - 4) Matters relating to multi-site study.

**(10) Article 12**

- (a) Items “recorded” as stated in paragraph (1) should include the source and the date of receipt of test systems.
- (b) Isolated animals pursuant to the provision of paragraph (2) may be treated, if necessary, following authorization of the treatment by the study director, provided that such treatment does not interfere with studies. In this case, the reason for the treatment, authorization of such treatment, method of treatment, drugs used for treatment, date of treatment, the results of treatment, etc. should be recorded and retained.
- (c) “Necessary measures” as stated in paragraph (4) should include the following:
  - 1) Information to identify each animal within an animal room should be clearly indicated on the outside of cages, pens or racks, where necessary;
  - 2) Animals of different species should be housed in separate rooms in principle;
  - 3) In the case where animals of the same species are housed in the same room and used in different studies, an adequate degree of separation and identification should be necessary.
- (d) “Control of sanitary conditions” in paragraph (5) should include the following:
  - 1) Animal cages, pens, racks and accessory equipment should be kept clean and sanitized at appropriate intervals;
  - 2) Bedding used in animal cages or pens should not interfere with the purpose or conduct of the study and should be changed as often as necessary to keep the animal clean and dry;
  - 3) Feed and water used for animals should be analyzed periodically to ensure that contaminants, which are known to be capable of interfering with studies and reasonably expected to be present in such feed or water, are not present at levels above those specified in the protocol. Records of such analysis should be retained as raw data;
  - 4) Detergent or insecticides that may interfere with proper conduct of studies should not be used;
  - 5) In the case where any detergent or insecticide is used, the use should be recorded.

**(11) Article 13**

- (a) Measures to “appropriately handle” as stated in paragraph (1) should include the following:
  - 1) A proper storage area should be set up;
  - 2) Distribution should be made in a manner that precludes the possibility of contamination or the deterioration of quality;
  - 3) Proper identification should be ensured throughout the distribution process;
  - 4) In principle, the sponsor or test facility should ensure that the characteristics, such as the identity, content, purity, composition, etc., which will define the test or control article, have been determined before study initiation, except where its determination is difficult. In the cases where marketed products are used as the control articles, the determination of their characteristics may be substituted by the use of their labeling

information;

- 5) The stability of each test or control article should be determined before study initiation in principle. In the case where stability cannot be determined before study initiation, standard operating procedure(s) for the stability test should be prepared and periodical analysis should be conducted in accordance with the standard operating procedure(s). In this case, if the test or control article is apparently stable and the determination of its stability is impossible, the determination of its stability may be substituted by records of these facts. However, this does not apply to the cases where the leachables or extracts, whose stability is difficult to be determined, are used in accordance with the standard operating procedures immediately after the extraction;
  - 6) The name, abbreviation or code number, and lot number should be indicated on each storage container of the test or control article together with the expiration date, if available. When specific storage conditions are required, they should also be indicated. In this case, when the test article needs a particular type of storage container, such requirement should be specified;
  - 7) For studies of at least 4 weeks' duration, reserve samples from each lot of test and control articles should be retained for the period prescribed in Article 101 (including the cases where it is applied mutatis mutandis pursuant to Article 110) or Article 104, items (i) and (ii) of the Ordinance for Enforcement of the Pharmaceutical Affairs Act (Ordinance of Ministry of Health and Welfare No.1 of 1961). However, in the case where the quality of the test or control article may change markedly during the storage period, it may be retained only as long as the quality of the article affords evaluation.
- (b) Measures to "properly prepare and use" as stated in paragraph (2) should include the following:
- 1) In the case where the test or control article is used as a mixture with a vehicle, in principle, the stability of the test or control article in the mixture should be determined before the use of the article, except where its determination is difficult. If the stability cannot be determined before use, standard operating procedure(s) for the stability test should be prepared and periodical analysis should be conducted in accordance with the standard operating procedure(s). In this case, if the test or control article is apparently stable and the determination of its stability is difficult, such determination may be substituted by records of these facts. However, this does not apply to the cases where the leachables or extracts, whose stability is difficult to be determined, are mixed with a vehicle and used in accordance with the standard operating procedure immediately after the extraction. In addition, where necessary, the uniformity of the mixture should be determined before the use, and the concentration of the test or control article in the mixture should be periodically determined, except where its determination is difficult;
  - 2) Where any of the components in the mixture has an expiration date, that date should be indicated on the container. If more than one component has an expiration date, the earliest date should be indicated.

