

Ministerial Order on the Standard of Manufacturing Control and Quality Control for Pharmaceuticals and Quasi-Pharmaceuticals

(Order of the Ministry of Health, Labour and Welfare No. 179 of December 24, 2004)

[Latest amendment: Order of the Ministry of Health, Labour and Welfare No. 90 of April 28, 2021]

Pursuant to the provisions of Article 14, paragraph (2), item (iv) as well as such provisions applied mutatis mutandis as provided in Article 19-2, paragraph (5) of the Pharmaceutical Affairs Act\* (Law No. 145 of 1960), the Ministerial Order revising entire of the Regulation on Manufacturing Control and Quality Control for Pharmaceuticals and Quasi-Pharmaceuticals (Order of the Ministry of Health and Welfare No. 16 of 1999) is provided as follows.

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Supplementary Provisions

## Chapter 1 General Provisions

(Purpose)

Article 1 This Ministerial Order provides the standards prescribed by an Order of the Ministry of Health, Labour and Welfare pursuant to the provisions of Article 14, paragraph (2), item (iv) (including where applied mutatis mutandis as provided in Article 19-2,

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\* Translation annotation; currently renamed as “the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices”

paragraph (5); the same applies hereinafter) of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (Law No. 145 of 1960; hereinafter referred to as the “Act”).

(Definitions)

Article 2 (1) The term “product” as used in this Ministerial Order means an object that has undergone a production process at a manufacturing site (including “intermediate product” which has been produced through an intermediate production step, to become a product by undergoing subsequent production processes).

(2) The term “finished products” as used in this Ministerial Order means, among products, those subject to certification of releasing to the market or rejection pursuant to the provisions of Article 9, paragraph (2) (including where applied *mutatis mutandis* as provided in Article 20) of the Ministerial Order on the Standard of Quality Management for Pharmaceuticals, Quasi-Pharmaceuticals, Cosmetics, and Regenerative Medicine Products (Order of the Ministry of Health, Labour and Welfare No. 136 of 2004).

(3) The term “packaging/labeling materials” as used in this Ministerial Order means containers, wrappers and labels (including package inserts) for products.

(4) The term “batch” as used in this Ministerial Order means an aggregation that comprises products and/or starting materials (hereinafter referred to as “products, etc.”) which are produced so as to be homogeneous through a series of production processes in a certain production period.

(5) The term “reference sample” as used in this Ministerial Order means a sample for testing/analysis, which is stored for the case where a need to reconfirm quality of a released product arises.

(6) The term “retention sample” as used in this Ministerial Order means a sample from a batch of finished products, which is used for identification with the products in market distribution.

(7) The term “retest date” as used in this Ministerial Order means a date that has been established on which testing/analysis should be re-performed for ensuring whether products that a certain period of time has elapsed from the date of manufacture still conform to the prescribed specifications.

(8) The term “lot” as used in this Ministerial Order means an aggregation that comprises packaging/labeling materials whose uniformity of quality has been verified.

(9) The term “pharmaceutical quality system” as used in this Ministerial Order means a system under which a manufacturer or a foreign manufacturer of pharmaceuticals, etc. as provided in Article 13-3, paragraph (1) of the Act (hereinafter referred to as “foreign manufacturer”) for products of pharmaceuticals (excluding in-vitro diagnostics treated as pharmaceuticals; the same applies hereinafter) implement direction and control with regard to quality of such products.

(10) The term “quality risk management” as used in this Ministerial Order means a process, throughout the lifecycle of products of pharmaceuticals, of specifying, assessment and

control, etc. of harm to quality and provability thereof (hereinafter referred to as “quality risks”).

- (11) The term “stability monitoring” as used in this Ministerial Order means on-going verification as to whether products, under the established storage conditions, remain within specifications throughout shelf-life or period until expiry date thereof (hereinafter simply referred to as “shelf-life”).
- (12) The term “review” as used in this Ministerial Order means to evaluate validity and effectiveness in achieving objectives set.
- (13) The term “validation” as used in this Ministerial Order means to demonstrate that any premises/equipment of a manufacturing site, and procedures, processes and other methods for production control and quality control (hereinafter these are referred to as “manufacturing procedures, etc.”) lead to the expected outcome, and to document such demonstrative process.
- (14) The term “corrective action” as used in this Ministerial Order means an action to eliminate the cause of a detected non-conformity (refers to non-conformity with requirements, etc. as provided in this Ministerial Order; the same applies hereinafter) or other undesirable situation, which is taken to prevent recurrence thereof.
- (15) The term “preventive action” as used in this Ministerial Order means an action to eliminate the cause of a possible non-conformity or other undesirable situations, which is taken to prevent occurrence thereof.
- (16) The term “controlled operation area” as used in this Ministerial Order means, among places where production operations for products of pharmaceuticals or quasi-pharmaceuticals are performed (hereinafter referred to as “operation areas”), places consisting of work rooms and corridors, etc., which are controlled so as to maintain cleanliness of the entire environment to the same extent.
- (17) The term “clean area” as used in this Ministerial Order means, among operation areas, places where weighing operations for starting materials are performed, where preparing operations of pharmaceutical/quasi-pharmaceutical preparations are performed, and where cleaned containers are exposed to the air in operation areas.
- (18) The term “aseptic area” as used in this Ministerial Order means, among operation areas, places where sterilized pharmaceutical/quasi-pharmaceutical preparations or containers are exposed to the air in operation areas, places where operations of filling pharmaceutical/quasi-pharmaceutical preparations are performed, places where operations of sealing filled containers are performed, and places where aseptic operations such as sterility tests are performed.
- (19) The term “cell/tissue-based pharmaceuticals” as used in this Ministerial Order means pharmaceuticals composed of human or animal cells or tissue (excluding pharmaceuticals composed of human blood or ingredients produced from human blood).
- (20) The term “biological origin starting materials” as used in this Ministerial Order means starting materials derived from organisms (excluding plants) to be used for producing a product of pharmaceuticals that are biological origin products as provided in Article 2,

paragraph (10) of the Act (hereinafter such pharmaceuticals are referred to as “biological origin pharmaceuticals”).

- (21) The term “donor” as used in this Ministerial Order means a person who donates the person’s cells or tissue to be used for starting materials for a cell/tissue-based pharmaceutical (excluding donors concerned with the body of a brain-dead person as provided in Article 6, paragraph (2) of the Act on Organ Transplantation (Law No. 104 of 1997)).
- (22) The term “donor screening” as used in this Ministerial Order means to evaluate whether each donor is adequately suitable for donating cells or tissue to be used for starting materials for products of cell/tissue-based pharmaceuticals, through performing medical interviews, examinations, etc. on the donor.
- (23) The term “donor animal” as used in this Ministerial Order means an animal from which cells or tissue to be used for starting materials for a cell/tissue-based pharmaceutical are sourced.
- (24) The term “donor animal screening” as used in this Ministerial Order means to evaluate whether each donor animal is adequately suitable as a source of cells or tissue to be used for starting materials for products of cell/tissue-based pharmaceuticals, through performing examination/testing and rearing control of the donor animal.

(Scope of Application)

Article 3 (1) Marketing license holders (including marketing license holders appointed pursuant to the provisions of Article 19-2, paragraph (4) of the Act; the same applies hereinafter) of pharmaceuticals or quasi-pharmaceuticals as provided in Article 14, paragraph (1) of the Act must have manufacturers and foreign manufacturers (hereinafter these are collectively referred to as “manufacturers, etc.”) for products of such pharmaceuticals or quasi-pharmaceuticals implement manufacturing control and quality control at their manufacturing sites, pursuant to the provisions of Chapter 2 in the case of pharmaceuticals and pursuant to the provisions of Chapter 3 in the case of quasi-pharmaceuticals.

- (2) Manufacturers, etc. for products of pharmaceuticals or quasi-pharmaceuticals must implement manufacturing control and quality control for such products at their manufacturing sites as provided in Article 96 of Enforcement Regulation of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (Order of the Ministry of Health and Welfare No. 1 of 1961; hereinafter referred to as the “Enforcement Regulation”), pursuant to the provisions of Chapter 2 in the case of pharmaceuticals and pursuant to the provisions of Chapter 3 in the case of quasi-pharmaceuticals.
- (3) Manufacturers for products of pharmaceuticals or quasi-pharmaceuticals for export as provided in Article 80, paragraph (1) of the Act must implement manufacturing control and quality control at their manufacturing sites for such products, pursuant to the provisions of Chapter 2 in the case of pharmaceuticals and pursuant to the provisions of Chapter 3 in the

case of quasi-pharmaceuticals.

(Compliance with the Product Authorization Requirements)

Article 3-2 Manufacturers, etc. for products of pharmaceuticals or quasi-pharmaceuticals as provided in Article 14, paragraph (1) of the Act must manufacture such products complying with the requirements of the product authorization pursuant to the provisions of Article 14, paragraph (1) or paragraph (15) (including where applied mutatis mutandis as provided in Article 19-2, paragraph (5); the same applies hereinafter in this Article) of the Act or Article 19-2, paragraph (1) of the Act (hereinafter these are referred to as the “product authorization requirements”); provided, however, in the case of a manufacturer, etc. implementing a minor change as provided in Article 14, paragraph (15) of the Act, this does not apply until a notification in pursuant to the provisions of paragraph (16) of the same Article (including where applied mutatis mutandis as provided in Article 19-2, paragraph (5) of the Act) be submitted.

Chapter II Manufacturing Control and Quality Control at Manufacturing Sites of Pharmaceutical Manufacturers, etc.

Section 1 General Rules

(Pharmaceutical Quality System)

Article 3-3 Manufacturers, etc. must establish an effective pharmaceutical quality system, and conduct the following tasks:

- (i) to establish, in a document, overall direction and intentions for ensuring product quality (hereinafter referred to as “quality policy”), and to include elements of pharmaceutical quality system such as procedures thereof, in the document;
- (ii) to have the pharmaceutical manufacturing supervisor as provided in Article 17, paragraph (6) of the Act and the person who supervises the manufacture of biological origin products as provided in Article 68-16, paragraph (1) of the Act (in the case of foreign manufacturers, a responsible person at the manufacturing site that has been accredited pursuant to the provisions of Article 13-3, paragraph (1) of the Act or personnel appointed by the foreign manufacturer) (hereinafter these are collectively referred to as “manufacturing supervisor”) or the quality assurance section as provided in Article 4, paragraph (3), item (i) prescribe, in a document, quality objectives at the manufacturing site, based on the quality policy;
- (iii) to disseminate the quality policy and quality objectives to all of the organizations and personnel involved in pharmaceutical quality system at the manufacturing site;
- (vi) to allocate necessary resources (refers to those to be utilized for manufacturing control and quality control at the manufacturing site, such as individual knowledge and skill, technique, equipment, etc.) in order to achieve the quality policy and quality objectives, review its pharmaceutical quality system regularly, and implement necessary measures

- based upon the review outcomes; and
- (v) to have their appointed personnel document and retain records of the tasks as provided in the preceding two items.

