

Tentative translation VER. 1¹

MHLW Ministerial Ordinance No. 179, 2004

In accordance with the provisions of Item (4) of Paragraph 2 of Article 14 and Item (4) of Paragraph 2 of Article 14 applied *mutatis mutandis* under Paragraph 5 of Article 19-2 of Pharmaceutical Affairs Law (Law No. 145, 1960), MHLW Ministerial Ordinance to revise the whole of Drugs and Quasi-drugs Manufacturing Control and Quality Control Regulations (MHLW Ministerial Ordinance No. 16, 1999) is established as follows.

24 December 2004

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Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs

CONTENTS

Chapter 1 General Provisions (Articles 1 to 3)

Chapter 2 Manufacturing Control and Quality Control in Manufacturing Sites of Drug Manufacturers, etc.

Section 1 General Rules (Articles 4 to 20)

Section 2 Manufacturing Control and Quality Control of APIs
(Article 21 and Article 22)

Section 3 Manufacturing Control and Quality Control of Sterile Drugs
(Articles 23 to 25)

Section 4 Manufacturing Control and Quality Control of Biological-origin Drugs, etc.
(Articles 26 to 30)

Section 5 Miscellaneous Provision (Article 31)

Chapter 3 Manufacturing Control and Quality Control in Manufacturing Sites of Quasi-drug Manufacturers, etc. (Article 32)

Supplementary Provisions

¹ Note/ This is a tentative translation of afore-mentioned Ordinance in English which is not an authentic and not formally authorised by Ministry of Health, Labour and Welfare of Japan.

Chapter 1 General Provisions

(Purpose)

Article 1 This Ministerial Ordinance shall provide the standards in accordance with the provision of Item (4) of Paragraph 2 of Article 14 (including the case where it is applied *mutatis mutandis* under Paragraph 5 of Article 19-2, and hereinafter referred to as such) of Pharmaceutical Affairs Law (Law No. 145, 1960) (hereinafter referred to as “Law”) which provides that such standards shall be provided by MHLW Ministerial Ordinances.

(Definitions)

Article 2 “**Product**” throughout this Ministerial Ordinance means the object (including those which have undergone the intermediate process and need to undergo subsequent process to be the (final) products (hereinafter referred to as “intermediate product”)) that has undergone the manufacturing process in the manufacturing site.

2. “**Packaging and labelling material**” throughout this Ministerial Ordinance means the container, wrapper and labelling (including the package insert, and hereinafter referred to as such) for the products.
3. “**Lot**” throughout this Ministerial Ordinance means a grouping of the products or raw materials (hereinafter referred to as “products, etc.”) that are manufactured so as to have a uniform quality in a series of the manufacturing process for a certain manufacturing period.
4. “**Controlled unit**” throughout this Ministerial Ordinance means a grouping of the packaging and labelling materials that have been verified to be same.
5. “**Validation**” throughout this Ministerial Ordinance means to verify and document that the buildings and facilities of the manufacturing site, procedures, processes and other procedures of the manufacturing control and quality control (hereinafter referred to as “manufacturing procedure, etc.”) provide the anticipated results.
6. “**Clean area**” throughout this Ministerial Ordinance means the place, among those areas where the manufacturing operations are conducted (hereinafter referred to as “work areas”), where the weighing operations for the raw materials or the formulating operations for the drug substances are conducted or where the cleaned containers are exposed to the air in the work areas.
7. “**Aseptic area**” throughout this Ministerial Ordinance means the place, among the work areas, where the aseptic drug substances or sterilised containers are exposed to the air in the work areas, where the filling operations for the drug substances are conducted, where the sealing operations for the containers are conducted, or where the aseptic operations including sterility tests are conducted.
8. “**Cell/tissue-based drug**” throughout this Ministerial Ordinance means the drug composed of human or animal cells or tissue (excluding human blood and the drugs which compose of the components manufactured using human blood).
9. “**Donor**” throughout this Ministerial Ordinance means the person who donates the cells or tissue that serves as the raw materials for the cell/tissue-based drugs (excluding those

concerned with the body of a brain-dead person specified in Paragraph 2 of Article 6 of Law on Organ Transplantation (Law No. 104, 1997)).

10. “**Donor animal**” throughout this Ministerial Ordinance means the animal which provides the cells or tissue that serves as the raw materials for the cell/tissue-based drugs.

(Scope)

Article 3 The marketing authorisation holder of the drugs specified in Paragraph 1 of Article 14 of Law (excluding in-vitro diagnostic reagents, and hereinafter referred to as such) or quasi-drugs, or the appointed marketing authorisation holder of drugs or quasi-drugs specified in Paragraph 4 of Article 19-2 of Law shall, in accordance with the provision of Chapter 2 or the provision of Chapter 2 applied *mutatis mutandis* under Chapter 3, have the manufacturer and the foreign manufacturer specified in Paragraph 1 of Article 13-3 of Law (hereinafter simply referred to as “foreign manufacturer”) (hereinafter collectively referred to as “manufacturer, etc.”) conduct the manufacturing control and quality control of the products in the manufacturing site.

2. The manufacturer, etc. of the products concerned with drugs or quasi-drugs shall, in accordance with the provision of Chapter 2 or the provision of Chapter 2 applied *mutatis mutandis* under Chapter 3, conduct the manufacturing control and quality control of the products in the manufacturing site specified in Article 96 of Enforcement Regulations of Pharmaceutical Affairs Law (MHW Ministerial Ordinance No. 1, 1961, and hereinafter referred to as “Enforcement Regulations”).
3. The manufacturer, etc. of the products concerned with drugs or quasi-drugs for export specified in Paragraph 1 of Article 80 of Law shall, in accordance with the provision of Chapter 2 or the provision of Chapter 2 applied *mutatis mutandis* under Chapter 3, conduct the manufacturing control and quality control of the products.

Chapter 2 Manufacturing Control and Quality Control in Manufacturing Sites of Drug Manufacturers, etc.

