Japan's New Drug GMP

Regulations for Manufacturing Control and Quality Control of Drug and Quasi-drugs (MHLW Ordinance No. 179 dated December 24, 2004)

In accordance with the provisions of Article 14, Paragraph 2, Item 4 (including cases where the provisions are applied mutatis mutandis under Article 19-2, Paragraph 5) of the Pharmaceutical Affairs Law (Law No. 145, 1960), the whole text of the Regulations for Manufacturing Control and Quality Control of Drug and Quasi-drugs (Ordinance of the Ministry of Health, Labor and Welfare No. 16, 1999) shall be amended as below.

December 24, 2004
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Minister of Health, Labor and Welfare

TABLE OF CONTENTS

Chapter 1 General Provisions

(Objective)
Article 1 This Ordinance shall state the standards which an Ordinance of the Ministry of Health, Labor and Welfare is supposed to establish under the provisions of Article 14, Paragraph 2, Item 4 (including cases where the provisions are applied mutates mutandis under Article 19-2, Paragraph 5) of the Pharmaceutical Affairs Law (Law No. 145, 1960, hereinafter referred to as the "Law").

(Definitions)
Article 2 The term "Product" used in this Ordinance means material (including a material manufactured during an intermediate process which must undergo subsequent processing before a final product is obtained ; hereinafter referred to as an "Intermediate Product") which has undergone a manufacturing process at a manufacturing site.
2. The term "Labeling and Packaging Materials" used in this Ordinance mean containers, wrappers and labels (including package inserts) of a Product.
3. The term "Lot" used in this Ordinance means a batch of Products manufactured so as to have a uniform quality during a series of manufacturing processes within a manufacturing period and raw materials (hereinafter referred to as the "Products, Etc.").

4. The term "Control Unit" used in this Ordinance means a batch of Labeling and Packaging Materials which are confirmed to have a uniform quality.
5. The term "Validation" used in this Ordinance means acts of validating and documenting that anticipated results yield from the buildings and facilities at a manufacturing site, as well as operating procedures, processing and other methods of manufacturing control and quality control (hereinafter referred to as the "Operating Procedures, Etc.").
6. The term "Clean Area" used in this Ordinance means, among the areas for performing manufacturing operations (hereinafter referred to as a "Work Area"), a place for performing the weighing operations of raw materials and the preparing operations of drugs, and a place where washed containers are exposed to the air in the Work Area.
7. The term "Aseptic Area" used in this Ordinance means, among the Work Areas, a place where drugs being sterile and sterilized containers are exposed to the air in the Work Area, a place for performing the filing operations of drugs and the sealing operations of containers, as well as a place for performing aseptic operations such as sterility tests, etc.
8. The term "Cellular/Tissue Based Drug" used in this Ordinance means a drug composed of human or animal cells or tissues (excluding human blood and drugs composed of ingredients manufactured from human blood).
9. The term "Donor" used in this Ordinance means an individual providing his/her cells or tissues as raw materials of Cellular/Tissue Based Drugs (excluding cells or tissues derived from the human body in brain death as defined under Article 6, Paragraph 2 of the Law on Organ Transplantation (Law No. 104, 1997)).
10. The term "Donor Animal" used in this Ordinance means an animal providing its cells or tissues as the source materials of a Cellular/Tissue Based Drug.

(Extent of Application)
Article 3 A manufacturer/distributor of drugs (excluding in-vitro diagnostic drugs; the same hereinafter) and quasi-drugs as defined under Article 14, Paragraph 1 of the Law, and a designated manufacturer/distributor of drugs and quasi-drugs, provided in Article 19-2, Paragraph 4 of the Law, shall require manufacturers and foreign manufacturers as defined under Article 13-3, Paragraph 1 of the Law (hereinafter referred to as a "Foreign Manufacturer") (hereinafter referred to collectively as a "Manufacturer, Etc.") to perform manufacturing control and quality control at manufacturing sites, in accordance with the provisions in chapter 2 or those applied mutates mutandis in chapter 3.
2. Manufacturer, Etc. of drug or quasi-drug Products shall perform manufacturing control and quality control of a Product at manufacturing sites as defined under in Article 96 of the Enforcement Rules of the Pharmaceutical Affairs Law (MHLW Ministerial Ordinance No. 1, 1961, hereinafter referred to as the "Enforcement Rules") in accordance with the provisions in chapter 2 or those applied mutates mutandis in chapter 3.
3. Manufacturer of drug or quasi-drug Products for export provided in Article 80, Paragraph 1 of the Law shall perform manufacturing control and quality control of a Product at manufacturing sites of drugs and quasi-drugs for export in accordance with the provisions in chapter 2 or those applied mutates mutandis in chapter 3.

Chapter 2 Manufacturing Control and Quality Control at Manufacturing Sites by Drug Manufacturer, Etc.

Subchapter 1 General Rules

(Manufacturing Control Department and Quality Control Department)
Article 4 Manufacturer, Etc. shall put, at each manufacturing site, an organizational department in charged of manufacturing control (hereinafter referred to as "Manufacturing Control Department") and an organizational department in charge of quality control (hereinafter referred to as "Quality Control Department") under the supervision of a drug manufacturing manager as defined under Article 17, Paragraph 3 of the Law and a person

who administrates manufacturing of biological products (as defined under Article 2, Paragraph 9 of the Law) as defined under Article 68-2, Paragraph 1 of the Law (for a Foreign Manufacturer, a person responsible at a manufacturing site approved in accordance with Article 13-3, Paragraph 1 of the Law or a person who is designated by the Foreign Manufacturer in advance) (hereinafter referred to collectively as a "Product Control Manager").