(Quality Risk Management)

Article 3-4 (1) Manufacturers, etc. must apply quality risk management to establish pharmaceutical quality system, and implement manufacturing control and quality control for products of pharmaceuticals at their manufacturing sites.

- (2) Manufacturers, etc. must have their appointed personnel document process of implementation of quality risk management and other necessary matters and records thereof, and retain such documents/records.

(Production Department and Quality Department)

Article 4 (1) Manufacturers, etc. must establish a department in charge of production control (hereinafter referred to as “production department”) and a department in charge of quality management (hereinafter referred to as “quality department”) at each of their manufacturing sites, under supervision of the manufacturing supervisor.

- (2) The quality department must be independent of the production department.
- (3) The quality department must establish the following sections:
  - (i) Quality assurance section; and
  - (ii) Section in charge of testing/analysis operations (including testing/analysis performed utilizing other quality control laboratories owned by the manufacturer, etc. or outsourcing to others pursuant to the provisions of Article 11-5, under its own responsibility, provided however, that this is limited to the case where such utilization or outsourcing would create no problem; the same applies hereinafter in this Chapter).

(Manufacturing Supervisor)

Article 5 (1) Manufacturing supervisor must conduct the following tasks:

- (i) to supervise activities regarding production control, quality assurance and quality control (hereinafter referred to as “production/quality related activities”) to ensure their suitable and timely implementation at the manufacturing site, and to manage the pharmaceutical quality system to be reasonably implemented there; and
- (ii) to check implementation of the pharmaceutical quality system, and to report in writing whether any rectification thereof is needed, to the manufacturer, etc. which the manufacturing supervisor is employed;
- (iii) to have the quality assurance section manage starting materials, packaging/labeling materials and products, and manufacturing procedures, etc., so as to avoid nonconformity with the product authorization requirements; and
- (iv) in the case where any quality defects or other concerns that could cause significant impact on product quality have occurred, to check that necessary actions are being promptly taken, to check progress of such actions, and to give instructions if necessary to

implement rectification and other necessary measures.

- (2) Manufacturers, etc. must ensure that their manufacturing supervisor conducts the tasks without any hindrance.

(Personnel)

Article 6 (1) Manufacturers, etc. must adequately appoint responsible persons capable of conducting production/quality related activities suitably and timely (hereinafter such persons are simply referred to as “responsible persons” in this Chapter) according to the organization, size, and type of activities, etc. of their manufacturing sites.

- (2) Manufacturers, etc. must assign an adequate number of responsible persons according to the organization, size, and type of activities, etc. of their manufacturing sites.
- (3) Manufacturers, etc. must secure adequate personnel capable of suitably conducting production/quality related activities.
- (4) Manufacturers, etc. must prescribe, suitably in documents, responsibilities of and management system for personnel (including the manufacturing supervisor and responsible persons) engaged in production/quality related activities.

(Pharmaceutical Product Specification File)

Article 7 Manufacturers, etc. must establish documents which prescribe the following matters with regard to their products (excluding intermediate products which are in the course of a series of production processes at a manufacturing site) of pharmaceuticals (hereinafter such documents are referred to as “pharmaceutical product specification files”) for each of their manufacturing sites involved in manufacture of such products, have endorsement therefor by the quality department, then place such files suitably at the manufacturing sites:

- (i) production procedures, specifications and testing/analytical methods and other necessary matters employed at the manufacturing site, among the product authorization requirements;
- (ii) matters on quality, among the specification requirements which are specified pursuant to the provisions of Article 42, paragraph (1) of the Act, and the requirements of other laws and regulations concerning pharmaceutical affairs, or the orders or actions based thereon;
- (iii) manufacturing procedures other than matters as provided in item (i); and
- (iv) other necessary matters.

(Written Procedures, etc.)

Article 8 (1) Manufacturers, etc. must establish documents which prescribe procedures (hereinafter such documents are referred to as “written procedures”) of followings for each of their manufacturing sites, then place such written procedures suitably at the manufacturing sites:

- (i) procedures for sanitation/hygiene control of premises/equipment and for personnel;

- (ii) procedures for control of production processes, production equipment, starting materials, packaging/labeling materials and products;
  - (iii) procedures necessary for performing suitable testing/analysis, including management of the quality control laboratories and samples;
  - (iv) procedures for stability monitoring;
  - (v) procedures for review of product quality;
  - (vi) procedures for supplier control for starting materials and/or packaging/labeling materials (hereinafter these are referred to as “starting materials, etc.”);
  - (vii) procedures for control of outsourced business entities performing some of the product/quality related activities such as testing/analysis and others which are contracted by the manufacturer, etc. (hereinafter referred to as “outsourced contractors”);
  - (viii) procedures for control of product release from the manufacturing site;
  - (ix) procedures for validation;
  - (x) procedures for change management as provided in Article 14;
  - (xi) procedures for deviation management as provided in Article 15;
  - (xii) procedures for management of quality information and quality defects, etc. as provided in Article 16;
  - (xiii) procedures for management of recalled products and others;
  - (xiv) procedures for internal audits;
  - (xv) procedures for education/training;
  - (xvi) procedures for establishing, revising and retention of documents/records; and
  - (xvii) other procedures necessary for suitable and timely production/quality related activities.
- (2) Manufacturers, etc. must establish matters regarding methods of the tasks as provided in each item of Article 20, paragraph (2), in documents, to ensure, throughout the document/record lifecycle, integrity of the pharmaceutical specification files and written procedures (hereinafter these are collectively referred to as “written procedures, etc.”) and records pursuant to the provisions of this Chapter.

(Prevention of Cross-Contamination)

Article 8-2 Manufacturers, etc. must implement necessary measures on manufacturing procedures, etc. in order to prevent cross-contamination with products of pharmaceuticals.

(Premises/Equipment)

Article 9 (1) Premises/equipment of a manufacturing site for products of pharmaceuticals must conform to the following requirements:

- (i) in accordance with the written procedures, etc., cleaning and maintenance are implemented in a manner suitable to their uses, sterilization is implemented as necessary, and records thereof are documented and retained;
- (ii) where any toxic gas is used depending upon products, etc., equipment necessary for



disposition thereof is provided;

(iii) work rooms among operation areas are provided with necessary premises/equipment in order to prevent contamination by drifting particles or microorganisms, according to type, dosage form and production processes of the products; provided, however, that this does not apply where the production equipment, etc. is provided with functions affording equivalent effectiveness;

(iv) among operation areas, work rooms for operations of weighing starting materials or for operations of preparing, filling or sealing products are designed so that those work rooms are not used as passageways by any individual other than personnel working there; provided, however, that this does not apply where work rooms have no risk of possible product contamination due to individuals other than personnel working in such work rooms;

(v) in the following cases, work rooms where products, etc. are handled (excluding work rooms where only products, etc. sealed in airtight containers are handled and work rooms where only samples taken from products, etc. are handled; the same applies to the next paragraph) are dedicated to the products, etc. and suitable measures to prevent leakage of the products, etc., such as separated air processing system, have been taken for such work rooms:

(a) the case where any easily dispersing products, etc. that cause hypersensitivity reactions with a trace amount are handled; or

(b) the case where no suitable measures can be implemented to prevent cross-contamination, while handling any products, etc. that could cause significant impact on other products, etc. due to cross-contamination (including those with strong pharmacological potency or toxicity);

(vi) equipment is provided for supplying water (including wash water for equipment, instruments and containers) of sufficient quality and quantity for manufacture of products.

(2) Production operations of articles to which this Ministerial Order is not applied must not be performed in the work rooms where products, etc. of pharmaceuticals are handled; provided, however, this does not apply where ingredients of such articles are suitably inactivated or eliminated through validated processes or cleaning and suitable measures have been implemented to prevent cross-contamination with products of pharmaceuticals, excluding in the following cases:

(i) the case where any easily dispersing substances that cause hypersensitivity reactions with a trace amount are handled during production operations of such articles; or

(ii) the case where such articles are not intended for use on human body and it is not verified that ingredients thereof have no strong pharmacological potency and toxicity.

(Production Control)

Article 10 Manufacturers, etc. must have their production department, suitably in accordance with the written procedures, etc., conduct the following tasks regarding

production control:

- (i) to document and retain documents which describe instructions, precautions and other necessary matters on the production process (hereinafter such documents are referred to as “written production directions”);
- (ii) a responsible person in the production department shall instruct the personnel that are engaged in production operations of the products to perform such operations in accordance with the written production directions;
- (iii) to perform production operations in accordance with the written production directions. With regard to products that consist of batches, to perform production operations so that an aggregation of products produced based on one written production direction will consist of one batch, in principle;
- (iv) to document and retain production records for each batch (for each production number, in the case of products that do not consist of batches; the same applies hereinafter, excluding in the paragraph (1) of Article 28);
- (v) for each batch of the products, etc. and for each lot of the packaging/labeling materials, to ensure that those are suitable, and to document and retain records regarding results thereof;
- (vi) for each batch of the products, etc. and for each lot of the packaging/labeling materials, to suitably store them, to manage their receipt/dispense, and to document and retain records thereof;
- (vii) to ensure cleanliness of the premises/equipment to be used for production, and to document and retain records regarding results thereof;
- (viii) to implement sanitation/hygiene control for personnel, and to document and retain records thereof;
- (ix) to implement regular maintenance of the premises/equipment to be used for production, and to document and retain records thereof; in addition, to suitably calibrate the measuring instruments for production control, and to document and retain records thereof;
- (x) to verify whether suitable production control has been implemented, by checking records of production, storage, stock receipt/dispense and sanitation/hygiene control, and to report the verification outcomes in writing to the quality assurance section; and
- (xi) to conduct other tasks necessary for production control.

