

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

MHLW Ministerial Ordinance No. 169 in 2004

December 17, 2004

Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

CONTENTS

- Chapter 1 General Provisions (Article 1 to Article 3)
- Chapter 2 Basic Requirements Regarding Manufacturing Control and Quality Control of Medical Devices, etc.
- Section 1 General Requirements (Article 4)
- Section 2 Quality Management System (Article 5 to Article 9)
- Section 3 Management responsibility (Article 10 to Article 20)
- Section 4 Resource Management (Article 21 to Article 25)
- Section 5 Product Realization (Article 26 to Article 53)
- Section 6 Measurement, Analysis and Improvement (Article 54 to Article 64)
- Chapter 3 Additional Requirements Regarding Manufacturing Control and Quality Control of Medical Devices, etc. (Article 65 to Article 72-3)
- Chapter 4 Manufacturing Control and Quality Control of Biological Medical Devices, etc. (Article 73 to Article 79)
- Chapter 5 Manufacturing Control and Quality Control of Radioactive *In Vitro* Diagnostic Reagents (Article 80 and Article 81)
- Chapter 6 Application *mutatis mutandis*, etc. to Manufacturers, etc. of Medical Devices, etc. (Article 82 to Article 84)

Chapter 1 General Provisions

(Purpose)

Article 1 This Ministerial Ordinance shall provide the standards specified by MHLW

Ministerial Ordinance pursuant to the provisions of Article 23-2-5, Paragraph 2, Item 4

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

(including cases where it shall apply *mutatis mutandis* under Article 23-2-17, Paragraph 5; the same hereinafter, and Article 80, Paragraph 2) of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Law No. 145, 1960) (hereinafter referred to as the "PMD Act").

(Definitions)

Article 2 The term "marketing approval holder, etc." used in this Ministerial Ordinance means marketing approval holders of medical devices or *in vitro* diagnostic reagents (hereinafter referred to as "medical devices, etc.") [excluding the appointed marketing approval holders for foreign manufacturers of medical devices, etc. specified under Article 23-2-17, Paragraph 4 of the PMD Act (hereinafter referred to as the "appointed marketing approval holder for foreign manufacturers of medical devices, etc.") and appointed marketing approval holders for foreign manufacturers of specially controlled medical devices, etc. pursuant to the provisions of Article 23-3, Paragraph 1 of the PMD Act (hereinafter referred to as the "appointed marketing approval holders for foreign manufacturers of specially controlled medical devices, etc.")], restrictive approval holders of foreign manufactured medical devices, etc. specified under Article 23-2-17, Paragraph 4 of the PMD Act (hereinafter referred to as the "restrictive approval holders of foreign manufactured medical devices, etc.") or foreign manufacturers of designated specially controlled medical devices specified under Article 23-2-23, Paragraph 1 of the PMD Act (hereinafter referred to as "foreign manufacturers of designated specially controlled medical devices").

2. The term "product" used in this Ministerial Ordinance means the object [including objects which have undergone the intermediate process and need to undergo the subsequent process to obtain the final products (hereinafter referred to as "intermediate products")] which is composed of constituent parts, etc. and has undergone the manufacturing process in the manufacturing site.
3. The term "constituent parts, etc." used in this Ministerial Ordinance means parts, assemblies (limited to those which are used in the products), raw materials, materials, containers, wrappers, labelings (including package inserts; the same hereinafter), etc. used in the manufacturing process which constitute parts of the products, as well as the

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

- software of the products (excluding the medical device programs specified under Article 2, Paragraph 13 of the PMD Act).
4. The term "process agent" used in this Ministerial Ordinance means the object used for the intermediate products in the manufacturing process (excluding those constituting parts of the products).
 5. The term "lot" used in this Ministerial Ordinance means a grouping of the products, process agents and constituent parts, etc. (hereinafter collectively referred to as "products, etc.") which are manufactured so as to have a uniform quality in a series of the manufacturing process for a certain manufacturing period.
 6. The term "sterile product" used in this Ministerial Ordinance means the medical device, etc. sterilized in the manufacturing process.
 7. The term "facility" used in this Ministerial Ordinance means facilities (including manufacturing sites) related to product realization included in the quality management system.
 8. The term "validation" used in this Ministerial Ordinance means to verify and document that the buildings and facilities of the institution, procedures, processes and other methods of manufacturing control and quality control (hereinafter referred to as "manufacturing procedures, etc. ") provide the anticipated results.
 9. The term "clean areas" used in this Ministerial Ordinance means the place, among the areas where the manufacturing operations are performed (hereinafter referred to as "work areas"), where the weighing operations of constituent parts, etc. and the formulating operations are performed, and the cleaned containers are exposed to the air in the work area.
 10. The term "aseptic areas" used in this Ministerial Ordinance means the place, among the work areas, where the aseptic products or constituent parts, etc. or sterilized containers are exposed to the air in the work areas, where the sealing operations of containers are performed, and the place where the aseptic operations such as sterility tests are performed in the work areas.
 11. The term "cell/tissue-based medical device" used in this Ministerial Ordinance means the medical device composed of human or animal cells or tissue.
 12. The term "donor" used in this ministerial Ordinance means the person who donates the cells or tissue to serve as the materials for the cell/tissue-based medical devices

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

[excluding those with the body of a brain-dead person specified under Article 6, Paragraph 2 of the Act on Organ Transplantation (Law No. 104, 1997)].

13. The term "donor animal" used in this Ministerial Ordinance means the animal which provides the cells or tissue to serve as the materials for cell/tissue-based medical devices.
14. The term "input" used in this Ministerial Ordinance means the information, etc. necessary for manufacturing control and quality control when performing a certain processes.
15. The term "output" used in this Ministerial Ordinance means the information, etc. obtained as the results of a certain process performed.
16. The term "top management" used in this Ministerial Ordinance means the executives, etc. who manages duties related to the quality management system of the marketing approval holder, etc. in the top position. Proviso: in Chapter 2 to Chapter 5 inclusive which shall read and apply *mutatis mutandis* in Article 82 and Article 83, the term "top management" means the executives, etc. who manage duties related to the quality management system of the manufacturer in the top position.
17. The term "customer" used in this Ministerial Ordinance means all the persons who handle the products after release of the products to market. Proviso: in Chapter 2 to Chapter 5 inclusive which shall read and apply *mutatis mutandis* in Article 82 and Article 83, the term "customer" means all the persons who handle the products after release of the products from the manufacturer.
18. The term "quality policy" used in this Ministerial Ordinance means the basic policy provided and expressed by the top management in order to ensure the quality of the products.
19. The term "quality management system" used in this Ministerial Ordinance means the management system in which the marketing approval holder, etc. implements to ensure the quality. Proviso: in Chapter 2 to Chapter 5 inclusive which shall read and apply *mutatis mutandis* in Article 82, the term "quality management system" means the management system in which the manufacturer manages the manufacturing site in order to ensure the quality and in Chapter 2 to Chapter 5 inclusive which shall read and apply *mutatis mutandis* in Article 83, the term "quality management system" means the management system in which the manufacturer performs management in order to

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

ensure the quality of the products.

20. The term "review" used in this Ministerial Ordinance means to determine the validity and effectiveness to achieve the established objectives.
21. The term "resources" used in this Ministerial Ordinance means the personal knowledge and skills and technology, facilities and other resources which are used for the operations of the facility.
22. The term "infrastructure" used in this Ministerial Ordinance means the system of the facilities, equipment and services which are necessary for the operations of the facility.
23. The term "product realization" used in this Ministerial Ordinance means a series of the operations performed in the stages from development to release of the products and supply of the related servicing.
24. The term "traceability" used in this Ministerial Ordinance means the ability to trace the history, application or location.
25. The term "advisory notice" used in this Ministerial Ordinance means the document issued after the delivery of the products in order to supplement the information provided when delivering the products or to advise what actions should be taken in the use, modification, return or destruction of the products.
26. The term "concession" used in this Ministerial Ordinance means the approval to use or operate the products which do not conform to the product requirements, the approval of proceeding to the next process or the decision of release after appropriately verifying that there is no problem in manufacturing control and quality control of the products and that the products comply with the laws and ordinances related to the pharmaceutical affairs or the orders or actions taken based on the laws and ordinances (hereinafter referred to as the "regulatory requirements, etc.")