Section 1 General Rules

(Manufacturing Department and Quality Department)

Article 4 The manufacturer, etc. shall, for each of the manufacturing sites, establish a department concerned with manufacturing control (hereinafter referred to as “manufacturing department”) and a department concerned with quality control (hereinafter referred to as “quality department”) under the supervision of the drug manufacturing manager specified in Paragraph 3 of Article 17 of Law and the manager controlling the manufacturing of the biological-origin products specified in Paragraph 1 of Article 68-2 of Law (the biological-origin products specified in Paragraph 9 of Article 2 of Law, and hereinafter referred to as such) (in case of a foreign manufacturer, the person responsible for the manufacturing site which has been recognised in accordance with the provision of Paragraph 1 of Article 13-3 of Law or the person designated beforehand by such a foreign manufacturer) (hereinafter collectively referred to as “manufacturing manager”).

2. The quality department shall be independent of the manufacturing department.

(Manufacturing Manager)

Article 5 The manufacturing manager shall conduct the following duties.

- (1) To supervise the duties of the manufacturing control and quality control (hereinafter referred to as “manufacturing and quality control duties”), and to manage the manufacturing and quality control duties so that they are conducted properly and efficiently, and
 - (2) To verify that necessary actions have been promptly taken to verify the progress of such actions, and to give instructions, where necessary, to take necessary actions such as improvements, in case where quality defects or a potential risk which could affect the quality of the products exists.
2. The manufacturer, etc. shall ensure that the manufacturing manager can conduct his/her duties without hindrance.

(Personnel)

Article 6 The manufacturer, etc. shall appropriately assign responsible persons who have competence for conducting the manufacturing and quality control duties properly and efficiently (hereinafter simply referred to as “responsible persons”) according to the organisation, size, type of the duties, etc. of the manufacturing site.

2. The manufacturer, etc. shall assign an appropriate number of responsible persons according to the organisation, size, type of the duties, etc. of the manufacturing site.
3. The manufacturer, etc. shall ensure sufficiently the personnel who have competence for appropriately conducting the manufacturing and quality control duties.
4. The manufacturer, etc. shall define and document appropriately the scope of the responsibilities of the personnel (including the manufacturing manager and the responsible persons) engaged in the manufacturing and quality control duties, and the system for supervising the personnel.

(Seihin Hyojun Sho)

Article 7 The manufacturer, etc. shall, for each of the products (excluding the intermediate products, and hereinafter referred to as such in this Article), establish and maintain *Seihin Hyojun Sho* describing the following items in each of the manufacturing sites concerned with the manufacturing of such products, and have *Seihin Hyojun Sho* approved by the quality department.

- (1) The items of the marketing approval of the drugs concerned with the products,
- (2) The items of the standards established in accordance with the provision of Paragraph 1 of Article 42 of Law and other laws, orders and ordinances related to pharmaceutical affairs or the orders or official actions based on the laws and

ordinances which are relevant to the quality of the drugs,

- (3) The manufacturing procedure (excluding the items indicated in preceding Item (1)),
- (4) The following items in case where the products the manufacturer, etc. intend to manufacture are those concerned with the drugs that correspond to the biological-origin products (hereinafter referred to as “biological-origin drugs”), the biological preparations specified in Item (3) a. of Paragraph 2 of Article 80 of Enforcement Order of Pharmaceutical Affairs Law (Cabinet Order No. 11, 1961), the drugs designated by Minister of Health, Labour and Welfare in accordance with the provision of Paragraph 1 of Article 43 of Law, the drugs manufactured by application of gene recombination technology, the drugs manufactured using as the raw materials the drugs manufactured by application of gene recombination technology, the drugs manufactured by application of incubation technology of human or animal cells, the drugs using as the raw materials the drugs manufactured by application of incubation technology of human or animal cells or the cell/tissue-based drugs (hereinafter collectively referred to as “biological-origin drugs, etc.”), and
 - a. The name, essence and property of the objects obtained from humans, animals, plants or microorganisms using as the raw materials or ingredients and their quantities therein, and other specifications, and
 - b. The specifications (including the keeping control methods) of the animals utilised in the manufacturing or testing (including the donor animals, and hereinafter referred to as “utilised animals”).
- (5) Other necessary items.

(Documented Procedure, etc.)

Article 8 The manufacturer, etc. shall, for each of the manufacturing sites, establish and maintain a sanitation control standard code describing sanitation control of the buildings and facilities and the personnel and other necessary matters.

2. The manufacturer, etc. shall, for each of the manufacturing sites, establish and maintain a manufacturing control standard code describing the storage of the products, etc., control of the manufacturing process and other necessary matters.
3. The manufacturer, etc. shall, for each of the manufacturing sites, establish and maintain a quality control standard code describing the methods of collecting samples, methods of judging the testing results and other necessary matters.
4. The manufacturer, etc. shall, for each of the manufacturing sites, establish and maintain documented procedure for the following items (hereinafter referred to as “documented procedure”) for proper and efficient conduct of the manufacturing control and quality control, in addition to the documents specified in preceding three Paragraphs 1, 2 and 3.
 - (1) The procedure for controlling the shipment from the manufacturing site,
 - (2) The procedure for conducting the validation,

- (3) The procedure for controlling changes specified in Article 14,
 - (4) The procedure for controlling deviation specified in Article 15,
 - (5) The procedure for handling the information on quality, etc. and quality defects, etc.,
 - (6) The procedure for handling recall,
 - (7) The procedure for the self-inspection,
 - (8) The procedure for the training,
 - (9) The procedure for controlling the documents and records, and
 - (10) Other necessary procedures for proper and efficient conduct of the manufacturing control and quality control.
5. The manufacturer, etc. shall place the *Seihin Hyojun Sho*, sanitation control standard code, manufacturing control standard code, quality control standard code, and documented procedure (hereinafter collectively referred to as “documented procedure, etc.”) in the manufacturing site.

(Buildings and Facilities)

Article 9 The buildings and facilities of the manufacturing site of the products shall comply with the following requirements.