#### (Quality Management)

Article 11 (1) Manufacturers, etc. must have their quality department, systematically and suitably in accordance with the written procedures, etc., conduct the following tasks regarding quality assurance and quality control:

- (i) to take samples necessary for performing testing/analysis on each batch of the products, etc. and examination/testing on each lot of the packaging /labeling materials, and to document and retain records thereof;
- (ii) to retain the collected samples and reference standard materials for testing/analysis

thereof in a suitable manner;

- (iii) a responsible person in the quality department shall instruct in writing the personnel that are engaged in quality control operations of the starting materials, packaging/labeling materials and products to perform such operations;
  - (iv) to perform testing/analysis on each batch of the products, etc. and examination/testing on each lot of the packaging/labeling materials, of the collected samples in accordance with the documents pursuant to the provisions of the preceding item, and to document and retain records thereof;
  - (v) with regard to finished products that consist of batches, to keep their reference samples in amounts of at least twice the quantity necessary for the prescribed testing/analysis on each batch under suitable storage conditions, for a period calculated by adding one year (in the case of finished products of radiopharmaceuticals, six months or suitable number of days based upon quality risk management) to the shelf-life of such finished products from the date of manufacture, and to keep their retention samples for the same period as the reference samples;
  - (vi) with regard to starting materials, etc. that impact on quality of the products of pharmaceuticals, among those which have been used for producing such products, to keep their reference samples in amounts of at least twice the quantity necessary for the prescribed testing/analysis on each batch of such starting materials and in amounts of the quantity necessary for the prescribed examination/testing on each lot of such packaging/labeling materials, under suitable storage conditions for two years from the date of release certification of the product batch (in the case of starting materials for products of radiopharmaceuticals, for a suitable period based upon the stability of such starting materials);
  - (vii) to conduct regular maintenance of the equipment and instruments for quality control, and to document and retain records thereof; in addition, to suitably calibrate the measuring instruments for quality control, and to document and retain records thereof;
  - (viii) to evaluate results of the testing/analysis pursuant to the provisions of item (iv) and to report the evaluation outcomes in writing to the production department, and when a testing/analysis has resulted in out of specification, to investigate the cause of such out of specification and take necessary corrective actions and preventive actions, and to document and retain records thereof; and
  - (ix) to conduct other tasks necessary for quality assurance and quality control.
- (2) In the case where it has been confirmed that the requirements for manufacturing control and quality control and the regulatory procedures to ensure conformity to such requirements in the exporting country are equivalent to those requirements and the regulatory procedures in Japan, manufacturers may omit the testing/analysis on their imported products (excluding appearance examination) specified upon the provisions of item (iv) in the preceding paragraph, by means of referring to records of the testing/analysis performed on such imported products by the foreign manufacturer in the exporting country. In this case, such manufacturers must have their quality assurance

section reasonably conduct the following tasks:

- (i) to confirm regularly that such imported products are manufactured in accordance with suitable manufacturing procedures, etc. at the manufacturing site in the foreign manufacturer;
  - (ii) to confirm regularly that the manufacturing site of the foreign manufacturer is in conformity to the requirements for manufacturing control and quality control provided in the country where such manufacturing site locates;
  - (iii) to document and retain records of the confirmations pursuant to the provisions of the preceding two items; and
  - (iv) to confirm records of the testing/analysis performed on the imported products by the foreign manufacturer, and to document and retain records of such confirmation.
- (3) Manufacturers, etc. must have their quality assurance section, in accordance with the written procedures, etc., check the verification outcomes of production control which have been reported by their production department pursuant to the provisions of item (x) in the preceding Article, for each batch.

(Stability Monitoring)

Article 11-2 (1) Manufacturers, etc. for finished products of pharmaceuticals must have their quality department, systematically and suitably in accordance with the written procedures, etc., conduct the following tasks regarding stability monitoring of such pharmaceuticals<sup>†</sup>:

- (i) to select the products for which stability monitoring should be performed, reasonably based upon outcome of specifying and assessing the quality risks, and to take samples in necessary amounts;
  - (ii) to select, among specifications of the pharmaceuticals subjected to stability monitoring, items which are vulnerable during storage or are deemed to have impact on efficacy and safety of such pharmaceuticals when out of specifications thereof occur, as testing/analysis items in the stability monitoring;
  - (iii) to keep the samples taken pursuant to the provisions of item (i), and to perform testing/analysis of the items selected pursuant to the provisions of the preceding item at suitable intervals;
  - (iv) to assess quality impact on the pharmaceuticals subjected to stability monitoring, based upon results of the testing/analysis pursuant to the provisions of the preceding item; and
  - (v) to document and retain records of the tasks as provided in each of the preceding items.
- (2) In the case where any actual or potential out of specifications on finished products of a pharmaceutical has been identified upon outcome of the assessment pursuant to the provisions of item (iv) in the preceding paragraph, the manufacturer, etc. of such products must take necessary actions, such as prompt notifications to concerned marketing license holders of the pharmaceutical, and providing such marketing license holders with

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<sup>†</sup> Translation annotation; finished products of pharmaceuticals

information necessary for a decision on product recalls, etc., and document and retain records of such actions.

(Review of Product Quality)

Article 11-3 (1) Manufacturers, etc. must have their quality assurance section, suitably in accordance with the written procedures, etc., conduct the following tasks:

- (i) to review the product quality regularly and whenever necessary, with the objective of verifying appropriateness of the manufacturing processes and specifications on the starting materials, packaging/labeling materials and products; and
- (ii) to report outcome of the review pursuant to the provisions of the preceding item in writing to the manufacturing supervisor.

(2) In the case where any rectification is needed on manufacturing control or quality control or in the case where any validation is required to be performed, based upon outcome of the review pursuant to the provisions of item (i) in the preceding paragraph, the manufacturers, etc. must implement necessary measures, and document and retain records of such measures.

(Supplier Control for Starting Materials, etc.)

Article 11-4 (1) Manufacturers, etc. must have their quality assurance section, suitably in accordance with the written procedures, etc., conduct the following tasks:

- (i) to prescribe suitable specifications in order to ensure quality of the starting materials, etc.;
- (ii) to select suppliers of the starting materials, etc. after qualifying their suitability;
- (iii) to check regularly whether suitable and timely manufacturing control and quality control on the starting materials, etc. have been implemented; and
- (vi) to document and retain records of the tasks as provided in the preceding three items.

(2) With regard to starting materials, etc. that impact on product quality, manufacturers, etc. must conclude necessary written agreements with suppliers thereof regarding methods of manufacturing control and quality control on such starting materials, etc.; provided, however, that this does not apply where the marketing license holder or the holder of product authorization pursuant to the provisions of Article 19-1, paragraph (1) of the Act., of pharmaceuticals relevant to the products using such starting materials, etc., has concluded such written agreements with the suppliers of such starting materials, etc.

(Control of Outsourced Contractors)

Article 11-5 (1) In the case where some of product/quality related activities, such as testing/analysis or others, are contracted to an outsourced contractor (limited to the case where it is found that such outsourcing would create no problem), the manufacturer, etc. must conclude necessary written agreements with the outsourced contractor; provided, however, that this does not apply where the marketing license holder or the holder of product authorization pursuant to the provisions of Article 19-1, paragraph (1) of the Act.,

of pharmaceuticals relevant to the products subjected to such outsourced activities, has concluded such written agreements with the outsourced contractor (the same applies hereinafter in item (i) of the next paragraph).

- (2) Manufacturers, etc. must have their appointed personnel, suitably in accordance with the written procedures, etc., conduct the following tasks:
  - (i) upon concluding a written agreement with a outsourced contractors, to confirm suitability and competence of the outsourced contractor;
  - (ii) to check regularly whether the outsourced contractors suitably and timely conduct the production/quality related activities outsourced, and to request such outsourced contractor to implement rectification as necessary; and
  - (iii) to document and retain records of the tasks as provided in the preceding two items.

#### (Control of Product Release from the Manufacturing Site)

- Article 12 (1) Manufacturers, etc. must have their quality assurance section, suitably in accordance with the written procedures, etc., conduct tasks of assessing whether the production/quality related activities have been conducted suitably for each batch and of certifying their products to release from the manufacturing site or reject.
- (2) Personnel in charge of the tasks as provided in the preceding paragraph must be personnel who have been qualified to conduct such tasks suitably and timely.
  - (3) Manufacturers, etc. must ensure that their personnel in charge of the tasks as provided in paragraph (1) do not have any difficulty with such tasks.
  - (4) Manufacturers, etc. must not release their products from the manufacturing sites before the release certification pursuant to the provisions of paragraph (1) is made suitably.

#### (Validation)

- Article 13 (1) Manufacturers, etc. must have their appointed personnel, in accordance with the written procedures, etc., conduct the following tasks:
- (i) to perform validation in the following cases:
    - (a) the case where commencing manufacture of a new pharmaceutical for the manufacturing site;
    - (b) the case where introducing any change to the manufacturing procedures, etc. that critically impact on the product quality; or
    - (c) other cases that it is deemed to be necessary to perform validation in order to implement production control and quality control suitably for the products; and
  - (ii) to report validation protocols and outcome of the validation in writing to the quality assurance section.
- (2) In the case where any rectification with regard to production control or quality control is needed based upon outcome of the validation pursuant to the provisions of item (i) in the preceding paragraph, the manufacturer, etc. must implement necessary measures, and document and retain records of such measures.

(Change Management)

Article 14 (1) Upon introducing any change to specifications of the starting materials, packaging/labeling materials or products, or to the manufacturing procedures, etc., such manufacturer, etc. must have its appointed personnel, in accordance with the written procedures, etc., conduct the following tasks:

- (i) to assess impact by the change on the product quality and the product authorization requirements;
  - (ii) when it is identified that the change causes any actual or potential impact on the product quality or the product authorization requirements, upon outcome of the assessment pursuant to the provisions of the preceding item, to notify the marketing license holders and the holders of product authorization pursuant to the provisions of Article 19-2, paragraph (1) of the Act, which are relevant to the products to be affected by such change, and to obtain consent thereof;
  - (iii) based upon outcomes of the assessment and consent pursuant to the provisions of the preceding two items, to have endorsement by the quality assurance section for introducing the change; and
  - (iv) to revise relevant documents, to educate and train the personnel, and to take other necessary actions, upon implementing a change with the endorsement pursuant to the provisions of the preceding item;
  - (v) to report operational status of the tasks as provided in each of the preceding items, in writing to the quality assurance section and the manufacturing supervisor; and
  - (vi) to document and retain records of the tasks as provided in each of the preceding items.
- (2) Manufacturers, etc. who have introduced a change pursuant to the provisions of the preceding paragraph must have their quality assurance section, in accordance with the written procedures, etc., conduct the following tasks:
- (i) to verify impact on the product quality, and to conduct assessment to ensure that the objectives of such change have been achieved;
  - (ii) after introduced a change that impacts on the product quality or the product authorization requirements, to notify the marketing license holders and the holders of product authorization pursuant to the provisions of Article 19-2, paragraph (1) of the Act, which are relevant to the products affected by such change; and
  - (iii) to document and retain records of the tasks as provided in the preceding two items.

