Japan's New Medical Device and Diagnostics GMP

Regulations for Manufacturing Control and Quality Control of Medical Device and In Vitro Diagnostics
(MHLW Ordinance No. 169 dated December 17, 2004)

In accordance with the provisions of Article 14, Paragraph 2, Item (4) (including cases where the provisions are applied mutatis mutandis under Article 19-2, Paragraph 5) of the Pharmaceutical Affairs Law (Law No. 145, 1960), the whole text of the Regulations for Manufacturing Control and Quality Control of Medical Device and Diagnostics shall be amended as below.

December 17, 2004
Hidehisa, Otsuji
Minister of Health, Labor and Welfare

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Chapter 1 General Provisions

(Objective)

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

(Definitions)

Article 2 The term "Product" used in this Ordinance means articles (including articles manufactured during an intermediate process which must undergo subsequent processing before a final product is obtained; hereinafter referred to as an "Intermediate Product") which have undergone a manufacturing process at a manufacturing site.

2. The term "Component, Etc." used in this Ordinance mean parts, assembled parts (only those used for Products), raw materials, source materials, containers, wrappers, labels (including package inserts) used in manufacturing process, which comprise part of a Product and software of the Product.

3. The term "Manufacturing Materials" used in this Ordinance mean articles used for Intermediate Products during an intermediate process, except for those which adverse comprise part of a Product.

4. The term "Labeling and Packaging Materials" used in this Ordinance mean containers, wrappers and labels (including package inserts) of a Components, Etc.

5. The term "Lot" used in this Ordinance means a batch of Products, Manufacturing Materials, and Components, Etc., which have been manufactured so as to have a uniform quality during a series of manufacturing processes within certain manufacturing period (hereinafter referred to as the "Products, Etc.").

6. The term "Testing and Inspection Unit" used in this Ordinance means a Lot or other batches of Products which have a uniform quality equivalent of a Lot.

7. The term "Control Unit" used in this Ordinance means a batch of Labeling and Packaging Materials which are confirmed to have a uniform quality.

8. The term "Sterilized Medical Devices" used in this Ordinance means medical devices sterilized during manufacturing process.

9. The term "Validation" used in this Ordinance means acts of verifying and documenting that buildings and facilities at a manufacturing site, as well as operating procedures, manufacturing processes and other methods of manufacturing control and quality control (hereinafter referred to as the "Operating Procedures, Etc.") yield expected results.

10 The term "Clean Area" used in this Ordinance means, among the areas for performing manufacturing operations (hereinafter referred to as a "Work Area"), a place for weighing and for preparing Components, Etc., and a place where washed containers are exposed to the air in the Work Area.

11. The term “Aseptic Area” used in this Ordinance means a Work Areas where Products, Components, Etc. or sterilized containers are exposed to the air in the Work Area, a Work Area for sealing operations of containers, as well as a Work Area for aseptic operations such as sterility tests, etc.

12. The term “Cellular/Tissue Based Medical Device” used in this Ordinance means a Medical Devices comprised of human or animal cells or tissues.

13. The term “Donor” used in this Ordinance means an individual providing his/her cells or tissues as source materials of Cellular/Tissue Based Medical Devices (excluding cells or tissues derived from the human body in brain death as defined under Article 6, Paragraph 2 of the Law on Organ Transplantation (Law No. 104 of 1997)).

14. The term “Donor Animal” used in this Ordinance means an animal providing its cells or tissues as source materials of Cellular/Tissue Based Medical Devices.

15. The term “Process Input Information” used in this Ordinance means information which is provided for operation of certain process and is necessary for manufacturing control and quality control.

16. The term “Process Output Information” used in this Ordinance means information acquired as a result of process operation.

17. The term “Controller/Manager” used in this Ordinance means those who manage and supervise a manufacturing site, such as operational officers.

18. The term “Quality Policy” used in this Ordinance means a basic policy that a Controller/Manager establishes and states in order to ensure the quality of a Product.

19. The term “Quality Control and Supervision System” used in this Ordinance means a system for manufacturers and foreign manufacturers as defined under Article 13-3, Paragraph 1 of the Law (hereinafter referred to as a “Foreign Manufacturer”) (hereinafter referred to collectively as a “Manufacturer, Etc.”) to administer and supervise a manufacturing site in connection with quality issues.

20. The term “Collation” used in this Ordinance means judging the appropriateness and effectiveness for achieving stated goals.