- (1) To be appropriately cleaned and maintained according to the use, to be sterilised where necessary, and to be ensured that records thereof are established and maintained, in accordance with the documented procedure, etc.,
- (2) To be provided with the facilities necessary for disposing of the poisonous gases, in case where they are handled according to the products, etc.,
- (3) To be ensured that the work rooms, among the work areas, are provided with the buildings and facilities necessary for preventing contamination with dust or microorganisms, according to the type, dosage form and manufacturing process of the products, with the proviso that this provision shall not apply in case where the manufacturing facilities, etc. provide equivalent functions,
- (4) To be ensured that the work rooms, among the work areas, where the weighing operations for the raw materials or the formulating operations, filling operations or sealing operations for the products are conducted are the buildings which do not allow passage of the personnel other than those conducting operations in such work rooms, with the proviso that this provision shall not apply in case where the products could not be contaminated by the personnel other than those conducting operations in such work rooms,

- (5) In case where the products, etc. are easily dispersed and cause hypersensitive reactions in a minute amount or could cross-contaminate and seriously affect other products, to be ensured that the work rooms are exclusively used for such products, etc. and their air-handling system is separated from those used for other products, and
- (6) To be provided with the facilities for supplying water (including those for cleaning the facilities and equipment and for washing the containers) of the quality and quantity necessary for the manufacturing.

(Manufacturing Control)

Article 10 The manufacturer, etc. shall have the manufacturing department appropriately conduct the following duties concerned with manufacturing control in accordance with the documented procedure, etc.

- (1) To establish and maintain documented manufacturing orders describing the instructions, precautions and other matters necessary for the manufacturing process,
- (2) To manufacture the products in accordance with the documented manufacturing orders,
- (3) To establish and maintain records concerned with the manufacturing of the products for each lot (for each manufacturing number in case where the products do not constitute a lot, and hereinafter referred to as such),
- (4) To verify, for each lot, that the packaging and labelling materials of the products are proper, and to establish and maintain records concerned with the results of the verification,
- (5) To properly store the products, etc. for each lot and the packaging and labelling materials for each controlled unit to control their receipt and delivery, and to establish and maintain records thereof,
- (6) To verify that the buildings and facilities are cleaned, and to establish and maintain records concerned with the results of the verification,
- (7) To conduct sanitation control of the personnel, and to establish and maintain records thereof,
- (8) To conduct periodical maintenance of the buildings and facilities and to establish and maintain records of the maintenance, and to calibrate, appropriately the measuring equipment and to establish and maintain records of the calibration,
- (9) To verify that the manufacturing control is appropriately conducted as evidenced by the records of the manufacturing, storage and receiving and delivering as well as the records of the sanitation control, and to report in writing the results of the verification to the quality department, and

- (10) To conduct other duties necessary for manufacturing control.

(Quality Control)

Article 11 The manufacturer, etc. shall have the quality department conduct appropriately as planned the following duties concerned with quality control of the products in accordance with the documented procedure, etc.

- (1) To collect samples necessary for testing from each lot of the products, etc. and from each controlled unit of the packaging and labelling materials, and to establish and maintain records of the collection,
 - (2) To conduct the testing (including those conducted on the manufacturer's, etc. own responsibilities using their testing facilities or other testing institutions and such conduct is verified to present no hindrance to the proper testing, and hereinafter referred to as such) of the collected samples for each lot or for each controlled unit, and to establish and maintain records of the testing,
 - (3) To store a reserve sample in an amount of at least twice of the quantity necessary for the required testing from the products (limited to those for which decisions on market release are made specified in Paragraph 2 of Article 9 of Ministerial Ordinance on Standards for Quality Assurance for Drugs, Quasi-drugs, Cosmetics and Medical Devices (MHLW Ministerial Ordinance No. 136, 2004), and hereinafter referred to as such in Paragraph 1 of Article 28) for each lot, under appropriate conditions for the shelf life or the period until the expiry date (hereinafter simply referred to as "shelf life") of such products plus 1 year (plus 1 month, in case where the products are those concerned with the radiopharmaceuticals) from the date of the manufacturing, with the proviso that this provision shall not apply to those products which do not constitute a lot,
 - (4) To conduct periodical maintenance of the facilities and equipment for the testing and to establish and maintain records of the maintenance, and to calibrate appropriately the measuring equipment and to establish and maintain records of the calibration,
 - (5) To judge the results of the testing specified in preceding Item (2), and to report in writing the results of the judgement to the manufacturing department, and
 - (6) To conduct other duties necessary for quality control.
2. In case where it is deemed that the standards for the manufacturing control and quality control in the exporting country and the procedures for verifying conformity to those standards are equivalent to those in Japan, the testing specified in Item (2) of preceding Paragraph 1 (excluding the testing of appearance) may be replaced by verification of the records of the testing for the imported objects which has been conducted by the foreign manufacturer of the exporting country. In this case, the manufacturer shall have the quality department conduct appropriately the following duties.
 - (1) To conduct periodical verification that the products, etc. are manufactured in accordance with appropriate manufacturing procedure, etc.,

- (2) To conduct periodical verification that the manufacturing sites of such foreign manufacturer conform to the standards for the manufacturing control and quality control established in the exporting country,
 - (3) To establish and maintain records of the verification specified in preceding two Items (1) and (2), and
 - (4) To verify records of the testing of such products conducted by such foreign manufacturer, and to establish and maintain records of the verification.
3. The manufacturer, etc. shall have the quality department verify, in accordance with the documented procedure, etc., for each lot of the products, the results of the verification concerned with manufacturing control which have been reported by the manufacturing department specified in the provision of Item (9) of preceding Article.

(Control of Shipment from Manufacturing Sites)

Article 12 The manufacturer, etc. shall have the quality department evaluate appropriately the results of the manufacturing control and quality control in accordance with the documented procedure, etc., and conduct the duties to make decisions of whether or not to release the products from the manufacturing site.

2. The personnel who conduct the duties specified in preceding Paragraph 1 shall have competence for conducting such duties properly and efficiently.
3. The manufacturer, etc. shall ensure that the personnel who conduct the duties specified in preceding Paragraph 1 can conduct such duties without hindrance.
4. The manufacturer, etc. shall not ship the products from the manufacturing site before the decisions specified in preceding Paragraph 1 are made properly.

(Validation)

Article 13 The manufacturer, etc. shall have the personnel designated beforehand conduct the following duties in accordance with the documented procedure, etc.