(Scope of Application)

- Article 3 The marketing approval holder, etc. shall, pursuant to the provisions of Chapter 2 and Chapter 3, perform the manufacturing control and quality control of the products.
2. The marketing approval holder, etc. shall perform the manufacturing control and quality control of the products with the medical devices which correspond to the biological products (hereinafter referred to as "biological medical devices"), the medical devices designated by the Minister of Health, Labour and Welfare (hereinafter referred to "the

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

Minister") pursuant to the provisions of Article 43, Paragraph 2 of PMD Act and the cell/tissue-based medical devices (hereinafter collectively referred to as "biological medical devices, etc.") pursuant to the provisions of Chapter 4, supplementary to the provisions of Chapter 2 and Chapter 3.

3. The marketing approval holder, etc. shall perform the manufacturing control and quality control of the products with the *in vitro* diagnostic reagents corresponding to radiopharmaceuticals (hereinafter collectively referred to as "radioactive *in vitro* diagnostic reagents") [the term "radiopharmaceuticals" means the radiopharmaceuticals specified under Article 1, Item 1 of the Regulations for Manufacturing Control and Handling of Radiopharmaceuticals (MHW Ministerial Ordinance No. 4, 1961)] pursuant to the provisions of Chapter 5, supplementary to the provisions of Chapter 2 and Chapter 3.

Chapter 2 Basic Requirements Regarding Manufacturing Control and Quality Control of Medical Devices, etc.

Chapter 2 of this Ministerial Ordinance is identical to Clauses 4 to 8 of ISO 13485:2003.

Chapter 3 Additional Requirements Regarding Manufacturing Control and Quality Control of Medical Devices, etc.

(Quality Management System of Registered Manufacturing Site)

Article 65 In case that the business facility to which the processes specified under Article 5, Paragraph 4 are outsourced or the business facility of the supplier of the purchased products is the registered manufacturing site pursuant to the provisions of Article 23-2-3, Paragraph 1 or Article 23-2-4, Paragraph 1 of the PMD Act (hereinafter referred to as the "registered manufacturing site"), the marketing approval holder, etc. shall perform necessary verification about that the manufacturer or the foreign manufacturer of medical devices, etc. specified in the same paragraph (hereinafter referred to as the "manufacturer, etc. related to the registered manufacturing site") related to the registered manufacturing site performs the manufacturing control and quality control based on the appropriate quality management system.

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

(Additional Requirements Regarding Quality Management System)

Article 66 The marketing approval holder, etc. shall establish, document, implement the quality management system pursuant to the provisions of Chapter 3 to Chapter 5 inclusive (limited to the provisions that shall apply pursuant to the provisions of Article 3, hereinafter the same in this article) as well as the provisions of Chapter 2 and also shall maintain its effectiveness.

2. The marketing approval holder, etc. shall manage processes pursuant to the provisions of Chapter 3 to Chapter 5 inclusive, as well as the provisions of Chapter 2.
3. The marketing approval holder, etc. shall describe the procedures and records specified in Chapter 3 to Chapter 5 inclusive, as well as the matters specified in Article 6, Paragraph 1, in the documents related to the quality management system specified under the same paragraph.

(Retention Period of Quality Management System Documents)

Article 67 The period during which the marketing approval holder, etc. retain the quality management system documents or their copies pursuant to the provisions of Article 8, Paragraph 4 shall be the following periods (5 years for the documents for training) from the date of abolition of the quality management system documents.
Proviso: This provision shall not apply to the quality management documents used for the manufacturing or testing of the products when they are maintained to be available for the period specified in the next article.

- (1) 15 years for the products with the specially designated maintenance control required medical devices [one year plus the shelf life for the products of which the shelf life or the expiry date (hereinafter simply referred to as the "shelf life") plus one year exceeds 15 years]
- (2) 5 years for the products with the medical devices, etc. other than the specially designated maintenance control required medical devices (one year plus the shelf life for the products of which the shelf life plus one year exceeds 5 years).

(Retention Period of Records)

Article 68 The marketing approval holder, etc. shall retain the records specified

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

under Article 9, Paragraph 1 or in this chapter for the following periods (5 years for the records of the training) from the preparation date.

- (1) 15 years for the products with the specially designated maintenance control required medical devices (one year plus the shelf life for the products of which the shelf life plus one year exceeds 15 years)
- (2) 5 years for the products with the medical devices, etc. other than the specially designated maintenance control required medical devices (one year plus the shelf life for the products of which the shelf life plus one year exceeds 5 years).

(Reporting Adverse Events, etc.)

Article 69 The marketing approval holder, etc. shall make all the facilities and relevant registered manufacturing sites establish and document the procedure to notify the marketing approval holder, etc. of the matters specified in the items of Article 228-20, Paragraph 2 of the Enforcement Regulations concerning the products when the facilities and relevant registered manufacturing sites recognize the matters concerned.

(Relationship with Good Vigilance Practice (GVP))

Article 70 The marketing approval holder, etc. shall perform the duties related to post-marketing safety control of the products pursuant to the provision of the Ordinance on the Standards for Post-Marketing Safety Control of Drug, Quasi-Drug, Cosmetics and Medical Devices and Regenerative and Cellular Therapy Products, Gene Therapy Products etc. [MHLW Ministerial Ordinance No. 135, 2004 (hereinafter referred to as the "Good Vigilance Practice (GVP)"), supplementary to the provisions of this Ministerial Ordinance.

(Duties of General Marketing Supervisor of Medical Devices, etc.)

Article 71 The marketing approval holder shall have the general marketing supervisor of medical devices, etc. specified under Article 23-2-14, Paragraph 2 of the PMD Act (hereinafter referred to as the "general marketing supervisor of medical devices, etc.") perform the following duties.

- (1) To supervise the duties of the manufacturing control and quality control such as decision of release of the products and to bear a responsibility for the duties.

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

- (2) When it is deemed necessary to fairly and properly perform the duties, to give a necessary opinion in writing to the marketing approval holder, the top management and other persons responsible for the duties concerned and to retain its copy for 5 years.
 - (3) To supervise the domestic quality assurance manager specified under Paragraph 1 of the next article (excluding cases where the General Marketing Supervisor of medical devices, etc. also serves as the domestic quality assurance manager pursuant to the provision of the next paragraph).
 - (4) To respect the opinions of the management representative and the domestic quality assurance manager specified under Paragraph 1 of the next article (excluding the management representative in the limited type 3 marketing approval holder of medical devices).
 - (5) To have the units related to the manufacturing control or quality control and the Safety Control General Division specified under Article 4, Paragraph 1 of the Good Vigilance Practice (GVP) (hereinafter referred to as the "Safety Control General Division" in Article 72, Paragraph 2, Item 9) closely collaborate with each other.
2. The General Marketing Supervisor of medical devices, etc. may also serve as the top management, the management representative or the domestic quality assurance manager specified under Paragraph 1 of the next article.

(Domestic Quality Assurance Manager)

Article 72 The marketing approval holder shall provide the facilities located in Japan with the domestic quality assurance manager who satisfies the following requirements as a responsible person for the duties of controlling quality of the domestic products performed pursuant to the provision of this Ministerial Ordinance (hereinafter referred to as the "quality control duties").

- (1) To be a responsible person of the Quality Assurance Division in the marketing approval holder
- (2) To be the person who was engaged in the quality control duties or equivalent duties for 3 years or longer
- (3) To be the person who has competence for proper and smooth conduct of the quality control duties in Japan

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

- (4) To be the person who does not belong to the units related to sales of medical devices, etc. and other than above, to be the person who is not suspected to bring about obstacles to proper and smooth conduct of the quality control duties in Japan
2. The marketing approval holder shall have the domestic quality assurance manager perform the following duties based on the procedures, etc. prepared pursuant to the provision of this Ministerial Ordinance.
- (1) To supervise the quality control duties in Japan
 - (2) To verify that the quality control duties in Japan are properly and smoothly performed
 - (3) For the products that are distributed in Japan, to decide release to market by lot (by manufacturing number or manufacturing code for medical devices, etc. which do not constitute a lot) and to prepare records of the decision result and release to market such as destination (when having the person appointed beforehand decide release to market pursuant to the provision of the next paragraph, to appropriately comprehend condition of deciding release of the products to market).
 - (4) For the products that are distributed in Japan, when the change in manufacturing method or testing method, etc. that may affect quality of the products is made, to collect information on the change from domestic and abroad and to comprehend the information. When the change concerned might seriously affect the quality of the products, to rapidly report in writing to the management representative (for the domestic quality assurance manager of the limited type 3 marketing approval holder of medical devices, the top management, hereinafter the same in Item 5 to Item 7 inclusive) and the general marketing supervisor of medical devices, etc. and to make necessary and appropriate measures be taken.
 - (5) For the products that are distributed in Japan, to collect information on quality, etc. of the products (including information on inferior quality or potential inferior quality) from domestic and abroad. When the information concerned is obtained, to rapidly report in writing to the management representative and the general marketing supervisor of medical devices, etc., to record and to make necessary and appropriate measures be taken.
 - (6) When the products distributed in Japan are recalled, to perform the following duties.