21. The term “Resources” used in this Ordinance means individuals’ knowledge and skills, equipment and other resources utilized in the operation of a manufacturing site.

22. The term “Operational Infrastructure” used in this Ordinance means a system of facilities, equipment and services necessary for operation of a manufacturing site.

23. The term “Traceability” used in this Ordinance means the ability to trace the history, application and location.

24. The term “Notice” used in this Ordinance means documents issued after the delivery of Products in order to supplement the information provided upon delivery, to advise measures to take for use, improvement, return and destruction of Products.

(Scope of Application)

Article 3 A manufacturer/distributor of medical devices and in-vitro diagnostic drugs as defined under Article 14, Paragraph 1 of the Law, a designated manufacturer/distributor of medical devices and in-vitro diagnostic drugs, as defined under Article 19-2, Paragraph 4 of the Law, and a manufacturer/distributor of designated control-required medical devices, etc., as defined under Article 23-2, Paragraph 1 of the Law (hereinafter referred to collectively as a "Manufacturer/Distributor, Etc."), shall require relevant Manufacturers, Etc. to perform manufacturing control and quality control at manufacturing sites, in accordance with the provisions in Chapter 2 or those applied mutates mutandis in Chapter 5, provided that a Manufacturer/Distributor, Etc. may require a manufacturer belonging to the category under Article 26, Paragraph 5, Item (4) of the Enforcement Rules of the Pharmaceutical Affairs Law (Ordinance of the Ministry of Health and Welfare No. 1, 1961, hereinafter referred to as the "Enforcement Rules") (hereinafter referred to collectively as a "Medical Device Custodian/Manufacturer") or of a foreign manufacturer belonging to the category under the Article 36, Paragraph 4, Item (4) of the Enforcement Rules (hereinafter referred to collectively as a "Foreign Medical Device Custodian/Manufacturer") (hereinafter collectively referred to as a "Medical Device Custodian/Manufacturer. Etc."), a manufacturer belonging to the category under the Article 26, Paragraph 2, Item (3) of the Enforcement Rules (hereinafter referred to as an "In Vitro Diagnostic Custodian/Manufacturer") or a foreign manufacturer belonging to the category under the Article 36, Paragraph 2, Item (3) of the Enforcement Rules (hereinafter referred to as a "Foreign In Vitro Diagnostic Custodian/Manufacturer") (hereinafter collectively referred to as an "In Vitro Diagnostic Custodian/Manufacturer, Etc.") to perform manufacturing control and quality control at manufacturing sites in accordance with the provisions in Chapter 3 or those applied mutates mutandis in Chapter 5, instead of the provisions in Chapter 2 or those applied mutates mutandis in Chapter 5.

2. A Manufacturer/Distributor, Etc. of medical devices shall require a manufacturer of medical devices which are biologically derived products as defined under the Article 2, Paragraph 9 of the Law (hereinafter referred to as a "Biological Medical Device"), products designated by the Minister of Health, Labor and Welfare pursuant to the provisions of Article 43, Paragraph 2 of the Law, or Cellular/Tissue Based Medical Devices (hereinafter collectively referred to as a "Biological Medical Device, Etc.") (hereinafter referred to as a "Biological Medical Device Manufacturer") or a foreign manufacturer of Biological Medical Devices, Etc. (hereinafter referred to collectively as a "Biological Medical Device Manufacturer, Etc.") to perform manufacturing control and quality control at manufacturing sites, in accordance with, in addition to the provisions in Chapter 2, the provisions in Chapter 4, provided that only Articles 78 and 79 shall apply to manufacturing sites whose purpose is limited to packing, labeling and storage.

3. A Manufacturer, Etc. of medical devices or in-vitro diagnostics shall perform manufacturing control and quality control of a Product at manufacturing sites defined under Article 96 of Enforcement Rules in accordance with the provisions in Chapter 2 and those applied mutates mutandis in Chapter 5, provided that a Manufacturer/Distributor, Etc. may require a Medical Device Custodian/Manufacturer, Etc. or an In Vitro Diagnostic Custodian/Manufacturer, Etc. to perform manufacturing control and quality control at their manufacturing sites in accordance with the provisions in Chapter 3 or those applied mutates mutandis in Chapter 5, instead of those in Chapter 2 and those applied mutates mutandis in Chapter 5. Manufacturing control and quality control at manufacturing sites of a Biological Medical Device Manufacturer, Etc. shall be performed in accordance with provisions in Chapter 4 in addition to the provisions in Chapter 2, provided that only Articles 78 and 79 shall apply to manufacturing sites whose purpose is limited to packing, labeling and storage.