- (1) To conduct the validation in the following cases, and
 - a. The case where the manufacturing of the drugs will newly start at such manufacturing site,
 - b. The case where any change will be made in the manufacturing procedure, etc. which seriously affect the quality of the products, or
 - c. Other cases where it is deemed to be necessary to conduct the validation for appropriate conduct of the manufacturing control and quality control of the products.
 - (2) To report the planning and results of the validation in writing to the quality department.
2. The manufacturer, etc. shall, in case where improvements are necessary for the

manufacturing control and quality control based on the results of the validation specified in Item (1) of preceding Paragraph 1, take necessary actions, and establish and maintain records of such actions.

(Change Control)

Article 14 The manufacturer, etc. shall, in case where any change will be made in the manufacturing procedure, etc. which could affect the quality of the products, have the person designated beforehand conduct the following duties in accordance with the documented procedure, etc.

- (1) To evaluate effects on the quality of the products due to such change, to be approved by the quality department with respect to the change being made based on the results of the evaluation, and to establish and maintain records of the evaluation and approval, and
- (2) To revise relevant documents, to train the personnel and to take other necessary actions in case where any change is made upon approval of the quality department specified in the provision of preceding Item (1).

(Deviation Control)

Article 15 The manufacturer, etc. shall, in case where any deviation from the manufacturing procedure, etc. (hereinafter simply referred to as “deviation”) has occurred, have the person designated beforehand conduct the following duties in accordance with the documented procedure, etc.

- (1) To record the details of the deviation, and
 - (2) To conduct the following duties in case where any serious deviation has occurred.
 - a. Evaluating effects on the quality of the products due to the deviation, and taking necessary actions,
 - b. Establishing and maintaining records of the results of the evaluation and the actions specified in preceding a., and reporting them in writing to the quality department, and
 - c. Being verified by the quality department of the results of the evaluation and the actions which have been reported in accordance with the provision of preceding b.
2. The manufacturer, etc. shall have the quality department establish and maintain records of the verification specified in the provision of Item (2) c. of preceding Paragraph 1 in accordance with the documented procedure, etc., and report appropriately in writing the records together with those specified in Item (2) b. of preceding Paragraph 1 to the manufacturing manager.

(Handling of Information on Quality, etc. and Quality Defects, etc.)

Article 16 The manufacturer, etc. shall, in case where they have received the information on the quality, etc. of the products (hereinafter referred to as “quality information”), have the person designated beforehand conduct the following duties in accordance with the

documented procedure, etc., with the proviso that this provision shall not apply in case where the matters concerned with the quality information are not obviously attributable to their manufacturing site.

- (1) To investigate the cause of the matters concerned with such quality information, and to take necessary actions in case where improvements are necessary for correcting the manufacturing control and quality control,
 - (2) To establish and maintain records describing the details of such quality information, the results of the investigation and the improvements, and to promptly report in writing the records to the quality department, and
 - (3) To be verified by the quality department of the reports specified in preceding Item (2).
2. The manufacturer, etc. shall, in case where they have identified quality defects or their possibility as a result of the verification specified in Item (3) of preceding Paragraph 1, have the quality department report in writing such matters to the manufacturing manager in accordance with the documented procedure, etc.

(Handling of Recall)

Article 17 The manufacturer, etc. shall, in case where recall of the products has been conducted due to their quality, etc., have the person designated beforehand conduct the following duties in accordance with the documented procedure, etc.

- (1) To segregate the products recalled, and to dispose of them appropriately after storing for a certain period, and
- (2) To establish and maintain records of handling of recall describing the details of the recall, and to report in writing them to the quality department and the manufacturing manager, with the proviso that this provision shall not apply in case where the reason for such recall is not obviously attributable to their manufacturing site.

(Self-inspections)

Article 18 The manufacturer, etc. shall have the person designated beforehand conduct the following duties in accordance with the documented procedure, etc.

- (1) To conduct the self-inspections periodically on the manufacturing control and quality control of the products in their manufacturing site,
 - (2) To report in writing the results of the self-inspections to the manufacturing manager, and
 - (3) To establish and maintain records of results of the self-inspections.
2. The manufacturer, etc. shall take necessary actions in case where improvements are necessary for correcting the manufacturing control and quality control based on the

results of the self-inspections specified in Item (1) of preceding Paragraph 1, and to establish and maintain records of such actions.

(Training)

Article 19 The manufacturer, etc. shall have the person designated beforehand conduct the following duties in accordance with the documented procedure, etc.

- (1) To implement as planned the training necessary for conducting the manufacturing control and quality control for the personnel engaged in the manufacturing and quality control duties of the products,
- (2) To report in writing the progress of the training to the manufacturing manager, and
- (3) To establish and maintain records of the implementation of the training.

(Control of Documents and Records)

Article 20 The manufacturer, etc. shall, for the documents and records specified in this Ministerial Ordinance, have the person designated beforehand conduct the following duties in accordance with the documented procedure, etc.

- (1) To approve, distribute, maintain, etc. the documents in case where they are established or revised in accordance with the documented procedure, etc.,
- (2) To put the date of the establishment or the revision of the documented procedures, etc. on them, and to maintain records of the history of previous revisions in case where they are established or revised, and
- (3) To maintain the documents and records specified in this Ministerial Ordinance for 5 years (1 year plus the shelf life, for the products concerned with such records, etc. (excluding those of the training) of which shelf life plus 1 year exceeds 5 years) from the date of the establishment (from the date when they fell into disuse, for the documented procedure, etc.).

Section 2 Manufacturing Control and Quality Control of APIs

(Quality Control)

Article 21 The manufacturer, etc. (limited to those of the products concerned with active pharmaceutical ingredients (APIs), and hereinafter referred to as such in next Article) shall, notwithstanding the provision of Item (3) of Paragraph 1 of Article 11, store a reserve sample in an amount of at least twice of the quantity necessary for the required testing from the products concerned with APIs for each lot, under appropriate conditions for the period specified in each of the following Items from the date of the manufacturing.

- (1) 3 years from the date of completion of the shipment of such a lot from their manufacturing site, for the products for which retest date (the date when the products, etc., after a period has passed from the date of the manufacturing,

should be retested to ensure that they still comply with the certain specifications, etc.) has been assigned and replaced the shelf life, or

- (2) 1 year plus the shelf life of the products, for such products other than those specified in preceding Item (1).