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

- A. The medical devices, etc. recalled shall be segregated, stored for a certain period and properly handled.
 - B. The record describing content of recall shall be prepared and to report to the management representative and the general marketing supervisor of medical devices, etc. in writing.
- (7) Other than those specified in Item 4 to Item 6, to report to the management representative and the general marketing supervisor of medical devices, etc. in writing when it is deemed necessary for performing the quality control duties in Japan.
- (8) When performing the quality control duties in Japan, to give a written notice or instruction to the manufacturer related to the relevant registered manufacturing site or foreign manufacturers of medical devices, etc., retailers, proprietors of a pharmacy, proprietors of a hospital or a clinic and other involved parties.
- (9) When recognizing the information on the safety assurance measures specified under Article 2, Paragraph 2 of the Good Vigilance Practice (GVP), to supply the Safety Control General Division with the information in writing without delay.
3. Release to market specified in Item 3 of the preceding paragraph may be decided by the person who is appointed beforehand by the domestic quality assurance manager [limited to the personnel of the Quality Assurance Division or the Personnel of the registered manufacturing site (limited to the sites which performs release of the products to market) who has competence for proper and smooth conduct of the duties concerned].
4. The person who decided release to market pursuant to the provisions of the preceding paragraph shall prepare records of the result and release to market such as destination and shall report in writing to the domestic quality assurance manager.
5. The domestic quality assurance manager may also serve as the management representative.

(Other Items to be Complied)

Article 72-2 The marketing approval holder shall consolidate necessary systems also based on relationship with the duties performed pursuant to the provisions of Article 55 so that collection of information pursuant to the provisions of Article 72, Paragraph 2, Item 4 and Item 5 is not interfered and also shall make and document the agreement on

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

necessary and sufficient matters between relevant facilities and the registered manufacturing site, respectively.

2. The marketing approval holder shall establish and document the procedures for the following matters.
 - (1) Response to notices from repairers of medical devices
 - (2) Ensuring quality in retailers or leasers of medical devices
 - (3) Response to notices from retailers or leasers of used medical devices

(Duties of Appointed Marketing approval Holders for Foreign Manufacturers of Medical Devices, etc.)

Article 72-3 The restrictive approval holders of foreign manufactured medical devices, etc. shall have the appointed marketing approval holders for foreign manufacturers of medical devices, etc. perform the following duties among the duties performed pursuant to the provision of this Ministerial Ordinance.

- (1) Of the duties performed pursuant to the provisions of Article 17, those related to domestic duties
- (2) Of the duties performed pursuant to the provisions of Article 29, those related to domestic duties
- (3) Of the duties performed pursuant to the provisions of Article 43, those related to domestic duties
- (4) Of the duties performed pursuant to the provisions of Article 48 and Article 49, those related to domestic duties
- (5) Of the duties performed pursuant to the provisions of Article 55, those related to domestic duties
- (6) Of the duties performed pursuant to the provisions of Article 60, those related to domestic duties
- (7) Recall handling related to domestic products
- (8) Duties related to post-marketing safety control of domestic products
- (9) Duties to make necessary cooperation with the restrictive approval holders of foreign manufactured medical devices, etc. for making necessary reports to and transfer of information and appropriately performing other duties concerned with the top management and the management representative of the restrictive approval

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

holders of foreign manufactured medical devices, etc. and other relevant persons concerning the duties performed as the appointed marketing approval holders for foreign manufacturers of medical devices, etc.

- (10) Control of documents and records related to the duties performed as the appointed marketing approval holders for foreign manufacturers of medical devices, etc.
2. For the foreign manufacturers of designated specially controlled medical devices, the provisions of the preceding paragraph shall apply *mutatis mutandis*. In such cases, the "appointed marketing approval holders for foreign manufacturers of medical devices, etc." shall read the "appointed marketing approval holders for foreign manufacturers of specially controlled medical devices, etc."
3. For the appointed marketing approval holders for foreign manufacturers of medical devices, etc. or the appointed marketing approval holders for foreign manufacturers of specially controlled medical devices, etc., the provisions from Article 70 to the preceding article (excluding Article 72, Paragraph 5) shall apply *mutatis mutandis*. In such cases, "other" in Article 71, Paragraph 1, Item 1 shall read "performed as other appointed marketing approval holders for foreign manufacturers of medical devices, etc. or the appointed marketing approval holders for foreign manufacturers of specially controlled medical devices, etc.", "the marketing approval holder, the top management" in Item 2 of the same paragraph shall read "the appointed marketing approval holders for foreign manufacturers of medical devices, etc. or the appointed marketing approval holders for foreign manufacturers of specially controlled medical devices, etc.", "the management representative and Paragraph 1 of the next article" in Item 4 of the same paragraph shall read "Paragraph 1 of the next article", "opinion of....(excluding the management representative in the limited type 3 marketing approval holder of medical devices)" shall read "opinion of", "the top management or the management representative or Paragraph 1 of the next article" in Paragraph 2 of the same article shall read "Paragraph 1 of the next article", "pursuant to" in Article 72, Paragraph 1 shall read "as the appointed marketing approval holders for foreign manufacturers of medical devices, etc. or the appointed marketing approval holders for foreign manufacturers of specially controlled medical devices, etc. pursuant to", "the management representative (for the domestic quality assurance manager of the limited type 3 marketing approval

holder of medical devices, the top management, hereinafter the same from the next article to Item 7) and the general marketing supervisor of medical devices, etc." in Article 72, Paragraph 2, Item 4 shall read "the general marketing supervisor of medical devices, etc." and "the management representative and the general marketing supervisor of medical devices, etc." in Item 5, 6-B and 7 of the same paragraph shall read the "general marketing supervisor of medical devices, etc. "

Chapter 4 Manufacturing Control and Quality Control of Biological Medical Devices, etc.

(Infrastructure of Manufacturing Sites of Marketing Approval Holder, etc. of Specified Biological Medical Devices, etc.)

Article 73 The marketing approval holder, etc. of the products with the medical devices corresponding to the specified biological products (hereinafter referred to as "specified biological medical devices"), the medical devices designated by the Minister pursuant to the provisions of Article 43, Paragraph 2 of PMD Act, or the cell/tissue-based medical devices (hereinafter collectively referred to as "specified biological medical devices, etc.") (hereinafter collectively referred to as "marketing approval holder, etc. of specified biological medical devices, etc.") shall conform to the following requirements as infrastructure of the manufacturing sites which manufacture the products (excluding the manufacturing sites which only perform packaging, labeling, storage or design among the manufacturing processes, hereinafter the same in this chapter).

- (1) The facilities for supplying the distilled water, etc. required to manufacture the products shall be provided with adequate structure for preventing contamination of the distilled water, etc. with foreign substances or microorganisms.
- (2) The work areas shall conform to the following requirements.
 - A. The work rooms or working controlled areas, among the work areas, shall be provided with the structures and facilities for maintaining appropriate temperature, humidity and the degree of cleanliness according to the manufacturing process.
 - B. The work rooms for the weighing operations of materials or the cleaning operations of containers shall be provided with the sealed structure for dust prevention.

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

- C. The work rooms for the drying operations or sterilizing operations of the cleaned containers shall be exclusively used for such operations. Proviso: This provision shall not apply when the cleaned containers are not suspected to be contaminated.
- D. The clean areas (the term "clean areas" means, among the work areas, the place where the weighing operations of constituent parts, etc. and formulating operations are performed and the place where the cleaned containers are exposed to the air in the work areas, hereinafter the same in this item) and the aseptic areas (the term "aseptic areas" means, among the work areas, the place where the aseptic products, intermediate products or constituent parts, etc. or sterilized containers are exposed to the air in the work areas, the place where the sealing operations of containers are performed and the place where the aseptic operations such as sterility tests are performed, hereinafter the same in this item) shall conform to the following requirements.
- (i) The surfaces of the ceilings, walls, and floors shall be smooth without trace of crack and shall not generate grit and dust.
 - (ii) The drain systems shall be provided with adequate structure to prevent the contamination by harmful discharged water.
- E. No drainage conduit shall be provided in the clean areas. Proviso: This provision shall not apply when the following requirements are satisfied and it is deemed to be unavoidable.
- (i) The drainage outlet shall have the trap easily cleaned and a device to prevent the backflow of discharged water.
 - (ii) The trap shall be provided with the structure that can be disinfected.
 - (iii) A ditch of the floor shall be shallow, be easily cleaned and be connected to outside the manufacturing areas via the drainage conduit (the term "manufacturing areas" means the places where the incubation, extraction and purification operations, the weighing operations of constituent parts, etc. and the formulating operations, the cleaning and drying operations of containers and the sealing and packaging operations of containers are performed and the place where gowning is implemented).
- F. The aseptic areas shall conform to the following requirements.
- (i) No drainage conduit shall be installed.