4. A manufacturer of medical devices or drugs (which shall mean in-vitro diagnostics in this Paragraph) for export purposes under Article 80, Paragraph 1 of the Law shall perform manufacturing control and quality control of a Product at manufacturing sites of medical devices and drugs for export purposes in accordance with the provisions in Chapter 2 or those applied mutates mutandis in Chapter 5, provided that the manufacturing control and quality control of a Product at manufacturing sites of a Medical Device Custodian/Manufacturer, Etc. or an In Vitro Diagnostic Custodian/Manufacturer, Etc. may be performed in accordance with the provisions in Chapter 3 and those applied mutates mutandis in Chapter 5, instead of those in Chapter 2 or those applied mutates mutandis in Chapter 5. Manufacturing control or quality control at manufacturing sites of a Biological Medical Device Manufacturer, Etc. for export purposes shall be performed in accordance with provisions in Chapter 4 in addition to the provisions in Chapter 2. provided that only Articles 78 and 79 shall apply to manufacturing sites whose purpose is limited to packing, labeling and storage.

Chapter 2 Manufacturing Control and Quality Control at Manufacturing Sites of a Medical Device Manufacturer, Etc.

Subchapter 1 General Rules

(Application)

Article 4 Articles 30 to 36 shall not apply to the Products related to medical devices other than designated medical devices as defined under Article 77-5, Paragraph 1 of the Law or those medical devices designated by the Minister of Health, Labor and Welfare as requiring control of the design and development (hereinafter referred to as “Design and Development”) in order to ensure appropriate implementation of manufacturing control and quality control.

2. If a Manufacturer, Etc. is unable to apply any of the provisions in Subchapter 5 of this Chapter because of the character of the medical device related to the Product, it may not apply the provision to its Quality Control and Supervision System.
3. If either of the foregoing paragraphs is applicable, a Manufacturer, Etc. shall identify to that effect in writing in the documents which provide the Quality Control and Supervision System (hereinafter referred to as "Basic Documentation for Quality Control and Supervision System") for the manufacturing site.

Subchapter 2 Quality Control and Supervision System

(Requirements of Quality Control and Supervision System)

Article 5 A Manufacturer, Etc. shall establish and implement the Quality Control and Supervision System and maintain its effectiveness in accordance with the provisions in this Chapter.
2. A Manufacturer, Etc. shall discharge the following duties:
(1) To define the extent (including the results achieved by the process) of the process necessary for the Quality Control and Supervision System (hereinafter refereed to as "the Process" in this Chapter) and identify how each step of the Process is applied to whole of the manufacturing sites;
(2) To define the order and relationship of the Processes.
(3) To define the criteria and method necessary to ensure the performance of the Process and effectiveness of the supervision;
(4) To ensure a system where resources and information necessary for the implementation of the Process and monitoring/measurement are available;
(5) To monitor and measure and analyze the Process;
(6) To take necessary measure for the Process in order to achieve the result of Item (1), and maintain its effectiveness.
3. A Manufacturer, Etc. shall control and supervise the Process in accordance with the provisions in this Chapter.
4. When a Manufacturer, Etc. intends to contract out the Process which impacts on compliance with product requirements (including laws and regulations on pharmaceutical affairs, and orders and measures thereunder (hereinafter referred to as "Laws and Regulations, Etc." in this Chapter); hereinafter referred to as the "Product Requirements"), except for those subject to permit under Article 13, Paragraph 1 of the Law, or to authorization under Article 13-3, Paragraph 1, it shall ensure that the Process concerned be under control.
5. A Manufacturer, Etc. shall identify and provide for the control under the preceding Paragraph in the Quality Control and Supervision System.

(Documentation of the Quality Control and Supervision System)

Article 6 When a Manufacturer, Etc. establishes the Quality Control and Supervision System in accordance with the Paragraph 1 of the preceding Article, it shall prepare the following documents and implement their provisions:

(1) Identification of Quality Policy and Identification of Quality Goal;

(2) Basic Documentation for the Quality Control and Supervision System;

(3) Any documents necessary to ensure effective and planned implementation and control of the Processes at manufacturing sites;

(4) Protocols and records under this Chapter;

(5) Any other documentation provided for in the laws and regulations on pharmaceutical affairs.