(Deviation Management)

Article 15 (1) In the case where any deviation from the manufacturing procedures, etc. (hereinafter simply referred to as “deviation”) has occurred, the manufacturer, etc. must have its appointed personnel, suitably in accordance with the written procedures, etc., conduct the following tasks:

- (i) to record detail of the deviation, to assess impact by the deviation, to report the assessment outcome in writing to the quality assurance section, and to have it checked by the quality assurance section;

- (ii) in the case where any significant deviation has occurred, to conduct the following tasks in addition to those provided in the preceding item, to report detail thereof in writing to the quality assurance section, and to have it checked by the quality assurance section;
    - (a) to notify promptly the marketing license holders which are relevant to products concerned with such deviation;
    - (b) to investigate the cause of such deviation; and
    - (c) to take necessary corrective actions and preventive actions; and
  - (iii) to document and retain records of the tasks as provided in the preceding two items.
- (2) Manufacturers, etc. must have their quality assurance section, suitably in accordance with the written procedures, etc., document and retain records of the checkings pursuant to the provisions of items (i) and (ii) in the preceding paragraph, and have the quality assurance section report such records in writing to the manufacturing supervisor.

(Management of Quality Information and Quality Defects, etc.)

Article 16 (1) In the case where information on quality, etc. (hereinafter referred to as “quality information”) of its products has been received, the manufacturer, etc. must have its appointed personnel, in accordance with the written procedures, etc., conduct the following tasks:

- (i) to document and retain records describing detail of the quality information;
  - (ii) except where matters of such quality information are obviously not attributable to the manufacturing site, to investigate the cause of such matters, and in the case where any rectification with regard to production/quality related activities is needed, to take necessary corrective actions and preventive actions;
  - (iii) to document and retain records of the investigation outcomes and of the corrective actions and preventive actions pursuant to the provisions of the preceding item, to report such records in writing to the quality assurance section, and to have such records checked by the quality assurance section; and
  - (iv) to document and retain records of the report and checking pursuant to the provisions of the preceding item.
- (2) In the case where any actual or possible quality defect has been identified upon the checking pursuant to the provisions of item (iii) in the preceding paragraph, the manufacturer, etc. must have its quality assurance section, in accordance with the written procedures, etc., report such matters in writing to the manufacturing supervisor. Further, the manufacturer, etc. must take necessary actions, such as prompt notifications to the marketing license holders which are relevant to products concerned with such quality information, providing such marketing license holders with information necessary for a decision on product recalls, etc., and document and retain records of such actions.

(Management of Recalled Products and Others)

Article 17 (1) Upon storing any recalled products, such manufacturer, etc. must have its appointed personnel, in accordance with the written procedures, etc., conduct the following



tasks:

- (i) after separate storage for a certain period, to suitably dispose of the recalled products;  
and
  - (ii) to document and retain records of the storage and disposal, describing detail of the recalled products, and to report in writing to the quality assurance section and the manufacturing supervisor.
- (2) The provisions of the preceding paragraph apply mutatis mutandis to storage and disposal of the starting materials, packaging/labeling materials and products which are rejected for use or release.

(Internal Audits)

Article 18 (1) Manufacturers, etc. must have their appointed personnel, in accordance with the written procedures, etc., conduct the following tasks:

- (i) to conduct regular internal audits on production/quality related activities;
  - (ii) to report the internal audit outcomes in writing to the quality assurance section and the manufacturing supervisor; and
  - (iii) to document and retain records of the internal audit outcomes.
- (2) In the case where any rectification with regard to production/quality related activities is needed based upon outcomes of the internal audits pursuant to the provisions of item (i) in the preceding paragraph, such manufacturer, etc. must implement necessary measures, and document and retain records of such measures.

(Education/Training)

Article 19 Manufacturers, etc. must have their appointed personnel, in accordance with the written procedures, etc., conduct the following tasks:

- (i) for personnel that are engaged in production/quality related activities, to systematically implement necessary education/training on production control and quality management;
- (ii) to report implementation of the education/training, in writing to the quality assurance section and the manufacturing supervisor;
- (iii) to document and retain implementation records of the education/training; and
- (iv) to assess practical effectiveness of the education/training regularly, to improve as necessary, and to document and retain records thereof.

(Management of Documents/Records)

Article 20 (1) Manufacturers, etc. must have their appointed personnel, in accordance with the written procedures, etc., conduct the following tasks with regard to documents/records pursuant to the provisions of this Chapter:

- (i) upon establishing or revising a document, to endorse, distribute, archive, etc. such document;
- (ii) upon establishing or revising written procedures, etc., to record dates of the establishment/revision on such written procedures, etc., and to retain records of the

history of previous revisions; and

- (iii) to retain documents/records pursuant to the provisions of this Chapter for five years (provided, however, in the case where the period calculated by adding one year to the shelf-life of the product concerned with such documents/records is longer than five years, those documents/records other than records of education/training shall be retained for a period calculated by adding one year to such shelf-life), from the date of documentation (in the case of written procedures, etc., from the date of discontinuance thereof).
- (2) Manufacturers, etc. must have their appointed personnel, in accordance with the documents pursuant to the provisions of Article 8, paragraph (2), conduct the following tasks with regard to the written procedures, etc. and records pursuant to the provisions of this Chapter:
  - (i) to manage the written procedures, etc. and records which should be documented and retained, to ensure that all of such documents/records are complete throughout the document/record lifecycle;
  - (ii) to manage the written procedures, etc. and records which have been documented, to ensure that all of such documents/records are accurate throughout the document/record lifecycle;
  - (iii) to manage the written procedures, etc. and records to ensure that these remain consistent with other written procedures, etc. and records throughout the document/record lifecycle;
  - (iv) when a written procedure, etc. or record has been found incomplete, or any inaccuracy or inconsistency in contents thereof has been found, to investigate the cause of such defects, and to take necessary corrective actions and preventive actions;
  - (v) to conduct other tasks necessary for ensuring integrity of the written procedures, etc. and records; and
  - (vi) to document and retain records of the tasks as provided in each of the preceding items.

## Section 2 Manufacturing Control and Quality Control for Active Ingredients treated as Pharmaceuticals

### (Quality Control)

Article 21 Manufacturers, etc. for active ingredients treated as pharmaceuticals must have their quality department, in accordance with the written procedures, etc., keep reference samples of such pharmaceuticals<sup>‡</sup> in amounts of at least twice the quantity necessary for the prescribed testing/analysis on each batch, under suitable storage conditions, for the period as provided in the following items from the date of manufacture:

- (i) with regard to pharmaceuticals (other than radiopharmaceuticals) for which a retest date has been established instead of its expiry date, for the period until the retest date of

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<sup>‡</sup> Translation annotation; active ingredients treated as pharmaceuticals (the same applies in Article 21-2)

such pharmaceutical or for three years after the batch concerned is completely released from the manufacturing site, whichever is longer; or

- (ii) with regard to pharmaceuticals other than those provided in the preceding item, for a period calculated by adding one year (in the case of radiopharmaceuticals, for six months or a suitable number of days based upon quality risk management) to the shelf-life of such pharmaceutical.

(Stability Monitoring)

Article 21-2 (1) Manufacturers, etc. for active ingredients treated as pharmaceuticals must have their quality department, systematically and suitably in accordance with the written procedures, etc., conduct the following tasks regarding stability monitoring of such pharmaceuticals:

- (i) to select the products for which stability monitoring should be performed, reasonably based upon outcome from specifying and assessing the quality risks, and to take samples in necessary amounts;
  - (ii) to select, among specifications of the pharmaceuticals subjected to stability monitoring, items which are vulnerable during storage or are deemed to have impact on efficacy and safety of such pharmaceuticals when out of specifications thereof occur, as testing/analysis items in the stability monitoring;
  - (iii) to keep the samples taken pursuant to the provisions of item (i), and to perform testing/analysis of the items selected pursuant to the provisions of the preceding item at suitable intervals;
  - (iv) to assess quality impact on the pharmaceuticals subjected to stability monitoring, based upon results of the testing/analysis pursuant to the provisions of the preceding item; and
  - (v) to document and retain records of the tasks as provided in each of the preceding items.
- (2) In the case where any actual or potential out of specifications on an active ingredient treated as pharmaceutical has been identified upon outcome of the assessment pursuant to the provisions of item (iv) in the preceding paragraph, the manufacturer, etc. of such products must take necessary actions, such as prompt notifications to the marketing license holders which are concerned with the pharmaceutical, providing such marketing license holders with information necessary for a decision on product recalls, etc., and document and retain records of such actions.

(Retention of Documents/Records)

Article 22 Notwithstanding the provisions of Article 20, paragraph (1), item (iii), manufacturers, etc. for products of active ingredients treated as pharmaceuticals must retain the documents/records pursuant to the provisions of this Chapter, which are concerned with such products, for the period as provided in the following items from the date of documentation (in the case of written procedures, etc., from the date of discontinuance thereof); provided, however, that records of education/training are to be

retained for five years from the date of documentation:

- (i) in the case of documents/records concerned with pharmaceuticals that consist of batches, for which a retest date has been established instead of its expiry date, for the period until the retest date of the batch concerned with such documents/records or for three years after the batch concerned with such documents/records is completely released from the manufacturing site, whichever is longer; or
- (ii) in the case of documents/records concerned with pharmaceuticals other than those provided in the preceding item, for a period calculated by adding one year to the shelf-life of such active ingredient.

### Section 3 Manufacturing Control and Quality Control for Sterile Pharmaceuticals

#### (Premises/Equipment of Manufacturing Sites for Sterile Pharmaceuticals)

Article 23 In the case of manufacturers licensed under the category provided in Article 25, paragraph (1), item (iii) of the Enforcement Regulation, and foreign manufacturers accredited under the category provided in Article 35, paragraph (1), item (iii) of the Enforcement Regulation, premises/equipment of their manufacturing sites must conform to the following requirements, in addition to those provided in Article 9, paragraph (1):

- (i) among operation areas, work rooms and controlled operation areas are provided with premises/equipment for maintaining the environmental cleanliness level according to type, dosage form and production processes of the products of sterile pharmaceuticals;
- (ii) work rooms for drying or sterilizing operations of cleaned containers are dedicated to such operations; provided, however, that this does not apply where the cleaned containers have no risks of possible contamination;
- (iii) work rooms conform to the following requirements:
  - (a) work rooms are provided with equipment necessary for suitable drying and storage for the containers after cleaning;
  - (b) work rooms are provided with sterilization apparatus necessary for the manufacture, according to type of the products of sterile pharmaceuticals;
  - (c) areas for aseptic operations are provided with premises/equipment necessary for supplying clean air treated with filters and for suitable pressure differential control; and
  - (d) in the case where products of injectable preparations are manufactured, the liquid-contacting pipework, etc. equipped therewith, which impacts on sterility assurance, is easily cleanable and sterilizable;
- (iv) work rooms and controlled operation areas, which are for preparing or filling operations of pharmaceutical preparations, or for operations after preparing operations for the purpose of product sterilization (excluding labeling and packaging operations), conform to the following requirements:
  - (a) such work rooms and controlled operation areas are segregated from the operation areas for non-sterile pharmaceuticals;

- (b) work rooms for preparing operations and work rooms for filling or sealing operations are dedicated to such operations; and
- (c) such work rooms and controlled operation areas have gowning rooms dedicated to the personnel who perform the operations specified in (b);
- (v) equipment for supplying distilled water, etc. necessary for manufacture of products of sterile pharmaceuticals has a structure needed to prevent contamination of such distilled water, etc. with foreign substances or microorganisms.