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

- (ii) No sink shall be installed.
- G. The areas where testing using animals or microorganisms is performed and the areas where animal tissue or microorganisms not necessary for manufacturing of the products with specified biological medical devices, etc. are handled shall be distinctly segregated from other areas for manufacturing the products and the air-handling system shall be a separate line.
- H. The areas where the aseptic operations are performed shall be provided with the clean air filtered and the structures and facilities for performing appropriate differential pressure control.
- I. The areas where pathogenic microorganisms, etc. are handled shall be provided with the adequate structures and facilities for performing appropriate negative pressure control.
- J. The areas where infectious microorganisms, etc. are handled shall be provided with the facilities for cleaning, disinfection and sterilization of the equipment used in the areas concerned and the facilities for disposal of wastewater, etc.
- K. The following facilities (excluding those which are deemed not to be necessary for the manufacturing of the products according to the type, manufacturing procedure, etc. of the products) shall be provided in the rooms distinctly segregated from other rooms.
 - (i) Facilities for storing the microorganisms
 - (ii) Facilities for controlling the animals for use in the manufacturing or testing after inoculation with the microorganisms
 - (iii) Facilities for treating the animals for use in the manufacturing or testing
 - (iv) Facilities for inoculating the microorganisms into the culture media, etc.
 - (v) Facilities for cultivating the microorganisms
 - (vi) Facilities for collecting, inactivating, sterilizing, etc. the cultured microorganisms
 - (vii) Facilities for disinfecting the equipment and instruments, etc. used in the manufacturing and testing
- L. The surfaces of the ceilings, walls, and floors of the rooms provided with the facilities specified in K-(ii) to (iv) and (vi) shall be the structure which can be easily cleaned and disinfected.

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

- M. The rooms provided with the facilities specified in K-(iv) and (vi) and the rooms provided with the facilities for performing sterility tests among the facilities necessary for testing the products, process agents and materials shall conform to the following requirements.
- (i) The work room shall be aseptic. Proviso: This provision shall not apply when such work rooms are provided with the facilities which have functions to perform aseptic operations without hindrance according to the type, manufacturing procedure, etc. of the products.
 - (ii) The aseptic rooms specified in (i) shall be provided with adjoining anterooms exclusively used for the rooms so that the rooms are normally accessible only through the anterooms and the entrances of the anterooms do not lead directly to the exterior.
- N. Other than the facilities specified in K above, the following facilities shall be provided.
- (i) Facilities necessary for breeding control of the animals for use in the manufacturing or testing
 - (ii) Facilities for preparing the culture media and other dilute solutions
 - (iii) Facilities necessary for cleaning, drying, sterilization and storage of the equipment and instruments, and containers, etc. for use in the manufacturing or testing
 - (iv) Facilities for sealing of containers
 - (v) Facilities for appropriate disposing of animal carcasses, other waste and purifying polluted water
- O. The storage facilities shall be equipped with constant-temperature unit, self-recording thermometer and other necessary measuring gauges.
- P. The air-handling system shall conform to the following requirements.
- (i) The system shall be the adequate structure to prevent contamination of the products and materials with microorganisms, etc.
 - (ii) In case that pathogenic microorganisms, etc. are handled, the system shall be the adequate structure to prevent air diffusion of the microorganisms, etc. concerned.
 - (iii) The system shall be the structure that the air emitted from the areas where

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

pathogenic microorganisms, etc. are handled is emitted after elimination of the microorganisms, etc. concerned by high-performance air filter.

- (iv) The system shall be the structure that the air emitted from the work rooms where pathogenic microorganisms, etc. could leak out is not recirculated.
Proviso: This provision shall not apply when the microorganisms, etc. concerned are sufficiently eliminated by the structure specified in the Item (iii) above and recirculation is deemed to be unavoidable.
- (v) A separate line shall be used for each work room as needed.

Q. Pipe fittings, valves and vent filters shall be the structure that is easily cleaned or sterilized depending on the intended use.

R. The following facilities and equipment for testing shall be provided. Proviso: This provision shall not apply when the testing is implemented on its own responsibility utilizing other testing institution of the marketing approval holder, etc. of specified biological medical devices, etc. concerned and it is deemed not to pose problem.

- (i) When sealed state test needs to be implemented, facilities and equipment for sealed state test
- (ii) Facilities and equipment for foreign substances test
- (iii) Facilities and equipment for physical and chemical science examinations of products, process agents and materials
- (iv) Facilities and equipment for sterility tests
- (v) When pyrogen test needs to be implemented, facilities and equipment for pyrogen test
- (vi) When biological test needs to be implemented, facilities and equipment for biological test

(3) The work areas for the products with the cell/tissue-based medical devices shall conform to the following requirements.

A. The areas for receiving and processing the materials and for storing the products, etc. shall be segregated from other areas for manufacturing the products with cell/tissue-based medical devices.

B. The areas for receiving and processing the materials and for storing the products, etc. shall be provided with adequate buildings and facilities for performing the

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

operations.

- (4) The areas for manufacturing the products using human blood or plasma as the materials shall be distinctly segregated from other areas, and shall be provided with the facilities and equipment exclusive used for the manufacturing. Proviso: This provision shall not apply to the manufacturing process subsequent to the process of inactivating or removing viruses.
- (5) The facilities for controlling the animals for use in the manufacturing or testing (including donor animals, hereinafter referred to as the "utilized animals") shall conform to the following requirements.
 - A. The areas for testing the utilized animals shall be segregated from other areas.
 - B. The facilities for storing feeding stuffs without danger of pest infestation shall be provided.
 - C. The facilities shall be provided with the breeding room of the animals for use in the manufacturing and the breeding room of the animals for use in the testing respectively.
 - D. A different line of the air-handling system shall be used in the breeding room from other areas. Proviso: This provision shall not apply to the animals that are regarded to be appropriate to be bred in the field.
 - E. When antigen, etc. is inoculated to the utilized animals, the inoculation room isolated from the necropsy room of the animals shall be provided.

(Documents Related to Manufacturing Control and Quality Control)

Article 74 The marketing approval holder, etc. of the products with biological medical devices, etc. (hereinafter referred to as the "marketing approval holder, etc. of biological medical devices, etc.") shall, when handling the products with the biological medical devices, etc., describe the following matters as well as those specified under Article 6, Paragraph 2 and Paragraph 3, in the *Seihin Hyojun Sho* (Device Master File).

- (1) Name, essence, property, ingredients, quantities therein, and other specifications of the objects obtained from human, animals, plants or microorganisms using as the constituent parts.
- (2) Specifications (including breeding control methods) of the utilized animals

(3) Other necessary items.

(Process Control)

Article 75 The marketing approval holder, etc. of biological medical devices, etc. shall, when handling the products with the biological medical devices, etc., control properly the following duties of the process control of the products with the biological medical devices, etc. in accordance with the *Seihin Hyojun Sho* (Device Master File) in addition to the duties specified in the preceding article and also shall establish and document the procedures for the duties.