2. A Manufacturer, Etc. shall prepare and maintain for each Product documents providing the specifications and requirements under the Quality Control and Supervision System (hereinafter referred to as the "Product Document" in this Chapter) or documents which describe the content of the Product Document.

3. A Manufacturer, Etc. shall identify all manufacturing processes at manufacturing sites of the Product in the Product Document, and the details of the duties, if applicable, under Paragraph 1 of Article 42 and Paragraph 1 of Article 43.

(Basic Documentation for Quality Control and Supervision System)

Article 7 A Manufacturer, Etc. shall describe the matters described below on Basic Documentation for Quality Control and Supervision System:

(1) The extent of Quality Control and Supervision System (for the matters excluded or not applied, their details and rationale for the exclusion or non-application);

(2) Details or the document number or other reference information of protocols prepared for the Quality Control and Supervision System;

(3) Mutual relationships of Processes.

2. A Manufacturer, Etc. shall describe, in the Basic Documentation for Quality Control and Supervision System, a schematic summary of how the documents described in each item of the Paragraph 1 of the preceding Article are used in the Quality Control and Supervision System.

(Management of Documents)

Article 8 A Manufacturer, Etc. shall maintain the documents under the preceding two Articles or in this Chapter and other documents necessary for the Quality Control and Supervision System (excluding records; hereinafter referred to as the "Quality Control Supervision Documents").

2. A Manufacturer, Etc. shall prepare a protocol providing for control necessary for the duties described below:

(1) To examine its appropriateness of the Quality Control Supervision Documents, and to

authorize their issue;
(2) To perform the necessary Collation of the Quality Control Supervision Documents and, to authorize its update;
(3) To ensure identification of changed items and the latest revision;
(4) On using the revised version of the Quality Control Supervision Documents, to ensure the availability of the properly revised version;
(5) To ensure the Quality Control Supervision Documents to be readable and easily understandable;
(6) To identify the Quality Control Supervision Documents prepared by a third party and to control their distribution;
(7) To prevent the use of the repealed Quality Control Supervision Documents against its intent; to classify them by proper labeling when they are maintained, irrespective of the objective.
3. When a Manufacturer, Etc. intends to change any of the Quality Control Supervision Documents, it shall ensure that, either the department which first authorized the document or another department designated in advance which is in the position to obtain the information for the decision perform the Collation of the change, and shall acquire the authorization of that department.
4. A Manufacturer, Etc. shall maintain, at least one original or copy of the Quality Control Supervision Documents for the following period (for the documents of education and training, five (5) years) from the repeal of the Quality Control Supervision Documents, provided, however, that the documents used for the manufacturing or testing and inspection of Products may be made available only during the period of retention of records of the Products concerned under the following Article:
(1) For the Products related to the designated maintenance/control-required medical devices under Article 2, Paragraph 8, of the Law, fifteen (15) years, provided that, for the medical devices of which the duration of use or the expiry date (hereinafter referred to as the “Expiry Date”) is required, the Expiry Date plus one year if it is longer than 15 years;
(2) For the Products related to the medical devices other than the designated maintenance/control-required medical devices, five (5) years, provided that, for the medical devices of which the Expiry Date is required, the Expiry Date plus one year if it is longer than 5 years.

(Retention of the Records)

Article 9 A Manufacturer, Etc. shall prepare the record under this Chapter and those which prove the compliance with the requirements and effective performance of the Quality Control and Supervision System so as to be easy to read and grasp and to be able to searched for and maintain them.

2. A Manufacturer, Etc. shall prepare a protocol setting forth control measures necessary for classification by labeling, maintenance, storage, protection, search, retention period and abolition of the records in preceding Paragraph.
3. A Manufacturer, Etc. shall maintain records under Paragraph 1 for the following period (for records of education and training, five (5) years) from the date of the record:
(1) For the Products related to the designated maintenance/control-required medical devices, fifteen (15) years, provided that, for the medical devices of which the duration of use or the expiry date (hereinafter referred to as the "Expiry Date") is required, the Expiry Date plus one year if it is longer than 15 years;
(2) For the Products related to the medical devices other than the designated maintenance/control-required medical devices, five (5) years, provided that, for the medical devices of which the Expiry Date is required, the Expiry Date plus one year if it is longer than 5 years.