(Production Control)

Article 24 Manufacturers, etc. for products of sterile pharmaceuticals must have their production department, suitably in accordance with the written procedures, etc., conduct the following tasks regarding production control in addition to the tasks as provided in Article 10:

- (i) to control work areas by defining control levels of the work environment, such as environmental cleanliness levels, suitably according to type, dosage form, characteristics and production processes of the products of sterile pharmaceuticals to be produced, the nature of operations performed in such work areas, and so on;
- (ii) to control the starting materials, packaging/labeling materials and products by defining necessary items to be controlled, such as levels of microorganisms, etc., suitably according to type, dosage form, characteristics, production processes of the products of sterile pharmaceuticals to be produced, and so on;
- (iii) to implement necessary measures during the production processes in order to prevent the starting materials, packaging/labeling materials and products from contamination, etc. by microorganisms, etc.;
- (iv) to control processes, etc. critical to ensure sterility of the products of sterile pharmaceuticals to be produced, by prescribing necessary control indices for the process control, suitably according to type, dosage form, characteristics, production processes, etc. of such products;
- (v) to control process water by prescribing necessary microbiological and physicochemical control indices, in a manner suitable to the use;
- (vi) to implement sanitation/hygiene control for personnel, by the following means:
  - (a) to restrict access of individuals other than personnel that are engaged in production operations to the operation areas, as far as possible;
  - (b) to establish strict procedures in order to prevent contamination due to the personnel that are engaged in operations of processing animal tissue-derived starting materials, or cultivation of microorganisms, etc. (excluding the microorganisms, etc. being used as starting materials or processing materials during the production process), and to prohibit such personnel from accessing the work areas for products of sterile pharmaceuticals unless they comply with such procedures; and
  - (c) to restrict access of the personnel to the clean areas or aseptic areas where operations are currently being carried on, as far as possible; and

(vii) to implement sanitation/hygiene control for the personnel in charge of operations in the clean areas or aseptic areas, by the following means:

- (a) before personnel that are engaged in production operations enter the clean areas or aseptic areas, to have such personnel implement gowning etc. in a suitable manner for the control levels of such areas; and
- (b) when any personnel are in a health condition with concerns of contaminating the starting materials, packaging/labeling materials and/or products with microorganisms, etc. (including when suffering from an infectious disease on skin or hair or a cold, when having an injury or when having such symptoms as diarrhea or fever of unknown cause; the same applies hereinafter), to have such personnel report the health condition.

#### (Education/Training)

Article 25 Manufacturers, etc. for products of sterile pharmaceuticals must have their appointed personnel, in accordance with the written procedures, etc., conduct the following tasks in addition to the tasks as provided in Article 19:

- (i) for personnel that are engaged in production or quality control, to implement education/training on sanitation/hygiene control and microbiology necessary for manufacture of the products of sterile pharmaceuticals, and other necessary education/training; and
- (ii) for personnel that are engaged in operations in clean areas and aseptic areas, etc., to implement education/training on necessary measures in order to prevent contamination by microorganisms, etc.

### Section 4 Manufacturing Control and Quality Control for Biological Pharmaceuticals

#### (Pharmaceutical Products Specification File for Biological Pharmaceuticals)

Article 25-2 Manufacturers, etc. for products of biological pharmaceuticals (“biological pharmaceuticals” collectively refers to biological origin pharmaceuticals, biological preparations as provided in Article 80, paragraph (2), item (iii), (a) of Enforcement Order of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (Cabinet Order No. 11 of 1961), pharmaceuticals designated by the Minister of Health, Labour and Welfare pursuant to the provisions of Article 43, paragraph (1) of the Act, pharmaceuticals produced utilizing genetic engineering techniques, pharmaceuticals for which any pharmaceuticals produced utilizing genetic engineering techniques are used as starting materials, pharmaceuticals produced utilizing human or animal cell cultivation techniques, pharmaceuticals for which any pharmaceuticals produced utilizing human or animal cell cultivation techniques are used as starting materials, and cell/tissue-based pharmaceuticals; the same applies hereinafter) must prescribe the following matters in the pharmaceutical product specification files in addition to the matters as provided in Article 7, and have endorsement therefor by the quality

department, then place such files suitably at the manufacturing sites:

- (i) name, nature, property/condition, ingredients and their quantities, and other specifications of the materials derived from humans, animals, plants or microorganisms to be used as starting materials; and
- (ii) specifications (including procedures for rearing control) of the animals to be used for production or testing/analysis (including donor animals; hereinafter referred to as “animals for use”).

(Premises/Equipment of Manufacturing Sites for Biological Pharmaceuticals)

Article 26 In the case of manufacturers, etc. for products of biological pharmaceuticals, premises/equipment of their manufacturing sites must conform to the following requirements, in addition to those provided in Article 9, paragraph (1) and Article 23:

- (i) premises/equipment of the manufacturing sites for products of other biological preparations than blood preparations that do not consist of batches conform to the following requirements:
  - (a) operation areas are provided with the following equipment in a room distinctly segregated from other rooms; provided, however, that this does not apply in the case of equipment that is found unnecessary for manufacture of the products depending upon their type, production procedures, etc.:
    1. storage equipment for microorganisms;
    2. equipment for keeping the animals for use which have been inoculated with a microorganism;
    3. equipment for processing the animals for use;
    4. equipment for transplanting microorganisms into the culture media, etc.;
    5. equipment for cultivating microorganisms;
    6. equipment for collecting, inactivating, sterilizing, etc., for the microorganisms cultured;
    7. equipment for preparing a diluting solution for a bulk material;
    8. equipment for diluting and subdividing a bulk material, and for sealing filled containers; and
    9. equipment for sterilizing the instruments and apparatus, etc. used in production or testing/analysis;
  - (b) the rooms provided with the equipment specified in (a), 4 and 6 to 8, and the rooms provided with equipment for sterility tests, among equipment necessary for quality control of the starting materials, packaging/labeling materials and products, conform to the following requirements:
    1. such rooms are aseptic rooms; provided, however, that this does not apply where the work rooms are provided with equipment functioning to enable aseptic operations to be performed without hindrance according to type, production procedures, etc. of the products; and
    2. the aseptic rooms as provided in 1. have a dedicated anteroom, with a structure

wherein the aseptic rooms are usually accessible only through the anteroom, and doorways of the anteroom do not face outside directly;

(c) the following equipment is provided, in addition to that provided in (a):

1. equipment necessary for rearing control of the animals for use;
2. equipment for formulating culture media and diluting solution thereof;
3. equipment for cleaning and sterilizing the instruments and apparatus, containers, etc. before using for production or testing/analysis; and
4. equipment for suitably disposing of animal carcasses and other wastes, and for decontaminating sewage;

(ii) premises/equipment of the manufacturing sites for products of the blood preparations that do not consist of batches conform to the following requirements:

(a) among operation areas, work rooms for operations of fractionating and mixing blood components, of injecting and discharging liquid materials, or of sealing filled containers, are segregated from work rooms for other products than blood preparations;

(b) among work rooms, work rooms for the operations as provided in (a), which are performed in an open-type system, conform to the following requirements:

1. work rooms are dedicated to such operations; and
2. work rooms are aseptic rooms, otherwise provided with equipment functioning to enable suitable aseptic operations to be performed;

(c) operation areas are provided with gowning equipment dedicated to the personnel that are engaged in operations in the aseptic room; and

(iii) the production areas for products using human blood or plasma as starting materials are distinctly segregated from other areas and provided with equipment and instruments dedicated to production thereof; provided, however, that this does not apply to production processes subsequent to those to inactivate or eliminate viruses.

#### (Production Control)

Article 27 (1) Manufacturers, etc. for products of biological pharmaceuticals must have their production department, suitably in accordance with the written procedures, etc., conduct the following tasks regarding production control in addition to the tasks as provided in Articles 10 and 24:

(i) in the case of inactivating the products, etc. or inactivating or eliminating microorganisms, etc. contained in the products, etc., during the production process, to implement necessary measures in order to prevent contamination from products, etc. that have not been processed through such inactivation or elimination yet;

(ii) in the case of utilizing biochemical techniques, such as fermentation, during the production process, to continuously monitor indices necessary to control such production process, such as temperature and/or hydrogen ion exponent;

(iii) in the case of using a column chromatography apparatus, etc. during the production process, to implement necessary measures in order to prevent contamination of such



- apparatus by microorganisms, etc., and to perform bacterial endotoxin monitoring as necessary;
- (iv) in the case of utilizing a cultivation system under which culture media are continuously supplied into the culture tanks and the cultured broth is continuously discharged from such culture tanks, during the production process, to implement necessary measures in order to maintain cultivation conditions in such culture tanks during cultivation;
  - (v) to implement sanitation/hygiene control for personnel, by the following means:
    - (a) to restrict access of individuals other than personnel that are engaged in production operations to the operation areas, as far as possible;
    - (b) to restrict access of personnel to the clean areas or aseptic areas where operations are currently being carried on, as far as possible; and
    - (c) to exclude personnel that are engaged in production operations from operations for control of the animals for use, other than those being used during the production process;
  - (vi) to implement sanitation/hygiene control for the personnel in charge of operations in clean areas or aseptic areas, by the following means:
    - (a) to have the personnel that are engaged in production operations wear sterilized work clothes, work shoes, work caps and work masks;
    - (b) to conduct health checks for personnel at least every six months, in order to ensure that none of them are suffering from a disease that could contaminate the starting materials, packaging/labeling materials and/or products with microorganisms, etc.; and
    - (c) when any personnel are in a health condition with concerns of contaminating the starting materials, packaging/labeling materials and/or products with microorganisms, etc., to have such personnel report the health condition;
  - (vii) to keep the animals for use (limited to those which are used for production; the same applies hereinafter in this paragraph) under suitable rearing control constantly, and to examine their health condition before using, so as not to use any animals unsuitable for use, such as animals suffering from a contagious disease;
  - (viii) with regard to all articles contaminated by microorganisms (limited to those contaminated in the course of production) and carcasses of the animals for use, to dispose so as not to cause any risks to public health;
  - (ix) to document and retain records regarding the following matters with regard to handling of the microorganism strains to be used for production:
    - (a) name of the microorganism strains, and number assigned to each of containers thereof;
    - (b) receipt date, and name and address of the provider (in the case of a corporation, its name and office location);
    - (c) biological property/condition, and date of examination thereof; and
    - (d) status of successive cultivation thereof;
  - (x) to prohibit the instruments and apparatus for use in the work rooms where pathogenic

smallpox viruses, pathogenic acute poliomyelitis viruses, spore-forming pathogens, or tubercle bacillus mycobacteria are handled, from being used for production of other products, by means of marking indications on them for each type of the products;

(xi) to ensure that biological origin starting materials to be used for producing the product of biological origin pharmaceuticals are suitable in line with the pharmaceutical product specification files for the product, and to document and retain records regarding results thereof;

(xii) with regard to biological origin starting materials used for producing the product of biological origin pharmaceuticals, to retain records of the matters required by the Minister of Health, Labour and Welfare for the period as provided in Article 30, item (i) and (ii), or by means of concluding an agreement pursuant to the provisions of Article 11-4, paragraph (2), to ensure that the provider, etc. of origin materials of such biological origin starting materials (“origin materials” refers to objects from which starting materials or other materials used for production (including those used during the production process) are derived) (hereinafter such provider, etc. is referred to as “origin material provider, etc.”) retains such records for the same period suitably; and

(xiii) to document and retain records pursuant to the provisions of Article 10, item (x) and the preceding two items, for each batch of the products of biological pharmaceuticals to be produced.