- (1) To have the person appointed beforehand perform the following duties according to the details of the duties
 - A. To take necessary actions, when the materials or products are inactivated or when the microorganisms, etc. contained in the materials or products are inactivated or eliminated in the manufacturing process, to prevent contamination with the materials or products which have not undergone inactivation or elimination
 - B. To perform the continuous measurement of the items necessary for controlling the manufacturing process such as temperature, hydrogen ion index, etc., when biochemical technology such as fermentation, etc. is applied to the manufacturing process.
 - C. To take necessary actions, as well as measure endotoxins where necessary, when the column chromatography equipment, etc. is used in the manufacturing process, to prevent contamination of the equipment with microorganisms, etc.
 - D. To take necessary actions, when the culture media are continuously supplied to and the cultured broth is continuously discharged from the tanks in the manufacturing process, to maintain the incubation conditions in the incubation tanks during the incubation.
 - E. To perform the validation in the following cases, and to prepare and retain the records thereof.
 - (i) The case where manufacturing of the products with biological medical devices, etc. is newly started in the manufacturing site
 - (ii) The case where changes are made in the manufacturing procedures etc, which might seriously affect the quality of the products with biological

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

- medical devices, etc.
- (iii) Other cases where it is deemed to be necessary to perform the validation for the proper conduct of the manufacturing control and quality control of the products with the biological medical devices, etc.
- F. To restrict as much as possible the personnel other than those engaged in the manufacturing from entering the work areas
- G. To perform the hygiene control of the personnel in accordance with the following requirements
- (i) Restricting as much as possible the personnel from entering the clean areas or aseptic areas during the operations
 - (ii) Not allowing the Personnel engaged in the manufacturing operations to perform the duties to control the utilized animals (excluding those actually used in the manufacturing process)
- H. To perform the hygiene control of the personnel engaged in the manufacturing operations in the clean areas or aseptic areas in accordance with the following requirements
- (i) Having the personnel engaged in the manufacturing operations wear clothes, work shoes, caps and masks, which have been disinfected
 - (ii) Having the personnel regularly undergo medical checkups so as to confirm that they do not suffer from the diseases suspected to contaminate with microorganisms, etc., the materials or products
 - (iii) Having the personnel declare of any health conditions suspected to contaminate the products or materials with microorganisms (including cases where they suffer from a skin or hair infectious disease or a cold, injured, or show such symptoms as diarrhea or fever of unknown cases; the same hereinafter)
- I. Constantly breeding the utilized animals (limited to those used in the manufacturing; the same hereinafter in this items) under proper control, and physically examining the animals when used so as not to use those suffering from infectious diseases and those unsuitable for use
- J. Disposing of all the objects contaminated with microorganisms (limited to those contaminated in the manufacturing process) and animal carcasses so as not to

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

cause hazards to the public health and hygiene

- K. Preparing and retaining records of the following items with respect to handling of the strains of the microorganisms for use in the manufacturing
 - (i) Name of the microorganisms and number assigned to each of the containers thereof
 - (ii) Date of receipt, and name and address of the person who has transferred (in case of a corporation, name and address of the company);
 - (iii) Biological property and date of testing
 - (iv) Status of the passage
- L. Verifying that the raw materials or materials derived from organisms (excluding plants) which are used in the manufacturing biological medical devices (hereinafter referred to as "biologically derived source materials) are appropriate in accordance with the *Seihin Hyojun Sho* (Device Master File) of the products, and preparing and retaining records of the results of the verification
- M. With respect to the biologically derived raw materials for use in the manufacturing of biological medical devices, maintaining the items which shall be recorded as specified by the Minister, or making the contract with the person collecting the biologically derived raw materials (hereinafter referred to as "biological raw material collectors, etc.") and maintaining them appropriately by the biological raw material collectors, etc.

(2) To prepare and retain the records specified in Item 1-E, L and M for each lot.

2. The marketing approval holder, etc. of biological medical devices, etc. shall, when handling the products with cell/tissue-based medical devices, control properly the following duties of the process control for the products with cell/tissue-based medical devices in the manufacturing site of the products in accordance with the *Seihin Hyojun Sho* (Device Master File) in addition to the duties specified in the preceding paragraph and shall establish and document the procedures for the duties.

(1) To have the person appointed beforehand perform the following duties according to the details of the duties

- A. To take necessary actions, when handling the cells or tissue collected from different donors or donor animals, to prevent the cells or tissue from being mixed up or cross-contaminated

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

- B. To verify that the cells or tissue which serves as the raw materials or materials when received are appropriate by reference to the records of the following items, in accordance with the *Seihin Hyojun Sho* (Device Master File) of the products, and preparing and retaining records of the results of the verification
- (i) Business facility where the cells or tissue has been collected
 - (ii) Date when the cells or tissue has been collected
 - (iii) For the cells or tissue derived from humans, the conditions of diagnosing by questioning, testing, etc. the donor for donor screening (the process to diagnose the donors by questioning, testing, etc. and to decide whether they are sufficiently qualified to donate their cells or tissue as the materials of the products with cell/tissue-based medical devices)
 - (iv) For the cells or tissue derived from animals, conditions of receiving the donor animals and conditions of the testing and breeding control of the donor animals for donor screening (the process to test the donor animals, to control their breeding and to decide whether they are sufficiently qualified to donate their cells or tissue as the materials of the products with cell/tissue-based medical devices)
 - (v) Progress of the operations to collect the cells or tissue
 - (vi) Other items required to ensure the quality of the products with cell/tissue-based medical devices, in addition to the items specified in the preceding item (i) to (v) inclusive.
- C. To take necessary actions, when collecting cells or tissue used as the raw materials from the donor animals, to prevent contamination with microorganisms, etc. in the course of collection, and preparing records of the actions
- D. Not to allow the personnel, when being under any one of the following items, to perform the operations in the clean areas or aseptic areas
- (i) The case where they are in the health conditions suspected to contaminate the products or materials with microorganisms, etc.
 - (ii) The case where they handle the microorganisms that are suspected to contaminate the cells or tissue just before collecting and processing the cells or tissue
- E. To comprehend name of the facilities of the consignee, date of delivery and lot

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

number per product, and prepare the records thereof

F. To take necessary actions to ensure the quality of the products while delivered, and prepare the records thereof

G. To prepare records of the breeding control of the donor animals after their receipt.

(2) To prepare and retain the records specified in Item 1-B, C and G for each lot, and to prepare and retain the records specified in F for each product.

3. The marketing approval holder, etc. of biological medical devices, etc. shall retain the records specified in the preceding two paragraphs so as to verify the series of the records from biological ingredients used in the manufacturing to the products manufactured by using the biological ingredients.

(Testing)

Article 76 The marketing approval holder, etc. of biological medical devices, etc. shall, when handling the products with the biological medical devices, etc., properly control the duties related to the testing of the products with the biological medical devices, etc. in the manufacturing site of the products in accordance with the *Seihin Hyojun Sho* (Device Master File), in addition to the duties specified in the preceding article, and shall establish and document the procedures for the duties.

(1) To separate the samples by proper identification so as to prevent them from being mixed up or cross-contaminated

(2) To perform the testing which is important for the quality control and inapplicable to the final products at the appropriate stage of the manufacturing process

(3) To constantly breed the utilized animals (limited to those used in the testing; the same hereinafter in this item) under proper control, and to physically examine the animals when used, so as not to use the animals which suffer from infectious diseases and those which are unsuitable for use

(4) To dispose of all the objects contaminated with microorganisms (limited to those contaminated in the processes of testing) and the animal carcasses so as not to cause hazards to the public health and hygiene

(5) To prepare and retain records of the following matters for handling of the strains of the microorganisms for use in the testing

A. Name of the microorganisms and number assigned to each of the containers

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

thereof.

B. Date of receipt, and name and address of the person (in case of a corporation, name and address of the company) who has transferred

C. Biological property and date of the testing

D. Status of the passage

(6) To store a reserve sample in an amount of at least twice of the quantity necessary for the required testing from the products with the specified biological medical devices, etc. specified for each lot (when the products are those with the specified biological medical devices which do not constitute a lot, the biologically derived raw materials used in the manufacturing of the products for each manufacturing number of the products which correspond to or for each lot of the biologically derived raw materials) under appropriate conditions for the appropriate period from the date of the manufacturing (when the medical devices with the products are the specified biological medical devices, 10 years plus the shelf life). Proviso: This provision shall not apply to the products with the specified biological medical devices which do not constitute a lot and of which the reserve sample is stored for the period by the biological raw material collectors, etc. under the contract between the marketing approval holder, etc. and the biological raw material collectors, etc. or the products with medical devices other than the specified biological medical devices which do not constitute a lot. For the products with the specified biological medical devices which constitute a lot, after one year plus the shelf life for the products have passed, storage of the biologically derived source materials used in the manufacturing of the products may be substituted for storage of the products.

2. The marketing approval holder, etc. of biological medical devices, etc. shall, when handling the products with the cell/tissue-based medical devices, properly control the following duties related to the testing of the products with the cell/tissue-based medical devices in the manufacturing site of the products in accordance with the *Seihin Hyojun Sho* (Device Master File), in addition to the duties specified in the preceding paragraph, and shall establish and document the procedures for the duties.