2. The Quality Control Department shall be independent of the Manufacturing Control Department.

(Product Control Manager)

Article 5 The Product Control Manager shall perform the following duties.

(1) To manage the duties relative to manufacturing control and quality control (hereinafter referred to as "Manufacturing/Quality Control Duties") and to administrate and supervise for appropriate and smooth implementation of the duties.

(2) In cases where a defect of a Product is detected or otherwise there is a possibility that quality of a Product might be affected seriously, to confirm that necessary actions have been taken promptly and monitor their progress, and to direct to take necessary action such as improvement, if necessary.

2. A Manufacturer, Etc. shall make efforts for the effective performance of the duties assigned to the Product Control Manager.

(Personnel)

Article 6 A Manufacturer, Etc. shall designate adequately a person responsible who is able to implement the Manufacturing/Quality Control Duties appropriately and smoothly (hereinafter referred to as a "Responsible Person") according to the organization, the scale or kinds of services, etc. of a manufacturing site.

2. A Manufacturer, Etc. shall distribute adequate number of Responsible Persons according to the organization, the scale or kinds of services, etc. of a manufacturing site.

3. A Manufacturer, Etc. shall secure a sufficient number of person(s) who are able to implement the Manufacturing/Quality Control Duties appropriately.

4. A Manufacturer, Etc. shall establish adequately in writing the responsibilities and the administrative system of personnel who are in charge of the Manufacturing/Quality Control Duties (including the Product Control Manager and the Responsible Person).

(Product Master Formula)

Article 7 A Manufacturer, Etc. shall prepare and maintain a product master formula for each Product (excluding the Intermediate Products; the same hereinafter in this Article) describing the following matters, at each manufacturing site involved in the manufacture of the Product, and have the formula approved by the Quality Control Department:

(1) Terms of the manufacturing/distributing approval;

(2) Terms of the standards established under Article 42, Paragraph 1 of the Law and other matters related to quality under the law and regulations concerning pharmaceutical affairs or any administrative order thereunder;

(3) Manufacturing procedures (excluding the terms set forth in (1));

(4) In cases where Products intended for manufacture are drugs which are biological products (hereinafter referred to as a "Biological Drug"), biological preparations of Article 80, Paragraph 2, Item 3-A of the Enforcement Order of the Law (Cabinet Order No. 11, 1961), drugs designated by the Minister of Health, Labor and Welfare, pursuant to the provisions of the Article 43, Paragraph 1 of the Law, drugs manufactured by application of the gene recombinant technology, drugs manufactured using drugs manufactured by application of the gene recombinant technology, drugs manufactured by application of the incubation technology of human or animal cells, drugs manufactured using drugs manufactured by application of the incubation technology of

human or animal cells, or Cellular/Tissue Based Drugs (hereinafter referred to collectively as "Biological Drugs, Etc."), the following matters:

A. The name, essence, description, ingredients and their contents, and other specifications of the substance obtained from humans, animals, plants or microorganisms as source materials;

B. Specifications of animals to be used in manufacturing or in testing and inspection (including methods of breeding and maintaining them) (including Donor Animals; hereinafter referred to as an "Animal Used").

(5) Other necessary matters.

(Operating Procedures, Etc.)

Article 8 A Manufacturer, Etc. shall prepare and maintain, at each manufacturing site, a hygiene control protocol; describing the sanitation and hygiene of the buildings and facilities, and of the personnel, and other necessary matters.

2. A Manufacturer, Etc. shall prepare and maintain, at each manufacturing site, a manufacturing control protocol describing storage of Products, etc., control of manufacturing processes and other necessary matters.

3. A Manufacturer, Etc. shall prepare, at each manufacturing site, a quality control protocol describing collecting method of samples, evaluating method of results of testing and inspection and other necessary matters, and shall store it.

4. A Manufacturer, Etc. shall prepare and maintain, in addition to those set forth in Paragraph 3 of this Article, at each manufacturing site, the following written operating procedures (hereinafter referred to as the "Operating Procedures") for the purpose of appropriate and smooth implementation of manufacturing control and quality control:

(1) Procedure for control of distribution from a manufacturing site;

(2) Procedure for Validation;

(3) Procedure for control of changes in Article 14;

(4) Procedure for control of Deviation in Article 15;

(5) Procedure for information on quality, etc. and management of quality deficiency, etc.;

(6) Procedure for product recalls;

(7) Procedure for self-inspection;

(8) Procedure for training;

(9) Procedure for management of documents and records;

(10) Other necessary procedures for appropriate and smooth implementation of manufacturing control and quality control.

5. A Manufacturer, Etc. shall keep a copy of a product master formula, a hygiene control protocol, a manufacturing control protocol, a quality control protocol and Operating Procedures (hereinafter referred to as "Operating Procedures, Etc.") at the manufacturing site.

(Buildings and Facilities)

Article 9 Buildings and facilities of manufacturing sites of Products shall meet the following requirements:

(1) That they are cleaned and maintained appropriately in accordance with the Operating Procedures, Etc., to be sterilized if necessary, and records of which are made and maintained;

(2) That they have facilities for disposal of poisonous gases if used for Products, etc.

(3) Inside the Work Areas, work rooms shall be provided with structures and facilities for prevention of contamination by dust or microorganisms corresponding to the type, dosage form and manufacturing process of the Product, provided that this provision shall not apply so long as the same effects are obtained from the functionalities of manufacturing facilities, etc.

(4) Inside the Work Areas, work rooms for weighing operation of raw materials, filling operation or

for sealing operation shall be constructed so as not to allow the passage of personnel other than those working in the work room, provided that this provision shall not apply so long as there is no risk of contamination to Product by personnel other than those working in the work room.