Subchapter 3 Responsibilities of Controller/Manager

(Participation of Controller/Manager)
Article 10 A Controller/Manager shall demonstrate its active participation in the establishment, implementation and maintenance of the effectiveness of the Quality Control and Supervision System, by performing the duties below:
(1) To establish the Quality Policy;
(2) To ensure the Quality Goal to be established;
(3) To perform the Collation under Article 18, Paragraph 1;
(4) To ensure the system with sufficient access to the Resources;
(5) To ensure at manufacturing sites that the importance of the compliance with the provisions of Laws and Regulations and the requirements of a Manufacturer/Distributor, Etc. or other recipients of the Products (hereinafter referred to as a "Product Recipient") (hereinafter referred to as the "Recipient Requirements") be fully understood.

(Attention to Product Recipient)
Article 11 A Controller/Manager shall ensure that the Recipient Requirements be made clear and that the Products be in compliance with the Recipient Requirements.

(Quality Policy)
Article 12 A Controller/Manager shall ensure the Quality Policy be compliant with the requirements below:
(1) To be appropriate in light of the intent of the Manufacturer, Etc. about the quality of the

Products;
(2) To provide for active participation in compliance with the requirements and in maintenance of effectiveness of the Quality Control and Supervision System;
(3) To establish a framework for establishing and collating the Quality Goal;
(4) To be understood and known at manufacturing sites;
(5) To be used in Collation for maintenance of the appropriateness.

(Quality Goal)

Article 13 A Controller/Manager shall ensure that the Quality Goal (including those necessary for the compliance with the Product Requirements) be established in related departments of manufacturing sites.
2. A Controller/Manager shall ensure that the Quality Goal enable evaluation of the extent of achievement and be consistent with the Quality Policy.

(Plan of the Quality Control and Supervision System)

Article 14 A Controller/Manager shall ensure that an implementation plan be established for the Quality Control and Supervision System so that the System adverse be compliant with the provisions of Article 5 and the Quality Goal.
2. When a Controller/Manager intends to plan and implement a change in the Quality Control and Supervision System, it shall maintain that the System be satisfactory.

(Responsibilities and Authority)

Article 15 A Controller/Manager shall ensure that the responsibilities and authority of the department and personnel in charge be clearly defined, documented, and known at manufacturing sites.
2. A Controller/Manager shall set forth the mutual relationships among all personnel involved in the duties affecting the quality, those in charge of management and supervision, and those in charge of verification, that they be afforded sufficient independence to discharge their duties, and that they are given necessary responsibilities and authority.

(Responsible Engineer)

Article 16 A Controller/Manager shall assign the responsibilities and authority for the following duties to a responsible engineer under Paragraph 5 of Article 17 of the Law and to a person, as defined under Article 68-2, Paragraph 1 of the Law, who is in charge of management of manufacturing biologically-derived products (as defined under Article 2, Paragraph 9 of the Law), or a person in charge of approved foreign manufacturing site under Article 13-3, Paragraph 1 of the Law, or otherwise designated in advance by a Foreign Manufacturer for the Foreign

Manufacturer (hereinafter referred to collectively as the “Responsible Engineer”):
(1) To establish and implement the processes and ensure their effectiveness;
(2) To report to the Controller/Manager on the implementation of the Quality Control and Supervision System and on the necessity of its improvement;
(3) To ensure improvement in the understanding of the provisions of laws and the Recipient Requirements throughout the manufacturing site.

(Internal Communications)

Article 17 A Controller/Manager shall ensure that a mechanism be in place to adequately transmit information in a manufacturing site and that the communications be made with due attention to the effectiveness of Quality Control and Supervision System.

(Collation by Controller/Manager)

Article 18 A Controller/Manager shall perform the Collation (including evaluation of possible improvement in and necessity of any change of the Quality Control and Supervision System, the Quality Policy and the Quality Goal; hereinafter referred to as “Collation by Controller/Manager”) at intervals set forth in the plan under Article 14, Paragraph 1, in order to confirm the appropriateness and effectiveness maintained of the Quality Control and Supervision System in that manufacturing site.
2. A Manufacturer, Etc. shall prepare and maintain records of the results of the Collation by Controller/Manager.