(1) To have the person appointed beforehand perform the testing of the donor animals when and after received and other necessary duties according to the details of the duties

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

- (2) To prepare and retain records of the duties specified in the preceding item
3. The marketing approval holder, etc. of biological medical devices, etc. shall retain the records specified in the preceding two paragraphs so as to verify the series of records from the biologically derived raw materials used in the manufacturing to the products manufactured by using the biologically derived raw materials.

(Training)

Article 77 The marketing approval holder, etc. of biological medical devices, etc. shall, when handling the products with the biological medical devices, etc., establish and perform the procedures for the following duties, in addition to the duties specified under Article 23, and document the procedures.

- (1) To provide the personnel engaged in the manufacturing or testing of the products with the biological medical devices, etc. with the training on microbiology, medical science, veterinary science, etc.
- (2) To provide the personnel engaged in the operations in the aseptic areas or the areas, etc. for handling the pathogenic microorganisms with the training for taking actions necessary to prevent contamination with microorganisms.
2. The marketing approval holder, etc. of biological medical devices, etc. shall prepare and retain records related to training specified in the preceding paragraph.

(Control of Documents and Records)

Article 78 The marketing approval holder, etc. of biological medical devices, etc. shall retain at least one copy of the documents or their copies specified in this chapter and the copies thereof for the following periods (5 years for the documents for the training) from the date of the abolishment. Proviso: This provision shall not apply to the documents used for the manufacturing or testing of the products when they are retained so as to be available for the retention period of the records of the products specified in the next paragraph.

- (1) 30 years plus the shelf life for the products with the specified biological medical devices or the biological medical devices manufactured using human blood as the origins of the biologically derived raw materials [refer to the origins of the raw materials or materials used in the manufacturing (including those used in the

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

manufacturing process; the same hereinafter)].

- (2) 10 years plus the shelf life for the products with the biological medical devices (excluding those specified in the preceding item) or the cell/tissue-based medical devices (excluding those specified in the preceding item)
2. The marketing approval holder, etc. of biological medical devices, etc. shall retain the records specified in this chapter for the periods specified in Item 1 or Item 2 of the preceding paragraph (5 years for the records for the training) from the date of the preparation.

(Exceptions in Retention of Records)

Article 79 The marketing approval holder, etc. of biological medical devices, etc. shall, notwithstanding the provisions of this chapter, retain the records specified in this chapter for the products with the biological medical devices designated by the Minister for the period designated by the Minister. Proviso: This provision shall not apply when the records are retained properly by the biological raw material collectors, etc. for the period under the contract-between the marketing approval holder, etc. and the biological raw material collectors, etc.

Chapter 5 Manufacturing Control and Quality Control of Radioactive *In Vitro* Diagnostic Reagents

(Infrastructure of Registered Manufacturing Sites of Radioactive *In Vitro* Diagnostic Reagents)

Article 80 The marketing approval holder, etc. of the products with radioactive *in vitro* diagnostic reagents shall conform to the following requirements (excluding the provisions related to the work rooms in Item 2-E and Item 4-D in the registered manufacturing sites which only perform packaging, labeling or storage of containers or wrappers specified on the proviso in Article 2, Paragraph 3, Item 1 of the Regulations for Manufacturing Control and Quality Control of Radiopharmaceuticals and the provisions related to the testing rooms in Item 2-E and Item 4-D when the testing is implemented on its own responsibility utilizing other testing facilities of the registered manufacturing site or other testing institutions and it is deemed to pose no problem) as infrastructure of the registered manufacturing sites which manufacture the products

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

(excluding the registered manufacturing sites which only perform design, hereinafter the same in this chapter).

- (1) It shall be established in a place where landsliding and water exposure are not likely to occur.
- (2) The work areas for the products with radioactive *in vitro* diagnostic reagents shall conform to the following requirements.
 - A. The work areas shall be distinctly separated from other facilities.
 - B. The principal structural part, etc. shall be the fireproof structure or shall be made of non-combustible materials [the term "non-combustible materials" means the non-combustible materials specified under Article 2, Item 9 of the Building Standards Act (Law No. 201, 1950), hereinafter the same].
 - C. The shield wall or other shielding objects necessary to decrease the following doses respectively to not more than the dose limits that are specified by the Minister.
 - (i) The radiation dose that humans could receive in the places which humans step into on a routine basis in the registered manufacturing site
 - (ii) The radiation dose in the boundary of the registered manufacturing site and the areas which humans inhabit in the registered manufacturing site
 - D. The entrance door through which humans move in and out on a routine basis shall be one.
 - E. The work areas shall be provided with the work rooms and testing rooms (including the animal test rooms when animal tests are performed, hereinafter the same) which conform to the following requirements.
 - (i) The inner walls, floors and other parts that are suspected to be contaminated by radioactive substances (the term "radioactive substances" means the radioactive substances specified under Article 1, Item 2 of the Regulations for Manufacturing Control and Quality Control of Radiopharmaceuticals, hereinafter the same) shall be the structure with few projections, indents and clearance gaps such as joints of finishing materials.
 - (ii) The surfaces of the inner walls, floors and other portions that are suspected to be contaminated by radioactive substances shall be flat and smooth, less

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

- likely to be penetrated with gas or liquid and shall be finished with corrosion-resistant materials.
- (iii) The work areas shall be equipped with the waste container from which radioactive substances or the objects contaminated by radioactive substances to be disposed shall not be likely to fly apart, leak, seep or flow out and which can be safely transported and disposed of.
 - (iv) The work areas shall be equipped with equipment such as hood and glove box to prevent spreading of radioactive substances in the form of gas or the air contaminated by radioactive substances in conjunction with the exhaust system.
- F. The work areas shall be provided with the contamination test room (the term "contamination test room" means the room where contamination by radioactive substances on the surfaces of human body or the objects putting on human body such as working clothes, footwears and protective equipment is tested and eliminated, hereinafter the same) which conforms to the following requirements. Proviso: This provision shall not apply when radioactive substances of quantities or concentrations not more than those specified by the Minister are handled.
- (i) It shall be established in the place most suitable to test and eliminate contamination by radioactive substances such as vicinity of entrances of the work areas where humans move in and out on a routine basis.
 - (ii) It shall conform to the requirements in Item E (i) and (ii).
 - (iii) The cleaning facility and the gowning facility shall be provided and a radiation counter for test of contamination and equipment necessary for elimination of contamination shall be provided.
 - (iv) The draining conduit of the cleaning facility specified in Item (iii) above shall be connected to the drain systems.
- (3) It shall be provided with the storage facilities which conform to the following requirements.
- A. The principal structural part, etc. shall be the fireproof structure and its opening section shall be equipped with a storage chamber having a fire-retarding door or a storage box of the fireproof structure.
 - B. The shield wall or other shielding objects which conform to the criteria in Item

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

2-C shall be provided.

- C. The entrance door through which humans move in and out on a routine basis shall be one.
- D. The portions leading to the outside such as doors and covers shall be provided with facilities or equipment for closing such as key.
- E. The storage facilities shall be provided with the facilities or equipment that is locked for storage of radiopharmaceuticals separately from other objects.
- F. The storage facilities shall be equipped with the containers for storing radioactive substances which conform to the following requirements.
 - (i) The containers for storing the radioactive substances that may contaminate the air outside the containers shall be provided with the sealed structure.
 - (ii) The containers for storing radioactive substance in the form of liquid shall be the structure where liquid is not likely to spill and the materials into which liquid is not likely to penetrate shall be used.
 - (iii) The containers for storing radioactive substance in the form of liquid or solid which may cause accidents such as crack and breakage shall be equipped with facilities or equipment such as tray and absorber to prevent spreading of contamination by radioactive substances.
- (4) It shall be provided with the disposal system which conforms to the following requirements.
 - A. It shall be distinctly separated from other facilities.
 - B. The principal structural part, etc. shall be the fireproof structure or shall be made of non-combustible materials.
 - C. The shield wall or other shielding objects which conforms to the criteria in Item 2-C shall be provided.
 - D. The exhaust systems which conform to the following requirements shall be provided. Proviso: This provision shall not apply when radioactive substances of quantities or concentrations not more than those specified by the Minister are handled or when installation of the exhaust systems significantly prevents intended purpose or is difficult due to the nature of the work and generation of radioactive substance in the form of gas or contamination of the air by radioactive substances are not likely to occur.