(5) When Products, Etc. which are easily dispersed and cause anaphylaxis in minute amounts, or Products, Etc. which are suspected to have serious effects on other Products by cross-contamination are manufactured, the work rooms for those Products shall be exclusively used for the operation, and an independent air-treatment system shall be installed.

(6) That they have facilities for a supply of water (including water for washing facilities, devices and containers) of the quality and quantity needed for manufacturing Products.

(Manufacturing Control)

Article 10 A Manufacturer, Etc. shall require its Manufacturing Control Department to perform appropriately the following duties related to the manufacturing control in accordance with the Operating Procedures, Etc..

(1) To prepare and maintain a manufacturing protocol describing instructions, precautions and other necessary matters during the manufacturing process;

(2) To manufacture the Products in accordance with the manufacturing protocol.

(3) To prepare and maintain records of manufacturing the Products by Lot (by the manufacturing number in case of Products not constituting a Lot; the same hereinafter);

(4) To confirm whether Labeling and Packaging Materials of Products are appropriate for each Lot, to prepare and maintain records of the confirmation results;

(5) To store appropriately the Products, Etc. by Lot, and Labeling and Packaging Materials by Control Unit, manage their receipt/release, and to prepare and maintain records thereof;

(6) To confirm cleanness of the buildings and facilities and to prepare and maintain records of the results of confirmation;

(7) To maintain the sanitation and hygiene of personnel, to prepare and maintain records thereof;

(8) To perform periodical inspection and maintenance of the buildings and facilities, to prepare and maintain records thereof, and to perform appropriately calibration of meters, to prepare and maintain records thereof;

(9) To confirm from records of manufacturing, storage, receipt/release, as well as those of hygiene control that manufacturing control is properly performed, and to report the results of the confirmation in writing to the Quality Control Department;

(10) Other duties necessary for manufacturing control.

(Quality Control)

Article 11 A Manufacturer, Etc. shall have the Quality Control Department perform systematically and appropriately the following duties related to the quality control in accordance with the Operating Procedures, Etc..

(1) To collect samples of the Products, Etc from each Lot, and those of Labeling and Packaging Materials from each Control Unit, which are necessary for testing and inspection, and to prepare and maintain records thereof;

(2) To perform testing and inspection of samples collected from each Lot or from each Control Unit (including those performed in other testing and inspection facilities of the Manufacturer, Etc., or those performed by other testing and inspection organizations in its account whenever such use is deemed not to cause any problem), and prepare and maintain records thereof.

(3) To preserve samples, under proper conditions of storage, from each Lot of Products (only those which are used to make a market release decision under Article 9, Paragraph 2 of the Ordinance on Standard for Quality Control of Drug, Quasi-drugs, Cosmetics and Medical Devices (Ordinance of the Ministry of Health,

Labor and Welfare No.136, 2004); the same for Article 28, Paragraph 1), constituting of at least twice the quantity needed for all the required testing and inspection, for a period from the date of manufacturing equal to the duration of use or the expiry date (hereinafter referred to as "Expiry Date") plus one year (one month for radiopharmaceuticals), provided that this provision shall not apply to Products not constituting a Lot.

(4) To perform the periodical inspection and maintenance of the testing facilities and equipments, to prepare and maintain records thereof, and to perform calibration of meters appropriately, to prepare and maintain records thereof;

(5) To evaluate results of testing and inspection as defined in Item (2), and to report in writing to the Manufacturing Control Department;

(6) Other duties necessary for quality control.

2. When the standards for manufacturing and quality control in an exporting country and the procedures to evaluate conformity with those standards are recognized to be equivalent to those in Japan, testing and inspection as defined in preceding Paragraph, Item (2) (excluding visual inspection), may be substituted for confirmation of records of the testing and inspection performed by the Foreign Manufacturer of imported substances in an exporting country. In this case Manufacturer shall have the Quality Control Department perform appropriately the following duties:

(1) To confirm periodically that the Products, Etc. are manufactured through proper manufacturing procedures, etc.;

(2) To confirm periodically that manufacturing sites of the Foreign Manufacturer conform to standards for manufacturing control and quality control in the country;

(3) To prepare confirmation records of preceding two Item and to maintain the records thereof;

(4) To confirm records of the testing and inspection performed by the Foreign Manufacturer for the Product, to prepare and maintain confirmation records.

3. A Manufacturer, Etc. shall have the Quality Control Department confirm, for each Lot, in accordance with Operating Procedures, Etc., the confirmation results concerning manufacturing control reported by the Manufacturing Control Department as defined in preceding Article 10, Item (9).

(Control of Release from Manufacturing Site)

Article 12 A Manufacturer, Etc. shall have the Quality Control Department evaluate appropriately results of the manufacturing control and the quality control in accordance with Operating Procedures, Etc., and determine whether or not to release Products from the manufacturing site.

2. Persons in charge of the duties of the preceding Paragraph shall be able to perform the duty appropriately and smoothly.

3. A Manufacturer, Etc. shall ensure that the person(s) in charge of the duties under Paragraph 1 of this Article perform them unhindered.

4. A Manufacturer, Etc. shall not release Products from the manufacturing site until a determination is properly made under Paragraph 1 of this Article.

(Validation)

Article 13 A Manufacturer, Etc. shall have person(s), designated in advance, perform the following duties in accordance with the Operating Procedures, Etc..

(1) To perform Validation in the following cases;

A. When manufacturing of drugs commences at the manufacturing site;

B. When there are changes made in the manufacturing procedures, etc., which have a significant impact on the quality of Product;

C. When Validation is considered necessary to perform properly the manufacturing control and the quality control of a Product.

(2) To report in writing to the Quality Control Department the results of Validation.