(Control of Documents and Records)

Article 22 The manufacturer, etc. shall, notwithstanding the provision of Item (3) of Article 20, maintain the documents and records specified in this Ministerial Ordinance regarding the products concerned with APIs for 1 year plus the shelf life of such products from the date of the establishment (for the documented procedure, etc., the date when they fell into disuse) (for the products for which retest date has been assigned and replaced the shelf life, for 3 years from the date of completion of the shipment of the lot concerned with such documents and records from their manufacturing site).

Section 3 Manufacturing Control and Quality Control of Sterile Drugs

(Buildings and Facilities of Manufacturing Sites of Sterile Drugs)

Article 23 The buildings and facilities of the manufacturing site of the manufacturer in the category specified in Item (3) of Paragraph 1 of Article 26 of Enforcement Regulations and the foreign manufacturer in the category specified in Item (3) of Paragraph 1 of Article 36 of Enforcement Regulations shall comply with the following requirements, in addition to those specified in Article 9.

- (1) To be ensured that the work rooms or controlled work areas (the areas consisting of the work rooms, corridors, etc. that are controlled so as to maintain a uniform quality of cleanliness, and hereinafter referred to as such) among the work areas are provided with the buildings and facilities for maintaining the degree of cleanliness according to the type, dosage form and manufacturing process of the products concerned with sterile drugs,
- (2) To be ensured that the work rooms for the drying operations or sterilising operations for the cleaned containers are exclusively used for such operations, with the proviso that this provision shall not apply in case where the cleaned containers could not be contaminated,
- (3) To be ensured that the work rooms meet the following requirements,
 - a. Being provided with the facilities necessary for conducting appropriately the drying and storing operations for the cleaned containers,
 - b. Being provided with the sterilisation apparatuses necessary for the manufacturing according to the type of the products concerned with the sterile drugs,
 - c. Being provided with the clean air treated with filters and the buildings and facilities for controlling appropriately the pressure differential in the areas for conducting the aseptic operations, and
 - d. Being ensured that the facilities of which liquid-contacting piping, etc. affecting the sterility assurance level are easily cleanable and sterilisable in case of manufacturing the products concerned with injectable drugs.

- (4) To be ensured that the work rooms or controlled work areas for the formulating operations or filling operations for the drug substances, or for the sterilising operations for the products subsequent to the formulating operations (excluding the labelling and packaging operations) meet the following requirements, and
 - a. Being segregated from the work areas for non-sterile drugs,
 - b. Being ensured that the work rooms for the formulating operations and the work rooms for the filling operations or sealing operations are exclusively used for such purposes, and
 - c. Being provided with the gowning rooms exclusively used for the personnel who conduct the operations specified in preceding b.
- (5) To be ensured that the facilities for supplying distilled water, etc. necessary for manufacturing the products concerned with sterile drugs are provided with the structure necessary for preventing contamination of the distilled water, etc. with foreign particulate matter or microorganisms.

(Manufacturing Control)

Article 24 The manufacturer, etc. shall, in case where they manufacture the products concerned with sterile drugs, have the manufacturing department conduct appropriately the following duties concerned with manufacturing control in accordance with the documented procedure, etc., in addition to the duties specified in Article 10.

- (1) To appropriately establish and control a degree of control of the work environment in the work areas such as a degree of cleanliness according to the type, dosage form, property and manufacturing process of the products concerned with sterile drugs to manufacture and the details of the operations in such work areas,
- (2) To appropriately establish and control necessary control items for the products, etc. and packaging and labelling materials, such as number of microorganisms, etc. according to the type, dosage form, property, manufacturing process, etc. of the products concerned with sterile drugs to manufacture,
- (3) To take actions necessary for preventing contamination, etc. of the products, etc. and packaging and labelling materials with microorganisms, etc. in the manufacturing process,
- (4) To appropriately establish and control the control values necessary for process control of the process, etc. which are essential to assure sterility level of the products according to the type, dosage form, property, manufacturing process, etc. of the products concerned with sterile drugs to manufacture,
- (5) To appropriately establish and control the control values concerned with microorganic and physicochemical items for the manufacturing water according to that purpose,
- (6) To conduct sanitation control of the personnel in accordance with the following requirements, and

- a. Placing as much restriction as possible on the personnel other than those engaged in the manufacturing operations entering the work areas,
 - b. Establishing strict procedures for preventing contamination by the personnel engaged in the operations concerned with the processing of the animal-tissue-origin raw materials, cultivation of the microorganisms, etc. (excluding those actually used as the raw materials, etc. in the manufacturing process of the work areas), and not allowing the personnel, excluding the case where they strictly adhere to the procedure, to enter the work areas for the products concerned with sterile drugs, and
 - c. Placing as much restriction as possible on the personnel entering the clean areas or aseptic areas under operation.
- (7) To conduct sanitation control of the personnel conducting operations in the clean areas or aseptic areas in accordance with the following requirements.
- a. Having the personnel engaged in the manufacturing operations, when they enter the clean areas or aseptic areas, appropriately be gowned, etc. according to the extent of the control of such areas, and
 - b. Having the personnel declare of any health condition that could contaminate the products, etc. with microorganisms, etc. (including when suffering from a skin or hair infectious disease or a cold, when injured, when showing such symptoms as fever or diarrhoea of unknown cause, and hereinafter referred to as such).

(Training)

Article 25 The manufacturer, etc. shall, in case where they manufacture the products concerned with sterile drugs, have the person designated beforehand the following duties in accordance with the documented procedure, etc. in addition to the duties specified in Article 19.

- (1) To provide the personnel engaged in the manufacturing or testing operations with the training necessary for manufacturing the products concerned with sterile drugs such as those on sanitation control, microbiology, etc., and
- (2) To provide the personnel engaged in the operations in the clean areas, aseptic areas, etc. with the training for taking actions necessary for preventing contamination with microorganisms, etc.

Section 4 Manufacturing Control and Quality Control of Biological-origin Drugs, etc.