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

- (i) The exhaust systems shall be capable of decreasing concentration of radioactive substances in the exhaust air at an exhaust vent to not more than the limit of concentration specified by the Minister or shall be capable of decreasing concentration of radioactive substances in the air outside the boundary of the registered manufacturing site (when measures are taken to restrict persons from entering, without reason, the area adjacent to the boundary of the registered manufacturing site, it shall be the boundary of the area, hereinafter the same in this item) to not more than the limit of concentration specified by the Minister by providing the exhaust air monitoring system and monitoring concentration of radioactive substances in the exhaust air. Proviso: This provision shall not apply when installation of the exhaust systems having the capability concerned is significantly difficult and the Minister approved that the exhaust systems have the capability to decrease the dose that humans outside the boundary of the registered manufacturing site receive to not more than the dose limit specified by the Minister.
- (ii) The exhaust systems shall be provided with the structure where gas is not likely to leak and shall be made of corrosion-resistant materials.
- (iii) The exhaust systems shall be provided with the equipment that can rapidly prevent spreading the air contaminated by radioactive substances in case of malfunction.
- (iv) The exhaust systems shall be capable of decreasing concentration of radioactive substances in the air in the places where humans step into on a routine basis inside the work rooms, the testing rooms or the disposal operation rooms [the term "disposal operation rooms" mean the rooms where radioactive substances or the objects contaminated by radioactive substances are burned up and their residues are transported from a calcinator and solidified by concrete or other solidifying materials, hereinafter the same (including processing to solidify, hereinafter the same)] to not more than the limit of concentration specified by the Minister.

E. In case that radioactive substance in the form of liquid or the solution

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

contaminated by radioactive substances is purified or drained, the drain systems which conform to the following requirements shall be provided.

- (i) The drain systems shall be capable of decreasing concentration of radioactive substances in discharged fluid at a drainage port to not more than the limit of concentration specified by the Minister or shall be capable of decreasing concentration of radioactive substances in discharged water in the boundary of the registered manufacturing site to not more than the limit of concentration specified by the Minister by providing the discharged water monitoring system and monitoring concentration of radioactive substances in discharged water. Proviso: This provision shall not apply when installation of the drain systems having the capability concerned is significantly difficult and the Minister approved that the drain systems have the capability to decrease the dose that humans outside the boundary of the registered manufacturing site receive to not more than the dose limit specified by the Minister.
 - (ii) The drain systems shall be provided with the structure where discharged fluid is not likely to leak and the corrosion-resistant materials into which discharged fluid is not likely penetrate shall be used.
 - (iii) The discharged water purification tank shall be the structure that can collect discharged fluid or the structure that can measure concentration of radioactive substances in discharged fluid and shall be equipped with equipment adjusting outflow of discharged fluid.
 - (iv) The opening section in the upper part of the discharged water purification tank shall be the structure possible to be covered or shall be equipped with the facility such as fence around it that restricts persons from entering without reason.
- F. When radioactive substances or the objects contaminated by radioactive substances are burned up, it shall be provided with the exhaust systems conforming to the provisions of Item D, the disposal operation room conforming to the provisions of Item 2-E (i), (ii) and (iv), the contamination test room conforming to the provisions of Item 2-F (i) to (iii) and a calcinator conforming to the following requirements.

- (i) The calcinator shall be the structure from which gas is not likely to leak and ash is not likely to fly apart.
 - (ii) The calcinator shall be connected to the exhaust systems.
 - (iii) The carry-out hatch of incineration residue shall be connected to the disposal operation room.
- G. When radioactive substances or the objects contaminated by radioactive substances are solidified by concrete or other solidifying materials, it shall be provided with the exhaust systems conforming to the provisions of Item D, the disposal operation room conforming to the provisions of Item 2-E (i), (ii) and (iv), the contamination test room conforming to the provisions of Item 2-F (i) to (iii) and the solidifying process system conforming to the following requirements.
- (i) It shall be the structure that radioactive substances or the objects contaminated by radioactive substances is not likely to leak or spill out and powder dusts are not likely to fly apart.
 - (ii) The corrosion-resistant materials into which liquid is not likely to penetrate shall be used.
- H. When radioactive substances or the objects contaminated by radioactive substances are stored and disposed of, the storage and disposal facilities conforming to the following requirements shall be equipped.
- (i) It shall be the structure that is separated from the outside.
 - (ii) The portions leading to the outside such as doors and covers shall be provided with facilities or equipment for closing such as key.
 - (iii) The containers conforming to the provisions of the preceding item F (limited to those of the fireproof structure) shall be provided.
- (5) The boundary of the controlled areas specified under Article 1, Item 3 of the Regulations for Manufacturing Control and Quality Control of Radiopharmaceuticals shall be equipped with the facilities such as fence that restrict persons from entering without reason.
2. When the exhaust systems or the drain systems that were approved in Item 4-D (i) or 4-E (i) of the preceding paragraph are regarded as not having the capability approved anymore, the Minister may revoke the approval concerned.
3. Proviso: the provisions of Item 1, Item 2-B to -E, Item 3-A to -D and F, Item 4 and Item

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

5 of the preceding paragraph shall not apply when only radioactive substances of quantities or concentrations not more than those specified by the Minister are handled.

(Compliance with Regulations for Manufacturing Control and Quality Control of Radiopharmaceuticals)

Article 81 Other than those specified under the preceding article, the marketing approval holder, etc. of the products with radioactive *In Vitro Diagnostic Reagents* shall verify that the registered manufacturing site performs duties based on the Regulations for Manufacturing Control and Quality Control of Radiopharmaceuticals.

Chapter 6 Application *mutatis mutandis*, etc. to Manufacturers, etc. of Medical Devices, etc.

(Manufacturing Control and Quality Control of Manufacturers of Medical Devices, etc. for Export)

Article 82 The provisions of Chapter 2 and Chapter 3 (excluding Article 49, Paragraph 2 and Paragraph 3, Article 65 and from Article 69 to Article 72-3) (in manufacturers of the products with biological medical devices, etc., in addition to these provisions, the provisions of Chapter 4 and in manufacturers of the products with radioactive *in vitro* diagnostic reagents, in addition to these provisions, the provisions in Chapter 5) shall apply *mutatis mutandis* to the manufacturing control and quality control of manufacturers of the products with medical devices, etc. for export in Article 80, Paragraph 2 of the PMD Act. In such cases, in the provisions described in the left column in the following table, the letters described in the middle column in the table shall read the letters described in the right column in the table.

Article 5, Paragraph 2, Item 1	respective facilities	respective sections of the manufacturing site
Article 6, Paragraph 1	matters (in the limited type 3 marketing approval holder of medical devices [it refers to the marketing approval holders that market	matters

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In*

Vitro Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

	only the medical devices other than those designated by the Minister as those requiring caution in the manufacturing control and quality control among general medical devices (hereinafter referred to as "limited general medical devices"), hereinafter the same)], excluding Item 1)	
Article 6, Paragraph 1, Item 3 and Paragraph 3	respective facilities	manufacturing site
Article 10	Duties (in the top management of the limited type 3 marketing approval holder of medical devices, limited to the duties specified in Item 4 and Item 5)	duties
	(hereinafter referred to as the "customer requirements") (in the top management of the limited type 3 marketing approval holder of medical devices, limited to the regulatory requirements, etc.)	(hereinafter referred to as the "customer requirements")
	to all the facilities	in the manufacturing site
Article 11	the top management (excluding the top management of the limited type 3 marketing approval holder of medical devices, hereinafter the same from the next article to Article 14, Article 16 and Article 18)	the top management
Article 12, Item 4	to all the facilities	in the manufacturing site
Article 13, Paragraph 1	respective facilities	manufacturing site
Article 15,	all the facilities	manufacturing site

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In*

Vitro Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

Paragraph 1		
Article 16, Paragraph 2, Item 3	all the facilities	whole manufacturing site
Article 17	inside the respective facilities and between the respective facilities	the manufacturing site
Article 19, Item 3	the product requirements (in the products with limited general medical devices, limited to process performance)	product requirements
Article 20	matters (in the products with limited general medical devices, excluding the matters specified in Item 2)	matters
Article 21, Item 2	the customer requirements (in the limited type 3 marketing approval holder of medical devices, limited to the regulatory requirements, etc.)	the customer requirements
Article 23	the duties (in the limited type 3 marketing approval holder of medical devices, excluding the duties specified in Item 3)	the duties
Article 24, Paragraph 1	respective facilities	manufacturing site
Article 24, Paragraph 2.	shall be documented. Proviso: This provision shall not apply to the limited type 3 marketing approval holder of medical devices when appropriate operation of the maintenance duties is established and documented	shall be documented
Article 25, Paragraph 1	the products (excluding the products with limited general medical devices, hereinafter the same from this article to Article 36)	the products
Article 28,	respective facilities	manufacturing site