**(12) Article 15**

- (a) The study director should assume responsibility for preparation of the protocol.
- (b) Each item of paragraph (1) should include the following information:

- 1) For “identification of the test and control articles” as stated in item (v), the name, abbreviation or code number;
  - 2) For “information concerning the test systems” as stated in item (vi), the species, strain, number, age, sex, body weight range, source of supply, reason for selection, and procedure for identification;
  - 3) For “information concerning methods” as stated in item (vii), experimental design for the control of bias; environmental conditions for the test system; name or code number of feed (including specifications for acceptable levels of contaminants that may be present and interfere with the purpose or conduct of studies if present at levels greater than the specifications); solvents, emulsifiers, and other materials used as vehicles to dissolve or suspend the test or control article; the method and duration of application of the test and control articles and reasons for selection; the title of the standard for biological safety study used as reference; and the type, frequency, method, and schedule of observation, measurement, examination, and analysis to be performed.
- (c) “Other necessary matters to plan a study” as stated in item (xi) should include the following information:
- 1) In the case where a multi-site study is conducted, name and address of any test sites involved, name and department of principal investigator(s) and the phase(s) of the study delegated to them;
  - 2) Name(s) and organization(s) of expert(s) who is scheduled to contribute to the final report.

**(13) Article 16**

- (a) Measures to be “properly conducted” as stated in paragraph (1) should include the following:
- 1) Each study should have unique identification, and records, specimens, etc. related to the study should be accompanied by such identification;
  - 2) Specimens should be identified by the type of the study, identification number of the test system and date of collection using a proper method;
  - 3) Records of gross necropsy findings for a specimen should be available to a pathologist when examining the specimen histopathologically;
  - 4) In the case where a multi-site study is conducted, the principal investigator and personnel engaged in the study at the test site should conduct their respective functions at the test site according to the standard operating procedures prepared at the test site unless the study director gives special instructions.
- (b) Procedures to “properly record” as stated in paragraph (2) should include the following:
- 1) Raw data should be recorded directly, immediately and legibly, and in a way where the data cannot be readily deleted, except in the case of direct computer input;
  - 2) In the case of direct computer input of raw data, the input date and the name of the individual responsible for direct data entries should be recorded.
- (c) Procedures to “appropriately change the data” as stated in paragraph (3) should include the following:



Any change in the raw data should be made so as not to obscure the original entry, should be accompanied by the reason for such change, and should be dated and signed by the individual making the change, or followed by his/her name and seal affixed, at the time of the change so that the individual will be identified. Any change to the data stored in the computer should be made so as not obscure the original data. The reason for the change should also be entered, with the date and the name of the individual making the change.

- (d) “Any unexpected or unforeseen circumstances” as stated in paragraph (4) should include deviations from the protocol and standard operating procedures.

**(14) Article 17**

- (a) The study director should assume responsibility for preparation of the final report.
- (b) For a multi-site study, a single final report including the results obtained at all test sites should be prepared.
- (c) “Study initiation date” as stated in paragraph (1), item (iii) should be the date the study director signs or affixes his/her name and seal to the protocol, and “study completion date” should be the date the study director signs or affixes his/her name and seal to the final report.
- (d) Each item of paragraph (1) should include the following information:
  - 1) For “name of the study director and names of other personnel engaged in the study” as stated in item (iv), assigned functions;
  - 2) For “Information concerning the test and control articles” as stated in item (v), the name, abbreviation or code number, and lot number, identity, content, purity, composition, etc. which characterize the test and control articles, and stability and uniformity under the conditions of administration;
  - 3) For “information concerning the test system” as stated in item (vi), the species, strain, number, age, sex, body weight range, source of supply, date of receipt, and animal care conditions;
  - 4) For “information concerning methods” as stated in item (viii), the method of application of the test or control article, the reason for its selection; and the type, frequency, and method of observation, measurement, examination and analysis performed, and the titles of the standards for biological safety studies used as reference.
  - 5) “Other necessary matters” as stated in item (xiv) should be as follows:
    - (i) In the case where a study is commissioned, name and address of the sponsor (name and location of the main office in the case of a legal entity);
    - (ii) In the case where a multi-site study is conducted, name and address of any test sites, name(s) and department(s) of the principal investigator(s) and the phase(s) of the study delegated to them;
    - (iii) Name(s) and organization(s) of expert(s) having contributed to the final report.