(Buildings and Facilities of Manufacturing Sites of Biological-origin Drugs, etc.)

Article 26 The buildings and facilities of the manufacturing site of the manufacturers, etc. of the products concerned with the biological-origin drugs, etc. shall meet the following requirements, in addition to those specified in Article 9 and Article 23.

- (1) To be ensured that the buildings and facilities of the manufacturing site of the products concerned with the biological preparations (excluding the blood preparations which do not constitute a lot) meet the following requirements,

- a. Being ensured that the work areas are provided with the following facilities in the rooms distinctly segregated from other rooms, with the proviso that this provision shall not apply in case where such facilities are verified not to be necessary for the manufacturing of the products according to the type, manufacturing procedure, etc. of such products,
 - (i) The facilities for storing the microorganisms,
 - (ii) The facilities for keeping the animals for utilising in the manufacturing or testing after inoculation with the microorganisms,
 - (iii) The facilities for treating the animals for utilising in the manufacturing or testing,
 - (iv) The facilities for inoculating the microorganisms into the culture media, etc.,
 - (v) The facilities for cultivating the microorganisms,
 - (vi) The facilities for collecting, inactivating, sterilising, etc., the cultured microorganisms,
 - (vii) The facilities for preparing the solution for diluting the undiluted solution,
 - (viii) The facilities for diluting and subdividing the undiluted solution as well as for sealing the containers,
 - (ix) The facilities for disinfecting the equipment and instruments used in the manufacturing or testing.
 - b. Being ensured that the rooms provided with the facilities specified in preceding a.(iv) and (vi) to (viii) as well as the rooms provided with facilities, among the facilities necessary for conducting the testing of the products, etc. and packaging and labelling materials, for conducting the sterility tests meet the following requirements,
 - (i) Being aseptic rooms, with the proviso that this provision shall not apply in case where such work rooms are provided with the facilities which have functions to allow that the aseptic operations are conducted without hindrance according to the type, manufacturing procedure, etc. of the products, and
 - (ii) Being provided, in the aseptic rooms specified in preceding (i), with the adjoining anterooms exclusively used for such rooms so that the rooms are routinely accessible only through such anterooms, and not being placed the entrances of the anterooms directly leading to the outside.
 - c. Being provided with the following facilities in addition to the those specified in preceding a.
 - (i) The facilities necessary for keeping control for the animals utilised in the manufacturing or testing,
 - (ii) The facilities for formulating the culture media and their diluted solution,
 - (iii) The facilities for prior washing and sterilising the equipment and instruments, containers, etc. for use in the manufacturing or testing, and
 - (iv) The facilities for appropriately disposing of the animal carcasses and other wastes as well as for decontaminating the sewage.
- (2) To be ensured that the buildings and facilities of the manufacturing site of the products concerned with the blood preparations which do not constitute a lot meet

the following requirements, and

- a. Being ensured that the work rooms, among the work areas, for separating and mixing the blood components, injecting and discharging the drug substance solutions as well as conducting the sealing operations for the containers are segregated from the work rooms for the products other than the blood preparations.
 - b. Being ensured that the work rooms, among the work areas, for conducting the operations specified in preceding a. in an open-system operation meet the following requirements, and
 - (i) Being exclusively used for the operations, and
 - (ii) Being aseptic or being provided with the facilities which have functions to allow that aseptic operations are conducted appropriately.
 - c. Being ensured that the work areas are provided with the gowning facilities exclusively used for the personnel conducting operations in the aseptic room.
- (3) To be ensured that the areas for manufacturing the products using human blood or plasma as the raw materials are distinctly segregated from other areas and provided with the facilities and equipment exclusively used for such manufacturing, with the proviso that this provision shall not apply to the manufacturing process subsequent to the process of inactivating or removing viruses.

(Manufacturing Control)

Article 27 The manufacturer, etc. shall, in case where they manufacture the products concerned with the biological-origin drugs, etc., have the manufacturing department conduct appropriately the following duties concerned with manufacturing control in accordance with the documented procedure, etc. in addition to the duties specified in Article 10 and Article 24.

- (1) To take necessary actions, in case where the products, etc. are inactivated or where microorganisms, etc. contained in the products, etc. are inactivated or eliminated, for preventing contamination by the products, etc. which have not undergone such inactivation or elimination,
- (2) To conduct continuous measurement of the items necessary for controlling the manufacturing process such as temperature, hydrogen ion index, etc., in case where biochemical technology such as fermentation, etc. is applied in the manufacturing process,
- (3) To take necessary actions, in case where the column chromatography apparatuses, etc. are used in the manufacturing process, for preventing contamination of such apparatuses with microorganisms, and to measure endotoxins, where necessary,
- (4) To take necessary actions, in case where the culture media are continuously supplied to and the cultured broth is continuously discharged from the tanks, for maintaining the incubation conditions in such incubation tanks during the incubating,

- (5) To conduct sanitation control of the personnel in accordance with the following requirements,
 - a. Placing as much restriction as possible on the personnel other than those engaged in the manufacturing operations entering the work areas,
 - b. Placing as much restriction as possible on the personnel entering the clean areas or aseptic areas under operation, and
 - c. Not allowing the personnel engaged in the manufacturing operations to conduct the duties concerned with the control of the utilised animals (excluding those actually utilised in the manufacturing process of the work areas).
- (6) To conduct sanitation control of the personnel conducting the duties in the clean areas or aseptic areas in accordance with the following requirements,
 - a. Having the personnel engaged in the manufacturing operations wear the clothes, work shoes, caps and masks, which have been disinfected,
 - b. Having the personnel undergo medical checkups at intervals not exceeding 6 months in order to verify that they do not suffer from the diseases which could contaminate, with microorganisms, etc., the products, etc., and
 - c. Having the personnel declare of any health conditions which could contaminate, with microorganisms, etc., the products, etc.
- (7) To constantly keep the utilised animals (limited to those which are utilised in the manufacturing, and hereinafter referred to as such in this Paragraph 1) under proper control, and to physically examine the animals, when utilising them, so as not to utilise those suffering from communicable diseases nor those otherwise unsuitable for being utilised.
- (8) To dispose of all the objects contaminated with microorganisms (limited to those contaminated in the manufacturing process) and the animal carcasses so as not to jeopardise the public health and hygiene,
- (9) To establish and maintain records of the following items concerned with the handling of the strains of the microorganisms for use in the manufacturing,
 - a. The name of the microorganisms and the number assigned to each of containers thereof,
 - b. The date of receipt, and the name and address of the person (in case of a corporation, its name and address) who transferred the strains,
 - c. The biological property and the date of the testing, and
 - d. The status of the passage.
- (10) To put labels to the equipment and instruments, according to the type of the products, used in the work rooms for handling small pox viruses, acute poliomyelitis viruses, spore-forming pathogens or tubercle bacillus mycobacteria, and to prohibit them from being used in the manufacturing of other products,
- (11) To verify that the raw materials originated in organisms (except plants) that are used in the manufacturing of the products concerned with the biological-origin drugs (hereinafter referred to as "biological-origin raw materials") are appropriate based on *Seihin Hyojun Sho* of such products, and to establish and maintain records of the results of the verification,