(2) Manufacturers, etc. for products of cell/tissue-based pharmaceuticals must have their production department, suitably in accordance with the written procedures, etc., conduct the following tasks regarding production control in addition to the tasks as provided in Article 10 and the preceding paragraph:

(i) in the case of handling cells or tissue collected from different donors or donor animals, to implement necessary measures in order to prevent such cells or tissue from being mixed up and cross-contaminated;

(ii) to ensure, upon receipt, that the cells or tissue to be used for starting materials are suitable in line with the pharmaceutical product specification files for the product, by checking records of the following matters, and to document and retain records regarding results of such checking:

(a) facilities where such cells or tissue were collected;

(b) date on which such cells or tissue were collected;

(c) in the case where such cells or tissue are derived from humans, results of diagnosis by medical interviews, examinations, etc. on the donors for the purpose of donor screening;

(d) in the case where such cells or tissue are derived from animals, conditions of receipt of the donor animals, implementation of examination/testing and rearing control of the donor animals for the purpose of donor animal screening;

(e) processes of collecting operations for such cells or tissue; and

(f) other necessary matters for ensuring quality of the products of cell/tissue-based pharmaceuticals, in addition to the matters as provided in (a) to (e);

- (iii) upon collecting the cells or tissue to be used for starting materials from donor animals, to implement necessary measures in order to prevent contamination by microorganisms, etc. in the course of such collection, and to document and retain records of such measures;
  - (iv) to exclude the personnel to whom any of the following applies from operations in clean areas or aseptic areas:
    - (a) person being in a health condition with concerns of contaminating the starting materials, packaging/labeling materials and/or products with microorganisms, etc.; or
    - (b) person having handled microorganisms, etc. that could contaminate the cells or tissue, immediately before collecting or processing of the cells or tissue;
  - (v) for individual products, to confirm names of the establishments to which the products are delivered, date of the product release and batch number of the products, and to document and retain records thereof;
  - (vi) to implement necessary measures on distribution in order to secure the product quality, and to document and retain records of such measures;
  - (vii) to document and retain records of rearing control of the donor animals after their receipt; and
  - (viii) to document and retain records pursuant to the provisions of items (ii), (iii), (v) and (vi), for each batch (for individual products, in the case of records pursuant to the provisions of item (v)).
- (3) In the case of products of biological origin pharmaceuticals, production records pursuant to the provisions of Article 10 and the preceding two paragraphs must be retained in a suitable manner to trace a series of records, from records concerned with the biological origin starting materials used for their production through to records concerned with the products produced using such biological origin starting materials.

#### (Quality Management)

Article 28 (1) Notwithstanding the provisions of Article 11, paragraph (1), item (v) and (vi), manufacturers, etc. for finished products of pharmaceuticals designated as specified biological origin products as provided in Article 2, paragraph (11) of the Act (hereinafter such pharmaceuticals are referred to as “specified biological origin pharmaceuticals”), or those of cell/tissue-based pharmaceuticals must keep reference samples of such finished products for each batch (in the case of specified biological pharmaceuticals that do not consist of batches, reference samples of biological origin starting materials used for their production for each production number of the finished products or for each batch of the biological origin starting materials) in amounts of at least twice the quantity necessary for the prescribed testing/analysis under suitable storage conditions for the period as provided in the following items from the date of manufacture; provided, however, that this does not apply in the case of biological origin starting materials used for producing the specified biological origin pharmaceuticals that do not consist of batches, and in the case where it is ensured in an agreement concluded between the origin material provider, etc. and the

manufacturer, etc. pursuant to the provisions of Article 11-4, paragraph (2) that the origin material provider, etc. keeps such reference samples for the periods as provided in the following items, and, in the case of finished products of the specified biological origin pharmaceuticals or cell/tissue-based pharmaceuticals that consist of batches, sample retention of such finished products may be replaced with sample retention of the biological origin starting materials used for their production after a period calculated by adding one year (in the case of finished products of radiopharmaceuticals, six months or a suitable number of days based upon quality risk management) to the shelf-life of such finished product has elapsed:

- (i) in the case of finished products of the specified biological origin pharmaceuticals that consist of batches, and biological origin starting materials used for producing the specified biological origin pharmaceuticals that do not consist of batches, for a period calculated by adding ten years to the shelf-life of such finished product; or
  - (ii) in the case of finished products of cell/tissue-based pharmaceuticals other than those specified in the preceding item, for a suitable period.
- (2) Manufacturers, etc. for products of biological pharmaceuticals must have their quality department, systematically and suitably in accordance with the written procedures, etc., conduct the following tasks regarding quality control in addition to the tasks as provided in Article 11:
- (i) to distinguish samples by means of suitable identification labeling in order to prevent them from being mixed up or cross-contaminated;
  - (ii) in the case of the testing/analysis that is critical for quality control but not applicable to the products after production, to perform such testing/analysis at a suitable intermediate stage during the production processes;
  - (iii) to keep the animals for use (limited to those which are used for testing/analysis; the same applies hereinafter in this paragraph) under suitable control constantly, and to examine their health condition before use, so as not to use any animals unsuitable for use, such as animals suffering from a contagious disease;
  - (iv) with regard to all articles contaminated by microorganisms (limited to those contaminated in the course of testing/analysis) and carcasses of the animals for use, to dispose so as not to occur any risks to public health;
  - (v) to document and retain records of the following matters with regard to handling of the microorganism strain to be used for testing/analysis:
    - (a) name of the microorganism strain, and number assigned to each of containers thereof;
    - (b) receipt date, and name and address of the provider (in the case of a corporation, its name and office location) of the microorganism strain;
    - (c) biological property/condition, and date of examination thereof; and
    - (d) status of successive cultivation thereof; and
  - (vi) to document and retain records of the testing/analysis results for each batch of the products of biological pharmaceuticals to be manufactured.
- (3) Manufacturers, etc. for products of cell/tissue-based pharmaceuticals must have their

quality department, suitably in accordance with the written procedures, etc., conduct the following tasks regarding quality assurance and quality control in addition to the tasks as provided in Article 11 and the preceding paragraph:

- (i) to perform examination/testing and other necessary tasks upon and after receipt of the donor animals internally at the quality department, or to delegate such tasks to other personnel appointed according to contents of the task; and
  - (ii) to document and retain records of the tasks as provided in the preceding item.
- (4) In the case of biological origin pharmaceuticals, quality records pursuant to the provisions of the preceding three paragraphs must be retained in a suitable manner to trace a series of records, from records concerned with the biological origin starting materials used for their production through to records concerned with the products produced using such biological origin starting materials.

#### (Education/Training)

Article 29 Manufacturers, etc. for products of biological pharmaceuticals must have their appointed personnel, in accordance with the written procedures, etc., conduct the following tasks in addition to the tasks as provided in Articles 19 and 25:

- (i) for personnel that are engaged in production or quality control of biological pharmaceuticals, to implement education/training on microbiology, medicine, veterinary medicine, etc.; and
- (ii) for personnel that are engaged in operations in aseptic areas or the areas, etc. where pathogenic microorganisms are handled, to implement education/training on necessary measures in order to prevent contamination by microorganisms, etc.

#### (Retention of Documents/Records)

Article 30 Notwithstanding the provisions of Article 20, paragraph (1), item (iii) and Article 22, manufacturers, etc. for products of biological pharmaceuticals must retain the documents/records pursuant to the provisions of this Chapter, which are concerned with such products, for the period as provided in the following items from the date of documentation (in the case of written procedures, etc., from the date of discontinuance thereof); provided however, that records of education/training are to be retained for 5 years from the date of documentation:

- (i) with regard to products of specified biological origin pharmaceuticals or biological origin pharmaceuticals produced using human blood as origin materials, for a period calculated by adding thirty years to the shelf-life of such product;
- (ii) with regard to products of biological origin pharmaceuticals or cell/tissue-based pharmaceuticals other than those specified in the preceding item, for a period calculated by adding ten years to the shelf-life of such product; or
- (iii) with regard to products other than those in the preceding two items, for five years; provided, however, in the case where the period calculated by adding one year to the shelf-life of such product is longer than five years, for a period calculated by adding one

year to such self-life.

## Section 5 Miscellaneous Provisions

### (Exceptions to Retention of Records)

Article 31 Notwithstanding the provisions of the preceding Article, manufacturers, etc. for products of biological origin pharmaceuticals designated by the Minister of Health, Labour and Welfare must have their appointed personnel retain records pursuant to the provisions of the preceding Article for the period specified by the Minister of Health, Labour and Welfare; provided, however, that this does not apply in the case of records concerned with the biological origin starting materials used for producing such biological origin pharmaceuticals, and where ensuring that the origin material provider, etc. retains such records suitably for the required period, by means of concluding an agreement pursuant to the provisions of Article 11-4, paragraph (2).

## Chapter 3 Manufacturing Control and Quality Control at Manufacturing Sites of Quasi-Pharmaceutical Manufacturers, etc.

### Section 1 General Rules

#### (Production Department and Quality Department)

Article 32 (1) Manufacturers, etc. must establish a production department and a quality department at each of their manufacturing sites, under supervision of the technical supervisor as provided in Article 17, paragraph (10) of the Act, or a responsible person at the manufacturing site that has been accredited pursuant to the provisions of Article 13-3, paragraph (1) of the Act or personnel appointed by the foreign manufacturer) (hereinafter these are collectively referred to as “technical supervisor”).