2. A Manufacturer, Etc. shall take actions when it is found necessary to improve the manufacturing control and the quality control from the results of the Validation in the preceding Paragraph, Item (1), and prepare and maintain records of the actions taken.

(Control of Changes)

Article 14 When changes are to be made in the manufacturing procedures, etc. which may affect the quality of Products, the Manufacturer, Etc. shall have person(s), designated in advance, perform the following duties in accordance with the Operating Procedures, Etc.:

(1) To evaluate the effect of the changes on the quality of Products, to procure from the Quality Control Department approval of the changes on the basis of such evaluation, and to prepare and maintain records thereof;

(2) When the changes are made with approval of the Quality Control Department, to revise of the related documents, to train personnel and to take all other necessary actions.

(Control of Deviation)

Article 15 When Deviation from the manufacturing procedures, etc. (hereinafter referred to as "Deviation") happened, the Manufacturer, Etc. shall have person(s), designated in advance, perform the following duties in accordance with the Operating Procedures, Etc.:

(1) To record particulars of the Deviation;

(2) When a serious Deviation happened, to perform the following duties:

A. To evaluate effects of the Deviation on quality of Product, and to take necessary actions;

B. To prepare and maintain records of evaluation of A. and actions taken, and to report them in writing to the Quality Control Department;

C. To receive confirmation from the Quality Control Department of the report of the evaluation and actions taken in accordance with the provision B.

2. A Manufacturer, Etc. shall have the Quality Control Department prepare and maintain confirmation records under the preceding Paragraph, Item (2), C., and report them in writing to the Product Control Manager together with the record as defined in B., appropriately in accordance with the Operating Procedures, Etc..

(Information on Quality, Etc. and Management of Quality Deficiency, Etc.)

Article 16 When a Manufacturer, Etc. receives information on quality, etc. of a Product (hereinafter referred to as "Quality Information"), the Manufacturer, Etc., shall have person(s), designated in advance, perform the following duties in accordance with the Operating Procedures, Etc., unless it is evident that the matter of the Quality Information is not attributable to the manufacturing site:

(1) To investigate into the cause of the matter of the Quality Information and to take all necessary actions when it is found necessary to improve the manufacturing control and quality control;

(2) To prepare and maintain records describing details of the Quality Information, result of the investigation and improvement actions taken, and to report in writing to the Quality Control Department without delay;

(3) To receive confirmation from the Quality Control Department of the report as defined in the preceding Item.

2. When quality deficiency or a risk thereof is found by the confirmation under the preceding Paragraph, Item (3), the Manufacturer, Etc. shall have the Quality Control Department report the matter in writing to the Product Control Manager in accordance with the Operating Procedures, Etc.

(Recall)

Article 17 A Manufacturer, Etc. shall, when taking a recall because of the quality, etc. of a Product, have person(s), designated in advance, perform the following duties in accordance with the Operating Procedures, Etc.:

(1) In case where the Manufacturer, Etc. retains the recalled Products, to store them separately for a certain period and to properly dispose of them thereafter;

(2) To prepare and maintain records of details of the recall, and to report in writing to the Quality Control Department and the Product Control Manager, unless it is evident that the reason of the recall is not attributable to the manufacturing site.

(Self-inspection)

Article 18 A Manufacturer, Etc. shall have person(s), designated in advance, perform the following duties in accordance with the Operating Procedures, Etc.:

(1) To perform a periodic self-inspection over the manufacturing control and quality control of Products at the manufacturing site;

(2) To report result of the self-inspection in writing to the Product Control Manager;

(3) To prepare and maintain records of the self-inspection.

2. A Manufacturer, Etc. shall take actions when it is found necessary to improve the manufacturing control and quality control in light of the results of the self-inspection under the preceding Paragraph, Item (1), and prepare and maintain records of the actions taken.

(Education and Training)

Article 19 A Manufacturer, Etc. shall have person(s), designated in advance, perform the following duties in accordance with the Operating Procedures, Etc.:

(1) To conduct systematically training of personnel engaged in the Manufacturing/Quality Control Duties regarding the manufacturing control and quality control;

(2) To report the status of the training in writing to the Product Control Manager;

(3) To prepare and maintain records of the training.

(Control of Documents and Records)

Article 20 A Manufacturer, Etc. shall have person(s), designated in advance, perform the following duties concerning documents and records as defined in this Ordinance in accordance with the Operating Procedures, Etc.:

(1) To process approval, distribution, storage, etc. of documents in accordance with the Operating Procedures, Etc., when they are prepared or revised;

(2) When Operating Procedures, Etc. are prepared or revised, to put the relevant date on the Operating Procedures, Etc. and to maintain records of previous revisions;

(3) To maintain documents and records under in this Ordinance for a period of five years (when the Expiry Date of the Product to which the documents or records relate to plus one year is longer than five years, the Expiry Date plus one year, except for records on training) from the date of the documents or records (for the Operating Procedures, Etc., the date when they cease to be used).

Subchapter 2 Manufacturing Control and Quality Control of Active Pharmaceutical Ingredients

(Quality Control)

Article 21 A Manufacturer, Etc. (only the Manufacturer, Etc. of Products related to active pharmaceutical ingredients; the same in the next Article) shall, notwithstanding the provision of Article 11, Paragraph 1, Item (3),

retain as reference samples from each Lot of the active pharmaceutical ingredient Product, at least twice the quantity needed for all the required testing and inspection, for the following period from the date of manufacturing, under proper conditions:

(1) Three years from the date of completion of release of the Lot from the manufacturing site, for a Product for which the re-testing date (a date established for necessary re-testing and re-inspection for a Product, Etc. to determine if the Product, Etc. meets the relevant specifications after certain period from the date of manufacture) instead of the Expiry Date is set.