**(15) Article 18**

- (a) Procedures to “properly retain” as stated in paragraph (1) should include the following:

- 1) When specimens or raw data are retained separately from the final report, this fact should be recorded at the facility where the final report is retained;
  - 2) The movement in and out of the archives and transfer from archives of study-related materials should be properly recorded;
  - 3) Study-related materials should be arranged and retained in a convenient way for retrieval, such as indexing by the test article, test system, and type of the study;
  - 4) Study-related materials should be transferred to the archives at an appropriate time.
- (b) Study-related materials should be retained for the periods prescribed in Article 101 (including the cases where it is applied mutatis mutandis pursuant to Article 110, paragraph (1)) or Article 104 of the Ordinance for Enforcement of the Pharmaceutical Affairs Act; provided, however, wet specimens and specially prepared specimens that may deteriorate markedly during storage, such as histochemical specimens, electron microscopic specimens, and blood specimens, should be retained only as long as their quality afford evaluation.
- (c) In addition to study-related materials, the following items should be handled in the same manner as the provisions pertaining to storage, etc. in Article 18:
- 1) Test and control articles prescribed in (11), (a), 7 of this notification;
  - 2) Records of inspections performed by the quality assurance unit;
  - 3) Records of qualifications, training, experience and job descriptions of personnel;
  - 4) Records and reports of the maintenance, calibration and cleaning of equipment;
  - 5) Validation documentation for computerized systems;
  - 6) Historical files of standard operating procedures;
  - 7) Environmental monitoring records;
  - 8) Others.

**(16) Article 19**

- (a) “Necessary measures” as stated in item (i) should include the following:
- 1) Select test sites according to their ability to correctly conduct a study at the test sites;
  - 2) Ensure that the test site management designates a principal investigator(s) pursuant to the provision of item (ii);
  - 3) Designate the quality assurance manager of the test facility as an individual who has overall responsibility for quality assurance of the entire study (hereinafter referred to as the “lead quality assurance manager”);
  - 4) Establish a communication system among those persons concerned in the study, such as the study director, principal investigator, quality assurance manager and personnel engaged in the study.
- (b) For item (ii), where the test facility management directly manages and administers a test site, the test facility management may also perform the functions of the test site management. In this case, procedures to specify the test site management and procedures to ensure that a principal investigator(s) has been designated may be

omitted.

- (c) For item (iii), where the study director directly controls and supervises a part of the study conducted at a test site, the study director may also perform the functions of the principal investigator. In addition, where the test facility management directly manages and administers a test site, procedures to designate a principal investigator may be omitted.
- (d) For item (iii), some functions relating to a part of the study conducted at a test site are performed under the responsibility of the principal investigator. However, the ultimate responsibility for the part of the study should lie with the study director.
- (e) For “unforeseen circumstances that may affect the quality and integrity of the study” prescribed in Article 7, item (iii), as applied *mutatis mutandis* pursuant to item (iii), at a test site, the principal investigator should determine whether the circumstances may affect the quality and integrity of the study, and should ensure that the details of and corrective actions for the circumstances that have been determined as so are documented. The results of and reasons for the determination should be reported to the study director.
- (f) For item (iv), the lead quality assurance manager should perform functions relating to multi-site studies by him/herself, or should have them performed by the individual(s) designated by him/her for each study (hereinafter referred to as the “lead quality assurance personnel”).
- (g) For item (iv), the quality assurance personnel at test site should inspect the study conducted at their site according to their own standard operating procedures unless the lead quality assurance manager (or the lead quality assurance personnel) gives special instructions. In addition, the inspection results should also be reported to the lead quality assurance manager (or the lead quality assurance personnel).
- (h) For Article 8, item (vii), as applied *mutatis mutandis* pursuant to item (iv), reports prepared at test sites which constitute a final report should be inspected at the test sites.
- (i) For item (vi), where personnel engaged in a phase of a study conducted at a test site fail to follow the standard operating procedures, it is necessary to obtain approval from the study director and principal investigator. In this case, it is sufficient if they ask the principal investigator for approval and the principal investigator that has approved the relevant matter eventually asks the study director for approval.
- (j) For item (vi), when any unexpected or unforeseen circumstances occur during a study, personnel engaged in a phase of a study at a test site should promptly report the fact to the study director and the principal investigator. In this case, it is sufficient if they eventually report to the study director via the principal investigator.

## **2. Abolition of existing notifications**

“Implementation of the Ministerial Ordinance on the Good Laboratory Practice for Nonclinical Safety Studies of Medical Devices” (PAB Notification No. 0331038, issued by Director-General of the Pharmaceutical and Food Affairs Bureau, Ministry of Health, Labour and Welfare, dated March 31, 2005) is abolished.

## **3. Timing of application**

The Ministerial Ordinance for Partial Revision and this Notification is to be applied to studies conducted on or after August 15, 2008.