(2) The quality department must be independent of the production department.

#### (Technical Supervisor)

Article 33 (1) Technical supervisor must conduct the following tasks:

- (i) to supervise activities regarding production control and quality control (hereinafter referred to as “production/quality control activities”), and to implement direction and control for such activities to ensure their suitable and timely implementation;
- (ii) in the case where any quality defect or other concerns that could cause significant impact on product quality has occurred, to ensure that necessary actions are being promptly taken, to check progress of such actions, and to give instructions as necessary to implement rectification and other necessary measures.

(2) Manufacturers, etc. must ensure that their technical supervisor conducts the tasks without any hindrance.

(Personnel)

Article 34 (1) Manufacturers, etc. must adequately appoint responsible persons capable of conducting production/quality control activities suitably and timely (hereinafter such persons are simply referred to as “responsible persons” in this Chapter) according to the organization, size, and type of activities, etc. of their manufacturing sites.

(2) Manufacturers, etc. must assign an adequate number of responsible persons according to the organization size, and type of activities, etc. of their manufacturing sites.

(3) Manufacturers, etc. must secure adequate personnel capable of suitably conducting production/quality control activities.

(4) Manufacturers, etc. must prescribe, suitably in documents, responsibilities of and management system for personnel (including the technical supervisor and responsible persons) engaged in production/quality control activities.

(Quasi-Pharmaceutical Product Specification File)

Article 35 Manufacturers, etc. must establish documents which prescribe the following matters with regard to their products (excluding intermediate products which are in the course of a series of production processes at a manufacturing site) of quasi-pharmaceuticals (hereinafter such documents are referred to as “quasi-pharmaceutical product specification files”) for each of their manufacturing sites involved in manufacture of the products, have endorsement therefor by the quality department, and then place such files suitably at the manufacturing sites:

(i) production procedures, specifications and testing/analytical methods and other necessary matters employed at the manufacturing site, among the product authorization requirements;

(ii) matters on quality, among the specification requirements which are specified pursuant to the provisions of Article 42, paragraph (2) of the Act, and the requirements of other laws and regulations concerning pharmaceutical affairs, or the orders or actions based thereon;

(iii) manufacturing procedures other than matters as provided in item (i); and

(iv) other necessary matters.

(Written Procedures)

Article 36 Manufacturers, etc. must establish written procedures which prescribe the following procedures for each of their manufacturing sites, then place such written procedures suitably at the manufacturing sites:

(i) procedures for sanitation/hygiene control of premises/equipment and for personnel;

(ii) procedures for control of production processes, production equipment, starting materials, packaging/labeling materials and products;

(iii) procedures necessary for performing suitable testing/analysis, including management of the quality control laboratories and samples;

(iv) procedures for control of product release from the manufacturing site;

- (v) procedures for validation;
- (vi) procedures for change management as provided in Article 42;
- (vii) procedures for deviation management as provided in Article 43;
- (viii) procedures for management of quality information and quality defects, etc. as provided in Article 44;
- (ix) procedures for management of recalled products;
- (x) procedures for internal audits;
- (xi) procedures for education/training;
- (xii) procedures for establishing, revising and retention of documents/records; and
- (xiii) other procedures necessary for conducting suitable and timely production/quality control activities.

#### (Premises/Equipment)

Article 37 Premises/equipment of a manufacturing site for products of quasi-pharmaceuticals must conform to the following requirements:

- (i) in accordance with the quasi-pharmaceutical product specification files and written procedures (hereinafter these documents are collectively referred to as “written procedures, etc.” in this Chapter), cleaning and maintenance are implemented in a manner suitable to their uses, sterilization is implemented as necessary, and records thereof are documented and retained;
- (ii) where any toxic gas is used depending upon products, etc., equipment necessary for the disposition thereof is provided;
- (iii) work rooms among operation areas are provided with necessary premises/equipment in order to prevent contamination by drifting particles or microorganisms according to type, dosage form and production processes of the products; provided, however, that this does not apply where the production equipment, etc. is provided with functions affording equivalent effectiveness;
- (iv) among operation areas, work rooms for operations of weighing starting materials or for operations of preparing, filling or sealing products are designed so that those work rooms are not used as passageways by any individual other than personnel working there; provided, however, that this does not apply where work rooms have no risk of potential product contamination due to individuals other than personnel working in such work rooms;
- (v) equipment is provided for supplying water (including wash water for equipment, instruments and containers) of sufficient quality and quantity for manufacture of products.

#### (Production Control)

Article 38 Manufacturers, etc. must have their production department, suitably in accordance with the written procedures, etc., conduct the following tasks regarding production control:



- (i) to document and retain written production directions;
- (ii) to perform production operations in accordance with the written production instructions;
- (iii) to document and retain production records for each batch;
- (iv) for each batch of the products, etc. and for each lot of the packaging/labeling materials, to ensure that those are suitable, and to document and retain records regarding results thereof;
- (v) for each batch of the products, etc. and for each lot of the packaging/labeling materials, to suitably store them, to manage their receipt/dispense, and to document and retain records thereof;
- (vi) to ensure cleanliness of the premises/equipment to be used for production, and to document and retain records regarding results thereof;
- (vii) to implement sanitation/hygiene control for personnel, and to document and retain records thereof;
- (viii) to implement regular maintenance of the premises/equipment to be used for production, and to document and retain records thereof; in addition, to suitably calibrate the measuring instruments for production control, and to document and retain records thereof;
- (ix) to verify whether suitable production control has been implemented, by checking records of production, storage, stock receipt/dispense and sanitation/hygiene control, and to report the verification outcomes in writing to the quality department; and
- (x) to conduct other tasks necessary for production control.

#### (Quality Control)

Article 39 (1) Manufacturers, etc. must have their quality department, systematically and suitably in accordance with the written procedures, etc., conduct the following tasks regarding quality control:

- (i) to take samples necessary for performing testing/analysis on each batch of the products, etc. and examination/testing on each lot of the packaging/labeling materials, and to document and retain records thereof;
- (ii) to perform testing/analysis on each batch of the products, etc. and examination/testing on each lot of the packaging/labeling materials (including those performed utilizing other quality control laboratories owned by the manufacturer, etc. or contract laboratories under its own responsibility, provided however, that this is limited to the case where such utilization would create no problem; the same applies hereinafter in this Chapter), of the collected samples, and to document and retain records thereof;
- (iii) with regard to finished products that consist of batches, to keep reference samples in amounts of at least twice the quantity necessary for the prescribed testing/analysis on each batch under suitable storage conditions for a period calculated by adding one year to the shelf-life of such finished product from the date of manufacture;
- (iv) to conduct regular maintenance of the equipment and instruments for quality control,

and to document and retain records thereof; in addition, to suitably calibrate the measuring instruments for quality control, and to document and retain records thereof;

(v) to evaluate results of the testing/analysis pursuant to the provisions of item (ii), and to report the evaluation outcomes in writing to the production department; and

(vi) to conduct other tasks necessary for quality control.

(2) In the case where it has been confirmed that the requirements for manufacturing control and quality control and the regulatory procedures to ensure conformity to such requirements in the exporting country are equivalent to those requirements and the regulatory procedures in Japan, manufacturers may omit the testing/analysis on their imported products (excluding appearance examination) specified upon the provisions of item (ii) in the preceding paragraph, by means of referring to records of the testing/analysis performed on such imported products by the foreign manufacturer in the exporting country. In this case, such manufacturers must have their quality department reasonably conduct the following tasks:

(i) to confirm regularly that such imported products are manufactured in accordance with suitable manufacturing procedures, etc., at the manufacturing site in the foreign manufacturer;

(ii) to confirm regularly that the manufacturing site of the foreign manufacturer is in conformity to the requirements for manufacturing control and quality control provided in the country where such manufacturing site locates;

(iii) to document and retain records of the confirmations pursuant to the provisions of the preceding two items; and

(iv) to confirm records of the testing/analysis performed on such imported products by the foreign manufacturer, and to document and retain records of such confirmation.

(3) Manufacturers, etc. must have their quality department, in accordance with the written procedures, etc., check the verification outcomes of production control which have been reported by the production department pursuant to the provisions of item (ix) in the preceding Article, for each batch.

#### (Control of Product Release from the Manufacturing Site)

Article 40 (1) Manufacturers, etc. must have their quality department, suitably in accordance with the written procedures, etc., conduct tasks of assessing the production control and quality control and of certifying their products to release from the manufacturing site or reject.

(2) Personnel in charge of the tasks as provided in the preceding paragraph must be personnel who have been qualified to conduct such tasks suitably and timely.

(3) Manufacturers, etc. must ensure that their personnel in charge of the tasks as provided in paragraph (1) do not have any difficulty with such tasks.

(4) Manufacturers, etc. must not release their products from the manufacturing sites before the release certification pursuant to the provisions of paragraph (1) is made suitably.

(Validation)

Article 41 (1) Manufacturers, etc. must have their appointed personnel, in accordance with the written procedures, etc., conduct the following tasks:

(i) to perform validation in the following cases:

(a) the case where commencing manufacture of a new quasi-pharmaceutical for the manufacturing site;

(b) the case where introducing any change to the manufacturing procedures, etc. that critically impact on the product quality; or

(c) other cases that it is deemed to be necessary to perform validation in order to implement production control and quality control suitably for the products; and

(ii) to report validation protocols and outcome of the validation in writing to the quality department.

(2) In the case where any rectification with regard to production control or quality control is needed based upon outcome of the validation pursuant to the provisions of item (i) in the preceding paragraph, such manufacturer, etc. must implement necessary measures, and document and retain records of such measures.

(Change Management)

Article 42 Upon introducing any change to manufacturing procedures, etc., such manufacturer, etc. must have its appointed personnel, in accordance with the written procedures, etc., conduct the following tasks:

(i) to assess impact on the product quality by the change, to have endorsement by the quality department for introducing the change, when it is identified that the change causes any actual or potential impact on the product quality upon outcome of such assessment, and to document and retain records thereof; and

(ii) to revise relevant documents, to educate and train the personnel, and to take other necessary actions, upon implementing a change with endorsement by the quality department pursuant to the provisions of the preceding item.

(Deviation Management)

Article 43 (1) In the case where any deviation has occurred, such manufacturer, etc. must have its appointed personnel, suitably in accordance with the written procedures, etc., conduct the following tasks:

(i) to record detail of the deviation; and

(ii) in the case where any significant deviation has occurred, to conduct the following tasks:

(a) to assess impact by the deviation on product quality, and to take necessary actions;

(b) to document and retain records of the assessment and measures pursuant to the provisions of (a), and to report such records in writing to the quality department; and

(c) to have outcome of the assessment and actions taken that have been reported pursuant to the provisions of (b) checked by the quality department.