(2) Expiry date of the Product plus one year, for other Products than those as defined in the preceding Item.

(Management of Documents and Records)

Article 22 A Manufacturer, Etc. shall, notwithstanding the provision of Article 20, Item (3), maintain the documents and records as defined in this Ordinance, of active pharmaceutical ingredient Products for the duration of the Expiry Date of the Product plus one year (for three years for Products for which the re-testing date has been established instead of the Expiry Date, from the completion of the release from the manufacturing site of the Lot to which the document and record are related) from the date of the document or the record (for the Operating Procedures, Etc., the date when they ceased to be used).

Subchapter 3 Manufacturing Control and Quality Control of Sterile Drugs

(Buildings and Facilities of Manufacturing Site of Sterile Drugs)

Article 23 The buildings and facilities of a manufacturing site of a Manufacturer as defined under the Article 26, Paragraph 1, Item (3) of the Enforcement Rules or of a Foreign Manufacturer as defined under the Article 36, Paragraph 1, Item (3) of the Enforcement Rules shall meet the following requirements in addition to those provided in Article 9:

(1) Inside the Work Areas, work rooms or working control areas (consisting of work rooms and passages, etc., which are controlled so as to maintain a consistent level of cleanness; the same hereinafter) shall be equipped with adequate structures and facilities to maintain and control the degree of cleanness according to the type, dosage form and manufacturing process of the Product related to a sterile drug;

(2) Work rooms for the drying and sterilization operations of washed containers shall be used exclusively for that purpose, provided that this provision shall not apply so long as there is no risk of contamination of washed containers;

(3) Work rooms shall meet the following requirements:

A. To have facilities necessary to dry and store washed containers appropriately;

B. To have sterilizing equipment necessary to manufacture the Products related to a sterile drug, according to its type.

C. Areas for performing aseptic operations shall be equipped with the structures and facilities necessary to supply clean air processed through a filter and to perform appropriate pressure differential control;

D. When a Product related to an injectable drug is manufactured, pipe arrangements, etc. of those sections exposed to drug liquid which affect the guarantee of sterility shall be the facilities which can be washed easily and can be sterilized.

(4) Work rooms and working control areas for preparation, filling or sterilization operations (excluding labeling and packaging operations) subsequent to preparation shall meet the following requirements:

A. To be separated from the Work Area for drugs other than sterile drugs;

B. Work rooms for preparation and work rooms for filling or sealing operations shall be used exclusively for their respective purpose.

C. To have dressing rooms for exclusive use by personnel engaged in operations under B.

(5) Facilities to supply distilled water, etc. for manufacturing a Product related to sterile drug shall be constructed so as to prevent contamination of distilled water, etc. by foreign matters or microorganisms.

(Manufacturing Control)

Article 24 When a Product related to a sterile drug is manufactured, a Manufacturer, Etc. shall have the Manufacturing Control Department perform appropriately the following duties related to the manufacturing control in accordance with the Operating Procedures, Etc., in addition to the duties defined under Article 10:

(1) As for working areas, to set appropriately the degree of control and control the working environment such as cleanness, according to the type, dosage form, specific characters and manufacturing process of the Product related to a sterile drug and details of operations performed in the area;

(2) As to the Product, Etc. and Labeling and Packaging Materials, to set appropriately necessary control items such as the number of microorganisms, etc., and control them according to the type, dosage form, specific characters and manufacturing process of the Product related to a sterile drug;

(3) In manufacturing process, to take actions necessary to prevent contamination of the Product, Etc. and the Labeling and Packaging Materials by microorganisms, etc.;

(4) As to the process, etc. which is important to guarantee the aseptic nature of the Product, to set and control appropriately control parameters necessary for process control, according to the type, dosage form, specific characters and manufacturing process of the sterile drug Product;

(5) As to the manufacturing water, to set and control appropriately control parameters on needed microbiological items and physicochemical items, according to its use;

(6) To perform the following duties related to the sanitation and hygiene of personnel.

A. To restrict as much as possible the access of personnel other than those who are engaged in manufacturing to the Work Area;

B. To establish a strict procedure to prevent contamination by personnel who are engaged in operations related to processing of animal tissue raw materials and cultivation of microorganisms, etc. (excluding those used in the same manufacturing process as raw materials, etc.), and not to allow their access to the working area of the sterile drug Product except in full compliance therewith;

C. To restrict as much as possible the access personnel to the Clean Area or the Aseptic Area where actual operations are carried out.

(7) To perform the following duties related to the sanitation and hygiene of personnel working in the Clean Area or in the Aseptic Area:

A. When personnel who are engaged in manufacturing enter the Clean Area or the Aseptic Area, to have them change their clothes, etc. appropriately, according to the degree of control of the area;

B. When personnel are under such conditions that are suspected to contaminate a Product, Etc with microorganisms, etc. (including infectious diseases of skin or hair, common cold, injuries, or symptoms such as diarrhea or fever for unidentified causes), to have them report the fact.

(Education and Training)

Article 25 When a sterile drug Product is manufactured, the Manufacturer, Etc. shall have person(s) designated in advance perform the following duties in accordance with the Operating Procedures, Etc. in addition to the duties under Article 19:

(1) To conduct education and training of personnel engaged in the manufacturing or testing and inspection, in respect of the sanitation and hygiene necessary for manufacturing of a sterile drug Product and of microbiology;

(2) To conduct education and training of personnel working in the Clean Area and the Aseptic Area,

etc. in respect of the necessary action to prevent contamination by microorganisms, etc.

Subchapter 4 Manufacturing Control and Quality Control of Biological Drugs, Etc.

(Buildings and Facilities of Manufacturing Site of Biological Drugs, Etc.)