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In*

Vitro Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

Paragraph 2, Item 3		
Article 37, Paragraph 3	shall be selected. Proviso: That provision shall not apply to the supplier of the purchased products related to the products with limited general medical devices when the supplier is evaluated	shall be selected
Article 37, Paragraph 4	re-evaluation (in the supplier of the purchased products of the products with limited general medical devices, evaluation and re-evaluation)	re-evaluation
Article 38, Paragraph 3	shall be retained. Proviso: This provision shall not apply to the products with limited general medical devices.	shall be retained
Article 40, Paragraph 1	the products (excluding the products with limited general medical devices, hereinafter the same in Paragraph 3)	the products
Article 40, Paragraph 1, Item 6	to market	from the manufacturer
Article 40, Paragraph 2	shall be retained. Proviso: This provision shall not apply to the products with limited general medical devices when the record that can identify the amount manufactured and amount approved for release is prepared for each lot of the products and is retained.	shall be retained.
Article 41	the products (excluding the products with limited general medical devices, hereinafter the same from this article to Article 51 and Article 53)	the products
Article 42,	handle	manufacture

Paragraph 1		
Article 44 and Article 46	handle	manufacture
Article 52, Paragraph 1	period until (in the limited type 3marketing approval holder of medical devices, the period of the duties that he/she takes charge of)	period until
	shall be documented. Proviso: for the products with limited general medical devices, it is limited to the period of the duties that the marketing approval holder, etc. takes charge of for the products	shall be documented
Article 52, Paragraph 2	shall be documented. Proviso: This provision shall not apply to the products with limited general medical devices	shall be documented
Article 52, Paragraph 3	shall be recorded. Proviso: This provision shall not apply to the products with limited general medical devices	shall be recorded.
Article 54, Paragraph 1, Item 1	the products (excluding the products with limited general medical devices)	the products
Article 55, Paragraph 1	all the facilities including the marketing approval holder, etc.	the manufacturing site
Article 55, Paragraph 4	the information, etc. collected based on the provisions of Article 68-2, Paragraph 1 of the PMD Act	from the manufacturing site
Article 56, Paragraph 1, Item 1	the quality management system (for the products with limited general medical devices, excluding the product realization plan)	the quality management system
Article 57,	the products (excluding the products with	the products

Paragraph 3 and Article 58, Paragraph 2	limited general medical devices)	
Article 58, Paragraph 5	necessary matters (for the products with limited general medical devices, monitoring of property of the products, measurements and other necessary matters in Paragraph 1)	necessary matters
Article 59	the products (excluding the products with limited general medical devices, hereinafter the same in the next article)	the products
Article 61, Paragraph 2	matters (for the products with limited general medical devices, limited to the matters specified in Item 1)	matters
Article 61, Paragraph 3	shall be stored. Proviso: This provision shall not apply to the products with limited general medical devices	shall be stored
Article 62, Paragraph 5	preventive action (in the limited type 3marketing approval holder of medical devices, it is limited to corrective action)	Preventive action
Article 62, Paragraph 6	for the products (excluding the products with limited general medical devices), when the marketing approval holder, etc. is aware of adverse event in the item of Article 228-20, Paragraph 2 of the Enforcement Regulations, the event shall be reported to the Minister based on the provisions of this paragraph.	when it is requested to notify regulatory authorities of the country or the area to which the products are exported of adverse event regarding the products, the notification concerned shall be made.
Article 73	the marketing approval holder, etc. of specified biological medical devices, etc.	the manufacturer of specified biological medical devices, etc. for

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In*

Vitro Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

		export
Article 74 and Article 75, Paragraph 1	the marketing approval holder, etc. of biological medical devices, etc.	the manufacturer of biological medical devices, etc. for export
	handle	manufacture
Article 75, Paragraph 2	the marketing approval holder, etc. of biological medical devices, etc.	the manufacturer of biological medical devices, etc. for export
	handle	manufacture
Article 75, Paragraph 3	the marketing approval holder, etc. of biological medical devices, etc.	the manufacturer of biological medical devices, etc. for export
Article 76, Paragraph 1 and Paragraph 2	the marketing approval holder, etc. of biological medical devices, etc.	the manufacturer of biological medical devices, etc. for export
	handle	manufacture
Article 76, Paragraph 3	the marketing approval holder, etc. of biological medical devices, etc.	the manufacturer of biological medical devices, etc. for export
Article 77, Paragraph 1	the marketing approval holder, etc. of biological medical devices, etc.	the manufacturer of biological medical devices, etc. for export
	handle	manufacture
Article 77, Paragraph 2, Article 78 and Article 79	the marketing approval holder, etc. of biological medical devices, etc.	the manufacturer of biological medical devices, etc. for export

(Manufacturing Control and Quality Control of Manufacturer, etc. Related to the Registered Manufacturing Site)

Article 83 When the business facility where processes are outsourced by the

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

marketing approval holder, etc. or other registered manufacturing sites or the business facility that supplies the marketing approval holder, etc. or other registered manufacturing sites with the purchased products is the registered manufacturing site, the provisions from Chapter 2 to Chapter 5 inclusive (excluding Article 49, Paragraph 2 and Paragraph 3 and from Article 69 to Article 72-3) shall apply *mutatis mutandis* to the manufacturing control and quality control of the products in the manufacturer, etc. related to the registered manufacturing site concerned. Proviso: The provisions that are deemed to be inappropriate to apply to the quality management system by referring to the processes performed by the registered manufacturing site concerned for the products are allowed not to apply to the quality management system. In such cases, the manufacturer, etc. related to the registered manufacturing site concerned shall describe that effect in the quality manual.

2. In the preceding paragraph, in Article 6, Paragraph 1, Article 7, Paragraph 2, Article 8, Paragraph 3, Article 10, Article 11, Article 20, Article 21, Item 2, Article 23, Article 24, Paragraph 2 and Paragraph 3, Article 25, Paragraph 1, Article 38, Paragraph 3, Article 40, Paragraph 1, Article 41, Article 52, Paragraph 1 and Paragraph 2, Article 54, Paragraph 1, Article 56, Paragraph 5, Article 57, Paragraph 2, Article 58, Paragraph 2, Article 59, Article 62, Paragraph 1, Paragraph 5 and Paragraph 6 and Article 64, Paragraph 1, "the limited type 3marketing approval holder of medical devices" shall read "the limited type 3 manufacturer, etc. of medical devices", in the provisions from Article 74 to Article 79, "the marketing approval holder, etc. of biological medical devices, etc." shall read "the manufacturer, etc. of biological medical devices, etc.", in Article 6, Paragraph 1, "the marketing approval holder that markets" shall read "the manufacturer, etc. related to the registered manufacturing site that manufactures" in Article 42, Paragraph 1, "handle" shall read "manufacture", in Article 44 and Article 46 "handle" shall read "manufacture", in Article 55, Paragraph 1, "all the facilities including the marketing approval holder, etc." shall read "the manufacturing site", in Article 55, Paragraph 4, "the information, etc. collected based on the provision of Article 68-2, Paragraph 1 of the PMD Act" shall read "from the registered manufacturing site concerned", in Article 62, Paragraph 6, "reported to the Minister pursuant to the provisions of the same paragraph" shall read "notified to the marketing approval holder, etc. of the events concerned", in Article 73, "the marketing approval

Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

(Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)

holder, etc. of specified biological medical devices, etc." shall read "the manufacturer, etc. of specified biological medical devices, etc.", in Article 74 and Article 75, Paragraph 1, "handle" shall read "manufacture", in Article 75, Paragraph 2, "handle the products " shall read "manufacture the products " and in Article 76, Paragraph 1 and Paragraph 2 and Article 77, Paragraph 1, "handle" shall read "manufacture".

(Verification by Marketing Approval Holder, etc.)

Article 84 When manufacturer, etc. related to the registered manufacturing site performs necessary verification pursuant to the provisions of Article 65 that applied *mutatis mutandis* in the preceding article, the marketing approval holder, etc. shall perform necessary verification about that the verification concerned by the manufacturer, etc. is appropriately performed.