- (12) To maintain the information that is provided to be recorded under the rules set forth by Minister of Health, Labour and Welfare, or to conclude a contract with the business that collects the origins of the biological-origin raw materials (hereinafter referred to as “biological-origin raw material origins collectors, etc.”) and to ensure that the information is maintained appropriately by such biological-origin raw material origins collectors, etc., for the period specified in Items (2) and (3) of Article 30, in case where the biological-origin raw materials are used in the manufacturing of the products concerned with the biological-origin drugs, and
 - (13) To establish and maintain records specified in Item (9) of Article 10 and preceding two Items (11) and (12) for each lot of the products concerned with the biological-origin drugs, etc. to manufacture.
2. The manufacturer, etc. shall, in case where they manufacture the products concerned with the cell/tissue-based drugs, have the manufacturing department conduct appropriately the following duties concerned with manufacturing control in accordance with the documented procedure, etc., in addition to the duties specified in Article 10 and preceding Paragraph 1.
- (1) To take actions necessary, in case where they handle the cells or tissue collected from the different donors or donor animals, for preventing such cells or tissue from being mixed up or cross-contaminated,
 - (2) To verify, upon receipt, that the cells or tissue that serve as the raw materials are appropriate, referring to the records of the following items, based on *Seihin Hyojun Sho* of such products, and to establish and maintain records of the results of the verification,
 - a. The premises where such cells or tissue was collected,
 - b. The date when such cells or tissue was collected,
 - c. In case where such cells or tissue is originated in humans, the conditions of diagnosing by questioning, testing, etc. the donors for the purpose of donor screening (the process to diagnose the donors by questioning, testing, etc. and to judge whether they are sufficiently qualified for donating cells or tissue as the raw materials of the products concerned with the cell/tissue-based drugs),
 - d. In case where such cells or tissue is originated in animals, the conditions of receiving the donor animals and the conditions of the testing and keeping control for the donor animals for the purpose of donor screening (the process to test the donor animals and control keeping thereof and to judge whether they are sufficiently qualified for providing cells or tissue as the raw materials of the products concerned with the cell/tissue-based drugs),
 - e. The course of the collecting operations for such cells or tissue, and
 - f. Other items necessary for ensuring the quality of the products concerned with the cell/tissue-based drugs, in addition to the items specified in preceding a. to e.
 - (3) To take actions necessary for preventing contamination with microorganisms, etc. in the course of the collection, and to establish and maintain records of such

actions, in case where the cells or tissue used as the raw materials are collected from the donor animals,

- (4) Not to allow the personnel, in case where they are applicable to any of the following cases, to conduct the operations in the clean areas or aseptic areas,
 - a. The case where they are in those health conditions which could contaminate the products, etc. with microorganisms, etc., or
 - b. The case where they handle microorganisms, etc. which could contaminate the cells or tissue right before the collecting or processing the cells or tissue.
 - (5) To comprehend the names of the shipping consignee premises, shipping date and lot number, and to establish and maintain records thereof,
 - (6) To take actions necessary for ensuring the quality of the products during the delivery and to establish and maintain records of such actions,
 - (7) To establish and maintain records of the keeping control for the donor animals after receipt, and
 - (8) To establish and maintain records specified in preceding Items (2), (3), (5) and (6) for each lot (for each of the products, in case of the records specified in preceding Item (5)).
3. The records of the products concerned with the biological-origin drugs specified in Article 10 and preceding two Paragraphs 1 and 2 shall be maintained in the manner which allows that the series of the records including those of biological-origin raw materials used in the manufacturing and those of the products manufactured using such biological-origin raw materials are appropriately verified.

(Quality Control)

Article 28 The manufacturer, etc. shall store, notwithstanding the provisions of Item (3) of Paragraph 1 of Article 11 and Article 21, a reserve sample in an amount of at least twice of the quantity necessary for the required testing from the products concerned with the drugs which correspond to the specified biological-origin products specified in Paragraph 10 of Article 2 of Law (hereinafter referred to as “specified biological-origin drugs”) or the products concerned with the cell/tissue-based drugs for each lot (in case where the products are those concerned with the specified biological-origin drugs which do not constitute a lot, the biological-origin raw materials used in the manufacturing of the products for each manufacturing number of such products corresponding to or for each lot of such biological-origin raw materials) under appropriate conditions for the period specified in each of the following Items (1) and (2) from the date of the manufacturing, with the proviso that this provision shall not apply to those products concerned with the specified biological-origin drugs which do not constitute a lot and of which reserve sample is stored for the period specified in each of the following Items (1) and (2) by the biological-origin raw material origins collectors, etc. under a contract concluded between the manufacturer, etc. and such biological-origin raw material origins collectors, etc. For the products concerned with the specified biological-origin drugs or the cell/tissue-based drugs which constitute a lot, after the shelf life of such products plus 1 year (plus 1 month, for the radiopharmaceuticals) have passed, storage

of the biological-origin raw materials used in the manufacturing of such products may be substituted for storage of the products.