Article 26 The buildings and facilities of the manufacturing site of a Manufacturer, Etc. of Products related to a Biological Drug, Etc., shall meet the following requirements in addition to those provided in Articles 9 and 23:

(1) The buildings and facilities of manufacturing sites for a biological preparation Product (excluding a blood preparation not constituting a Lot) shall meet the following requirement:

A. Work areas shall be equipped with the following facilities in a room distinctly separated from others, except for facilities confirmed unnecessary to manufacture the Product according to the type, manufacturing method, etc. of the Product:

(i) Storage facilities for microorganisms;

(ii) Facilities for keeping animals for use in manufacturing or in testing and inspection after inoculation of microorganisms;

(iii) Facilities for processing animals for use in manufacturing or in testing and inspection;

(iv) Facilities for inoculating microorganisms into culture media, etc.;

(v) Facilities for cultivating microorganisms;

(vi) Facilities for collecting, inactivating and sterilizing cultured microorganisms;

(vii) Facilities for preparing diluents for stock solutions;

(viii) Facilities for diluting and subdividing stock solutions and for sealing containers;

(ix) Facilities for disinfecting devices and equipments that have been used in manufacturing or in testing and inspection.

B. The room provided with the facilities in A. (iv) and (vi) through (viii) and the room provided with the facilities for sterility test, among the facilities for testing a Product, etc. or Labeling and Packaging Materials, shall meet the following requirements:

(i) Work rooms shall be aseptic, provided that this provision shall not apply so long as a room is provided with facilities where aseptic operations can be carried out, according to the type, manufacturing method, etc. of the Product;

(ii) The aseptic room in (i) shall have an adjacent anteroom which allows exclusive passage of personnel to the work room and whose entrance and exit are not facing directly the outside

C. Work areas shall be equipped with the following facilities in addition to those in A:

(i) Facilities for breeding and managing animals for use in manufacturing or in testing and inspection;

(ii) Facilities for preparing culture media and diluents for the media;

(iii) Facilities for washing and sterilization of equipments/instruments, containers, etc. which are used in manufacturing or in testing and inspection;

(iv) Facilities for treating animal carcasses and other biological waste as well as for purifying sewage.

(2) The buildings and facilities of the manufacturing site of a blood preparation Product not constituting a Lot shall meet the following requirements:

A. Inside the Work Areas, work rooms for operations to separate and mix blood components, operations to inject and discharge drug solutions and operations to seal containers shall

be separated from the work room for Products other than a blood preparation Product;

B. Inside the work rooms, work rooms for the operations in A shall meet the following requirements when these operations are performed in an open system:

(i) The work room shall be used exclusively for that purpose;

(ii) The work room shall be aseptic, or provided with facilities where aseptic operations can be carried out.

C. Work areas shall be provided with dressing facilities for the exclusive use by personnel working in the aseptic room.

(3) The area for manufacturing a Product with human blood or plasma as raw materials shall be distinctly separated from other areas and shall be provided with facilities and equipment for exclusively manufacturing such Product, provided that this provision shall not apply the area for performing the manufacturing processes subsequent to the virus inactivation or elimination.

(Manufacturing Control)

Article 27 When Products related to a Biological Drug, Etc. are manufactured, the Manufacturer, Etc. shall have the Manufacturing Control Department, in addition to the duties as defined under Article 10 and Article 24, perform appropriately the following duties related to the manufacturing control, in accordance with the Operating Procedures, Etc.:

(1) When the Product is inactivated, or microorganisms, etc. contained in the Product are inactivated or eliminated, during the manufacturing process, to take action necessary for preventing contamination from the Product that has not been inactivated or virus-eliminated;

(2) When biochemical technology such as fermentation, etc. is applied during the manufacturing process, to perform continuous measurements of the temperature, hydrogen ion index, etc. necessary for the control of manufacturing process;

(3) When equipment for column chromatography is used during the manufacturing process, to take action required to prevent contamination of the equipment by microorganisms, etc., and to perform measurements of endotoxins, where necessary.

(4) In employing the culture method of providing a continuous supply of culture media to an incubation tank and of performing a continuous discharge of liquid media during the manufacturing process, to take action required to maintain incubation conditions in the incubation tank during the incubation period.

(5) To perform the following duties related to the sanitation and hygiene of personnel:

A. To restrict as much as possible the access of personnel other than those who are engaged in manufacturing to the Work Area;

B. To restrict as much as possible the access personnel to the Clean Area or the Aseptic Area where actual operations are carried out;

C. Not to assign personnel engaged in manufacturing to the position to keep Use Animals (excluding those are used in the manufacturing process).

(6) To perform the following duties related to the sanitation and hygiene of personnel working in the Clean Area or in the Aseptic Area:

A. To have personnel engaged in manufacturing wear work clothes, shoes, caps and masks that have been disinfected;

B. To have personnel undergo medical checkups at intervals not exceeding six months in order to confirm that they do not have diseases that are suspected to contaminate a Product, Etc. by microorganisms, etc.;

C. When personnel are under such conditions that are suspected to contaminate a Product, Etc with microorganisms, etc., to have them report the fact.