(2) Manufacturers, etc. must have their quality department, suitably in accordance with the

written procedures, etc., document and retain records of the checking pursuant to the provisions of item (ii), (c) in the preceding paragraph, and report such records along with records pursuant to the provisions of (b) of the same item, in writing to the technical supervisor.

(Management of Quality Information and Quality Defects, etc.)

Article 44 (1) In the case where quality information of its products has been received, except where the matters of such quality information are obviously not attributable to its manufacturing sites, the manufacturer, etc. must have its appointed personnel, in accordance with the written procedures, etc., conduct the following tasks:

- (i) to investigate the cause of matters of such quality information, and in the case where any rectification with regard to production/quality control activities is needed, to implement necessary measures;
- (ii) to document and retain records describing detail of the quality information, the investigation outcome and the rectification, and to promptly report such records in writing to the quality department; and
- (iii) to have the report pursuant to the provisions of the preceding item checked by the quality department.

(2) In the case where any actual or possible quality defect has been identified upon the checking pursuant to the provisions of item (iii) in the preceding paragraph, the manufacturer, etc. must have its quality department, in accordance with the written procedures, etc., report such matters in writing to the technical supervisor.

(Management of Recalled Products)

Article 45 Upon storing any recalled products, such manufacturer, etc. must have its appointed personnel, in accordance with the written procedures, etc., conduct the following tasks:

- (i) after separate storage for a certain period, to suitably dispose of the recalled products; and
- (ii) to document and retain records of the storage and disposal, describing detail of the recalled products, and to report in writing to the quality department and the technical supervisor; provided, however, that this does not apply in the case where reason for the recall is obviously not attributable to its manufacturing sites.

(Internal Audits)

Article 46 (1) Manufacturers, etc. must have their appointed personnel, in accordance with the written procedures, etc., conduct the following tasks:

- (i) to conduct regular internal audits on production/quality control activities;
- (ii) to report the internal audit outcomes in writing to the technical supervisor; and
- (iii) to document and retain records of the internal audit outcomes.

(2) In the case where any rectification with regard to production/quality control activities is

needed based upon outcomes of the internal audits pursuant to the provisions of item (i) in the preceding paragraph, such manufacturer, etc. must implement necessary measures, and document and retain records of such measures.

(Education/Training)

Article 47 Manufacturers, etc. must have their appointed personnel, in accordance with the written procedures, etc., conduct the following tasks:

- (i) for personnel that are engaged in production/quality control activities, to systematically implement necessary education/training on production control and quality control;
- (ii) to report implementation of the education/training, in writing to the technical supervisor; and
- (iii) to document and retain implementation records of the education/training.

(Management of Documents/Records)

Article 48 Manufacturers, etc. must have their appointed personnel, in accordance with the written procedures, etc., conduct the following tasks with regard to documents/records pursuant to the provisions of this Chapter:

- (i) upon establishing or revising a document, to endorse, distribute, archive, etc. such document;
- (ii) upon establishing or revising written procedures, etc., to record dates of the establishment/revision on such written procedures, etc., and to retain records of the history of previous revisions; and
- (iii) to retain documents/records pursuant to the provisions of this Chapter for five years (provided, however, in the case where the period calculated by adding one year to the shelf-life of the product concerned with such documents/records is longer than five years, those documents/records other than records of education/training shall be retained for a period calculated by adding one year to such shelf-life), from the date of documentation (in the case of written procedures, etc., from the date of discontinuance thereof).

Section 2 Manufacturing Control and Quality Control for Active Ingredients to be used in Production of Quasi-Pharmaceuticals

(Quality Control)

Article 49 Manufacturers, etc. for active ingredients to be used in production of quasi-pharmaceuticals must have their quality department, in accordance with the written procedures, etc., keep reference samples of such products<sup>§</sup> in amounts of at least twice the quantity necessary for the prescribed testing/analysis on each batch, under suitable storage conditions for the period as provided in the following items from the date of manufacture:

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<sup>§</sup> Translation annotation; active ingredients to be used in production of quasi-pharmaceuticals

- (i) with regard to products for which a retest date has been established instead of its expiry date, for three years after the batch concerned is completely released from the manufacturing site; or
- (ii) with regard to products other than those provided in the preceding item, for a period calculated by adding one year to the shelf-life of such product.

(Retention of Documents/Records)

Article 50 Notwithstanding the provisions of Article 48, item (iii), manufacturers, etc. for products of active ingredients to be used in production of quasi-pharmaceuticals must retain the documents/records pursuant to the provisions of this Chapter, which are concerned with such products, for the period as provided in the following items from the date of documentation (in the case of written procedures, etc., from the date of discontinuance thereof); provided, however, that records of education/training are to be retained for five years from the date of documentation:

- (i) in the case of documents/records concerned with products that consist of batches, for which a retest date has been established instead of its expiry date, for three years after the batch concerned with such documents/records is completely released from the manufacturing site; or
- (ii) in the case of documents/records concerned with products other than those provided in the preceding item, for a period calculated by adding one year to the shelf-life of such active ingredient.

Section 3 Manufacturing Control and Quality Control for Sterile Quasi-Pharmaceuticals

(Premises/Equipment of Manufacturing Sites for Sterile Quasi-Pharmaceuticals)

Article 51 With regard to manufacturers licensed under the category provided in Article 25, paragraph (2), item (i) of the Enforcement Regulation, and foreign manufacturers accredited under the category provided in Article 35, paragraph (2), item (i) of the Enforcement Regulation, premises/equipment of manufacturing sites thereof must conform to the following requirements, in addition to those provided in Article 37:

- (i) among operation areas, work rooms and controlled operation areas are provided with premises/equipment for maintaining the environmental cleanliness level according to type, dosage form, and production process of the products of sterile quasi-pharmaceuticals;
- (ii) work rooms for drying or sterilizing operations of cleaned containers are dedicated to such operations; provided, however, that this does not apply where the cleaned containers have no risk of potential contamination;
- (iii) work rooms conform to the following requirements:
  - (a) work rooms are provided with equipment necessary for suitable drying and storage for the containers after cleaning;
  - (b) work rooms are provided with sterilization apparatus necessary for the manufacture,

- according to type of the products of sterile quasi-pharmaceuticals; and
- (c) areas for aseptic operations are provided with premises/equipment necessary for supplying clean air treated with filters and for suitable pressure differential control;
  - (iv) work rooms and controlled operation areas, which are for preparing or filling operations of quasi-pharmaceutical preparations, or for operations after preparing operations for the purpose of product sterilization (excluding labeling and packaging operations), conform to the following requirements:
    - (a) such work rooms and controlled operation areas are segregated from operation areas for non-sterile quasi-pharmaceuticals;
    - (b) work rooms for preparing operations and work rooms for filling or sealing operations are dedicated to such operations; and
    - (c) such work rooms and controlled operation areas have gowning rooms dedicated to the personnel who perform the operations specified in (b);
  - (v) equipment for supplying distilled water, etc. necessary for manufacture of products of sterile quasi-pharmaceuticals has a structure needed to prevent contamination of such distilled water, etc. with foreign substances or microorganisms.

#### (Production Control)

Article 52 Manufacturers, etc. for products of sterile quasi-pharmaceuticals must have their production department, suitably in accordance with the written procedures, etc., conduct the following tasks regarding production control in addition to the tasks as provided in Article 38:

- (i) to control work areas by defining control levels of the work environment, such as environmental cleanliness levels, suitably according to type, dosage form, characteristics and production processes of the products of sterile quasi-pharmaceuticals to be produced, the nature of operations performed in such work areas, and so on;
- (ii) to control the starting materials, packaging/labeling materials and products by defining necessary items to be controlled, such as levels of microorganisms, etc., suitably according to type, dosage form, characteristics, production processes of the products of sterile quasi-pharmaceuticals to be produced, and so on;
- (iii) to implement necessary measures during the production processes in order to prevent the starting materials, packaging/labeling materials and products from contamination, etc. by microorganisms, etc.;
- (iv) to control processes, etc. critical to ensure sterility of the products of sterile quasi-pharmaceuticals to be produced, by prescribing necessary control indices for the process control, suitably according to type, dosage form, characteristics, production processes, etc. of such products;
- (v) to control process water by prescribing necessary microbiological and physicochemical control indices, in a manner suitable to the use;
- (vi) to implement sanitation/hygiene control for personnel, by the following means:
  - (a) to restrict access of individuals other than personnel that are engaged in production

- operations to the operation areas, as far as possible; and
- (b) to restrict access of the personnel to the clean areas or aseptic areas where operations are currently being carried on, as far as possible; and
- (vii) to implement sanitation/hygiene control for the personnel in charge of operations in the clean areas or aseptic areas, by the following means:
  - (a) before personnel that are engaged in production operations enter the clean areas or aseptic areas, to have such personnel implement gowning, etc. in a suitable manner for the control levels of such areas; and
  - (b) when any personnel are in a health condition with concerns of contaminating the starting materials, packaging/labeling materials and/or products with microorganisms, etc., to have such personnel report the health condition.

#### (Education/Training)

Article 53 Manufacturers, etc. for products of sterile quasi-pharmaceuticals must have their appointed personnel, in accordance with the written procedures, etc., conduct the following tasks in addition to the tasks as provided in Article 47:

- (i) for personnel that are engaged in production or quality control, to implement education/training on sanitation/hygiene control and microbiology necessary for manufacture of the products of sterile quasi-pharmaceuticals, and other necessary education/training; and
- (ii) for personnel that are engaged in operations in the clean areas and aseptic areas, etc., to implement education/training on necessary measures in order to prevent contamination by microorganisms, etc.

#### Supplementary Provisions (Extract)

##### (Effective Date)

Article 1 This Ministerial Order comes into effect as of April 1, 2005.

Article 3 Regulation on Import and Marketing Control and Quality Control for Imported Pharmaceuticals and Quasi-Pharmaceuticals (Order of the Ministry of Health and Welfare No. 62 of 1999) ceases to be effective after March 31, 2005.

#### Supplementary Provisions (Order of the Ministry of Health, Labour and Welfare No. 87 of July 30, 2014) (Extract)

##### (Effective Date)

Article 1 This Ministerial Order comes into effect as of November 25, 2014, the date of enforcement of the Act Partially Amending the Pharmaceutical Affairs Act, etc. (hereinafter referred to as the “Amending Act”).



Supplementary Provisions (Order of the Ministry of Health, Labour and Welfare No. 90 of April 28, 2021) (Extract)

(Effective Date)

Article 1 This Ministerial Order comes into effect as of August 1, 2021.