- (1) 10 years plus the shelf life of the products for the products concerned with the specified biological-origin drugs, or
 - (2) Appropriate period for the products concerned with the cell/tissue-based drugs (excluding those specified in preceding Item (1)).
2. The manufacturer, etc. shall, in case where they manufacture the products concerned with the biological-origin drugs, etc., have the quality department conduct appropriately as planned the following duties concerned with the quality control duties, in accordance with the documented procedure, etc., in addition to the duties specified in Article 11.
- (1) To identify appropriately the samples in order to prevent them from being mixed up or cross-contaminated,
 - (2) To conduct the testing which is important for the quality control and inapplicable to the final products at the appropriate stage of the manufacturing process,
 - (3) To constantly keep the utilised animals (limited to those utilised in the testing, and hereinafter referred to as such in this Paragraph 2) under proper control, and to physically examine the animals when utilising them, so as not to utilise those animals suffering from communicable diseases nor those otherwise unsuitable for being utilised,
 - (4) To dispose of all the objects contaminated with microorganisms (limited to those contaminated in the testing process) and the animal carcasses so as not to jeopardise the public health and hygiene,
 - (5) To establish and maintain records of the following items concerned with the handling of the strains of the microorganisms for use in the testing, and
 - a. The name of the microorganisms and the number assigned to each of containers thereof,
 - b. The date of receipt, and the name and address of the person (in case of a corporation, its name and address) who transferred the strains,
 - c. The biological property and the date of the testing, and
 - d. The status of the passage.
 - (6) To establish and maintain records of the results of the testing for each lot of the products concerned with the biological-origin drugs, etc. to manufacture.
3. The manufacturer, etc. shall, in case where they manufacture the products concerned with the cell/tissue-based drugs, have the quality department conduct appropriately the following duties concerned with the quality control for the products concerned with the cell/tissue-based drugs in accordance with the documented procedure, etc., in addition to the duties specified in Article 11 and preceding Paragraph 2.
- (1) To have the person designated beforehand conduct the testing of the donor animals upon and after receipt, and other necessary duties according to the details

of such duties, and

- (2) To establish and maintain records of the duties specified in preceding Item (1).
4. The records concerned with the biological-origin drugs specified in preceding three Paragraphs 1, 2 and 3 shall be maintained in the manner which allows that the series of the records including those of biological-origin raw materials used in the manufacturing and those of the products manufactured using such biological-origin raw materials are appropriately verified.

(Training)

Article 29 The manufacturer, etc. shall, in case where they manufacture the products concerned with the biological-origin drugs, etc., have the person designated beforehand conduct the following duties in accordance with the documented procedure, etc. in addition to the duties specified in Articles 19 and 25.

- (1) To provide the personnel engaged in the manufacturing or testing of the biological-origin drugs, etc. with the training in microbiology, medicine, veterinary medicine, etc., and
- (2) To provide the personnel engaged in the operations in the aseptic areas or the areas, etc. where the pathogenic microorganisms are handled, with the training for taking actions necessary for preventing contamination with microorganisms.

(Control of Documents and Records)

Article 30 The manufacturer, etc. shall, in case where they manufacture the products concerned with the biological-origin drugs, etc., notwithstanding the provision of Item (3) of Article 20, maintain the documents and records specified in this Ministerial Ordinance for the period specified in each of the following Items (1), (2) and (3) from the date of the establishment, with the proviso that records of the training shall be maintained for 5 years.

- (1) 5 years (for the products concerned with such drugs of which shelf life plus 1 year exceeds 5 years, 1 year plus the shelf life) for the products other than those concerned with the biological-origin drugs and the cell/tissue-based drugs (hereinafter collectively referred to as “biological-origin and cell/tissue-based drugs”),
- (2) 30 years plus the shelf life for the products concerned with the specified biological-origin drugs or the biologically-origin drugs manufactured using human blood as the raw materials, or
- (3) 10 years plus the shelf life for the products concerned with the biological-origin and cell/tissue-based drugs (excluding those specified in preceding Item (2)).

Section 5 Miscellaneous Provision

(Exceptions to Retention of Records)

Article 31 The manufacturer, etc. shall, for the products concerned with the biological-origin drugs designated by Minister of Health, Labour and Welfare, notwithstanding the provision of preceding Article, have the person designated beforehand maintain the records specified in preceding Article for the period designated by Minister of Health, Labour and Welfare, with the proviso that this provision shall not apply in case where the records are maintained appropriately by the biological-origin raw material origins collectors, etc. for such period under a contract concluded between the manufacturer, etc. and such biological-origin raw material origins collectors, etc.

Chapter 3 Manufacturing Control and Quality Control in Manufacturing Sites of Quasi-drug Manufacturers, etc.

(Manufacturing Control and Quality Control of Quasi-drugs)

Article 32 The provision of preceding Chapter 2 (excluding Item (4) of Article 7, Item (5) of Article 9, Item (3) d. of Article 23 and Section 4) shall be applied *mutatis mutandis* to the manufacturer, etc. of the products concerned with quasi-drugs. In this case, “the drug manufacturing manager specified in Paragraph 3 of Article 17 of Law” in Paragraph 1 of Article 4 shall read “the responsible engineering manager specified in Paragraph 5 of Article 17 of Law”, “manufacturing manager” in Chapter 2 shall read “responsible engineering manager”, “Paragraph 1 of Article 42 of Law” in Item (2) of Article 7 shall read “Paragraph 2 of Article 42 of Law”, “Paragraph 2 of Article 9” in Item (3) of Paragraph 1 of Article 11 shall read “Paragraph 2 of Article 9 applied *mutatis mutandis* under Article 20”, “sterile drugs” in Section 2 shall read “sterile quasi-drugs”.

Supplementary Provisions

(Enforcement Date)

Article 1 This Ministerial Ordinance shall come into effect on 1 April 2005.

(Transitional Measures)

Article 2 For 2 years from the date of enforcement of this Ministerial Ordinance, the provisions of Article 9, Article 23 and Article 26, and Article 9 and Article 23 applied *mutatis mutandis* under Article 32 may not apply to the foreign manufacturer.

Article 3 Drug and Quasi-drug Import and Distribution Control and Quality Control Regulations (MHLW Ministerial Ordinance No. 62, 1999) shall expire on 31 March 2005.