(7) To breed a Use Animal (for use in manufacturing; the same in this Paragraph) under constant and

proper care, and not to use an animal with infectious diseases or animals not appropriate for use in manufacturing through observations of their physical conditions before use;

(8) To dispose of all articles (limited to those contaminated during the manufacturing process) that have been contaminated with microorganisms and animal carcasses so as not to cause hazards to the health and hygiene;

(9) To prepare and maintain the following records in handling of microbial strains for use in manufacturing:

A. Name of microorganisms and the number assigned to each container;

B. Date of assignment, the name and address of a person who assigned (in case of corporation, the name and address);

C. Biological properties and date of testing;

D. Status of subculture.

(10) As to equipments/instruments of the work room for treating small pox viruses, acute poliomyelitis viruses, spore-forming pathogens or Mycobacterium tuberculosis, to attach a marker for each type of Product and to prohibit use in manufacturing other Products;

(11) As to materials derived from organisms (excluding plants) for use in manufacturing a Biological Drug Product (hereinafter referred to as "Biologically Derived Source Material"), the Manufacturer, Etc. shall confirm that the Biologically Derived Source Material appropriately satisfies the product master formula of the Product, and prepare and maintain the records of confirmation;

(12) As to the Biologically Derived Source Material for use in manufacturing of a Biological Drug Product, the Manufacturer, Etc. shall retain by itself the matters which the Minister of Health, Labor and Welfare requires to be recorded, for the period in Article 30, Items (2) and (3), or conclude an arrangement with an enterprise, etc. who collect materials of the Biologically Derived Source Material (the source materials of those used in manufacturing (including those used during manufacturing process)) (hereinafter referred to as the "Source Material Collecting Enterprise, Etc.") so that the records shall be maintained appropriately by the Source Material Collecting Enterprise, Etc.;

(13) A Manufacturer, Etc. shall prepare and maintain the records under Article 10, Item (10) and the preceding two Items for each Lot of the Product which is a Biological Drug, Etc.

2. When a Cellular/Tissue Based Drug. Product is manufactured, the Manufacturer, Etc. shall have the Manufacturing Control Department, in addition to the duties as defined under Article 10 and the preceding Paragraph, perform appropriately the following duties related to the manufacturing control in accordance with the Operating Procedures, Etc.:

(1) In handling cells or tissues collected from different Donors or Donor Animals, to take necessary actions to prevent mixture and cross-contamination of the cells or tissues;

(2) As to cells or tissues as source materials, to confirm, at the time of their receipt, from records on the following matters that the cells or tissues appropriately satisfy the product master formula of the Product, and prepare and maintain the records of the confirmation:

A. Facilities where the cells or tissues were collected;

B. Date on which the cells or tissues were collected;

C. When the cells or tissues are derived from humans, the status of diagnosis of the Donor through their health checking or testing for the Donor screening (the decision as to, from the results of the health checking and testing of a Donor, whether or not such Donor is are fully eligible to provide their cells or tissues as source materials of the Cellular/Tissue Based Drug Product);

D. When the cells or tissues are derived from animals, the status of receipt of the Donor Animal, as well as conditions of the testing and inspection and breeding and keeping of such animals for the Donor screening (the decision as to, from the results of the testing and inspection, and breeding and keeping of the Donor Animal, whether or not such Donor Animal is fully eligible to provide their

cells or tissues as source materials of the Cellular/Tissue Based Drug Product);

E. History of collecting the cells or tissues;

F. Matters necessary for ensuring the quality of the Cellular/Tissue Based Drug Product, in addition to those in A through E. above.

(3) In collecting the cells or tissues as source materials from a Donor Animal, to take necessary action to prevent contamination by microorganisms during the collection, and to prepare and maintain records of the action taken;

(4) When personnel meet any of the following conditions, not to have the personnel work in the Clean Area or in the Aseptic Area:

A. When personnel are under physical conditions which may lead to contamination of a Product, Etc. with microorganisms, etc.;

B. When personnel have treated microorganisms, etc. which may contaminate cells or tissues immediately prior to their collecting or processing.

(5) To collect information, for each Product, the name of the destination facilities, the date of release and Lots, and to prepare and maintain records thereof;

(6) To take necessary action of delivery to ensure the quality of a Product, and to prepare and maintain records of the action taken;

(7) To prepare and maintain records of breeding and keeping of Donor Animals after their acceptance;

(8) To prepare and maintain records in Items (2), (3), (5) and (6) in this Paragraph by Lot (by Product for the records of Item (5)).

3. Records of a Biological Drug Product in Article 10 and in the preceding two paragraphs shall be maintained so as to enable confirmation of a series of records, from those of Biologically Derived Source Materials used in manufacturing to those of a Product manufactured with the Biologically Derived Source Materials.

(Quality Control)

Article 28 With respect to Products related to a drug which is a designated biological products under Article 2, Paragraph 10 of the Law (hereinafter referred to as a "Designated Biological Drug") or a Cellular/Tissue Based Drug Product, a Manufacturer, Etc. shall, notwithstanding the provision of Article 11, Paragraph 1, Item (3), retain as reference samples from each Lot of the Product (in the case of a Designated Biological Drug not constituting a Lot, from the Biologically Derived Source Material w used in manufacturing of the Product by each manufacturing number of the Product or by Lot of such Biologically Derived Source Material), at least twice the quantity needed for all the required testing and inspection, for the following period from the date of manufacturing, under proper conditions., constituting of at least twice the quantity needed for all the required tests, for the following periods from the date of manufacturing, provided that this provision shall not apply to a Designated Biological Drug Product not constituting a Lot under a contract, for which the Manufacturer, Etc. has concluded an arrangement with the Source Material Collecting Enterprise, Etc., that the Source Material Collecting Enterprise, Etc. shall retain the reference samples for the following period. For a Designated Biological Drug Product constituting a Lot or to a Cellular/Tissue Based Drug Product, retention of the Biologically Derived Source Material used in manufacturing of the Product may be substituted for retention of the Product, when a period of the Expiry Date plus one year (one month for the radiopharmaceutical Product) has passed:

(1) A period of the Expiry Date plus ten years for a Designated Biological Drug Product;

(2) An appropriate period for a Cellular/Tissue Based Drug Product (excluding a Product in Item (1))

2. When a Biological Drug Product is manufactured, the Manufacturer, Etc. shall have the Quality Control Department, in addition to the duties as defined under Article 11, perform systematically and appropriately the

following duties related to the quality control in accordance with the Operating Procedures, Etc.:

(1) To separate samples by proper labeling of identification in order to prevent mixture and cross-contamination of the samples;

(2) To perform, at z proper stage of manufacturing, the testing and inspection which is important for the quality control but may not be performed for the Product;

(3) To breed a Use Animal (for use in manufacturing; the same in this Paragraph) under constant and proper care, and not to use an animal with infectious diseases or animals not appropriate for use in manufacturing through observations of their physical conditions before use;

(4) To dispose of all articles (limited to those contaminated during the manufacturing process) that have been contaminated with microorganisms and animal carcasses so as not to cause hazards to the health and hygiene;

(5) To prepare and maintain the following records in handling of microbial strains for use in testing and inspection:

A. Name of microorganisms and the number assigned to each container;

B. Date of assignment, the name and address of a person who assigned (in case of corporation, the name and address);

C. Biological properties and date of testing;

D. Status of subculture.

(6) To prepare and maintain records of the results of testing and inspection for each Lot of the Product related to a Biological Drug, Etc.

3. When a Cellular/Tissue Based Drug. Product is manufactured, the Manufacturer, Etc. shall have the Quality Control Department, in addition to the duties as defined under Article 11 and the preceding Paragraph, perform appropriately the following duties related to the quality control in accordance with the Operating Procedures, Etc.:

(1) To perform by itself testing and inspection of a Donor Animal at the time of or after its receipt and other necessary duties, or to have designated person(s) perform the duties, according to the type of duties;

(2) To prepare and maintain records of the duties in the preceding Item.

4. Records of a Biological Drug in the preceding three paragraphs shall be maintained so as to enable confirmation of a series of records, from those of Biologically Derived Source Materials used in manufacturing to those of a Product manufactured with the Biologically Derived Source Materials.

(Education and Training)

Article 29 When a Product related to a Biological Drug, Etc. is manufactured, the Manufacturer, Etc. shall have a person designated in advance perform the following duties in accordance with the Operating Procedures, Etc. in addition to the duties as defined under Articles 19 and 25:

(1) To conduct education and training of personnel engaged in the manufacturing or testing and inspection of a Biological Drug, Etc. in respect of microbiology, medicine and veterinary medicine, etc.;

(2) To conduct education and training of personnel working in the Aseptic Area or other areas where pathogenic microorganisms are handled, in respect of necessary action to prevent contamination by microorganisms, etc.

(Control of Documents and Records)

Article 30 When a Product related to a Biological Drugs, Etc. is manufactured, the Manufacturer, Etc. shall, notwithstanding the provision of Article 20, Item (3), maintain documents and records under this Ordinance for the following period (five years for records on education and training) from the date of the document:

(1) Five years for Products other than a Biological Drug and a Cellular/Tissue Based Drug (hereinafter referred to as a “Biological – Cellular/Tissue Based Drug”), provided that, when the duration of

Expiry Date of the drug plus one year is longer than five years, the Expiry Date plus one year);

(2) A period of the Expiry Date plus thirty years for a Designated Biological Drug Product or a Biological Drug Product manufactured from human blood as the source material;

(3) A period of the Expiry Date plus ten years for a Biological – Cellular/Tissue Based Drug Product (excluding a Product in the preceding Item).

Subchapter 5 Miscellaneous Provision

(Exceptions of Retention of Records)

Article 31 Notwithstanding the preceding Article, a Manufacturer, Etc. shall have person(s) designated in advance maintain records of the preceding Article of Biological Drug Products designated by the Minister of Health, Labor and Welfare, for a period designated by the Minister of Health, Labor and Welfare, provided that this provision shall not apply to cases where an arrangement is concluded with a Source Material Collecting Enterprise, Etc. so that the records shall be maintained appropriately by the Source Material Collecting Enterprise, Etc., for the required period.

Chapter 3 Manufacturing Control and Quality Control in the Manufacturing Site of a Quasi-drug Manufacturer

(Manufacturing Control and Quality Control of Quasi-drugs)

Article 32 The provisions in Chapter 2 (excluding Article 7, Item (4), Article 9, Item (5), Article 23, Item (3), D and Subchapter 4) shall apply mutates mutandis to quasi-drugs. In this case, a "drug manufacturing manager as defined under Article 17, Paragraph 3 of the Law" under Article 4, Paragraph 1 shall read a "responsible engineer as defined under Article 17, Paragraph 5 of the Law," and a "Product Control Manager" in Chapter 2 shall read a "responsible engineer," "Article 42, Paragraph 1 of the Law" under Article 7, Item (2) shall read "Article 42, Paragraph 2 of the Law," "Article 9, Paragraph 2" under Article 11, Paragraph 1, Item (3) shall read "Article 9, Paragraph 2 as applied mutates mutandis under Article 20," and a "sterile drug" in Subchapter 2 shall read a "sterile quasi-drug."

Supplementary Provisions

(Date of Entry into Force)

Article 1 This Ordinance shall enter into effect on April 1, 2005.

(Measures in Transition)

Article 2 The provisions of Articles 9, 23, 26 and the provisions of Articles 9 and 23 applied mutates mutandis under Article 32 as revised by this Ordinance may not apply to a Foreign Manufacturer for two years from the date of entry into force of this Ordinance.

Article 3 Regulations on Importation Sales Control and Quality Control of Drugs and Quasi-drugs (Ordinance No. 62, 1999of the Minister of Health, Labor and Welfare) shall cease to be in effect on March 31, 2005.