(Process Input Information Related to Collation by Controller/Manager)

Article 19 A Manufacturer, Etc. shall perform the Collation by Controller/Manager with the Process Input Information described below:
(1) Results etc. of the internal audit;
(2) Opinions of Product Recipients;
(3) Implementing situation of the process and appropriateness for the Product Requirements of the Product;
(4) Situation of corrections (defined as the measures, in order to prevent the recurrence of the non-compliance (defined as the situation not in compliance with the requirements etc. under this Ordinance), of removing the causes of the non-compliance) and prevention measures (defined as the measures, in order to prevent the occurrence of the non-compliance; of removing the possible causes of the non-compliance);
(5) Measures taken considering the results of the former Collation by Controller/Manager;
(6) Change which may impact on the Quality Control and Supervision System;
(7) Suggestion for improvement of departments, personnel, etc.;

(8) Provisions of the Laws and Rules on Medicine newly enacted or amended after the preceding Collation by Controller/Manager.

(Process Output Information Related to Collation by Controller/Manager)

Article 20 A Manufacturer, Etc. shall gather the information related to the matter described below from the Collation by Controller/Manager and take necessary measures;

(1) Improvement necessary for maintaining the effectiveness of the Quality Control and Supervision System and the process;

(2) Improvement of Products related to Recipient Requirements;

(3) Resources necessary to ensure maintaining the appropriateness and effectiveness of the Quality Control and Supervision System.

Subchapter 4 Resource Administration and Supervision

(Securing Resources)

Article 21 A Manufacturer, Etc. shall identify and secure the Resources necessary for the following duties:

(1) To perform the Quality Control and Supervision System and maintain its effectiveness;

(2) To monitor the provisions of Laws and Regulations and Recipient Requirements.

(Personnel)

Article 22 A Manufacturer, Etc. shall allocate the duties affecting the quality of the Products to personnel whose ability is proved by satisfying the following requirements;

(1) To have been appropriately educated and trained;

(2) To have necessary skills and experiences.

(Education and Training)

Article 23 A Manufacturer, Etc. shall perform the following duties:

(1) To identify the ability required of the personnel in charge of the duties affecting the quality of the Products;

(2) To prepare a protocol to demonstrate the need for education and training for the personnel;

(3) To meet the requirements of the education and training the necessity of which has been demonstrated by the protocol under the preceding Paragraph;

(4) To assess the effectiveness of the measures in the preceding Paragraph;

(5) To ensure that the personnel recognize the relationship and importance of their duties for achievement of the Quality Goal and the means for contribution;

(6) To prepare and maintain the appropriate records on the education and training, skills and

experience of personnel.

(Operational Infrastructure)

Article 24 A Manufacturer, Etc. shall define, possess and maintain the Operational Infrastructure for the following duties necessary to achieve compliance with the Product Requirements, excluding the matters which are deemed not applicable in light of the content of the Product Requirements concerned:

(1) Work Areas, work rooms and any ancillary facilities including water supplies;

(2) Facilities related to the Process including software;

(3) Supporting services for manufacture of Products including transportation and communication.

2. When a Manufacturer, Etc. intends to manufacture the following Products, it shall possess and maintain the corresponding Operational Infrastructure:

(1) Products which require protection against dust, dampness, insects or rats: Facilities and structures for protection against dust, dampness, insects or rats;

(2) Products for which poisonous gases are used during the manufacturing process: Facilities necessary for disposal of the poisonous gases concerned;

(3) Products in liquid, sol, gel or powder forms (excluding the Products related to sterilized medical devices): Work rooms that meet the following requirements;

A. That they are built so as not to allow the passage of personnel other than those working in the work room concerned, provided that this provision shall not apply so long as there is no risk of contamination of the Product, Etc. by personnel other than those working in the work room;

B. That the entrance/exit (excluding emergency exit) are not facing directly the outside, provided that this provision shall not apply so long as the work rooms have buildings and facilities necessary to prevent contamination from the outside;

C. That the entrance/exit and windows can be closed;

D. That they are provided with structures and facilities for prevention of contamination by dust or microorganisms corresponding to the manufacturing process and the type of the Product, provided that this provision shall not apply so long as the functionalities of manufacturing facilities, etc. afford the equivalent effects;

E. That indoor drainage facilities, if any, have such a structure to prevent contamination of work rooms;

F. That they have facilities for a supply of water of the quality and quantity necessary for the type and the manufacturing process of the Product.

3. When the maintenance work of its absence for the Operational Infrastructure may affect the quality of the Product, a Manufacturer, Etc. shall prepare a requirements document for the maintenance work concerned (including the requirement on its frequency).

4. When a Manufacturer, Etc. has prepared the record on the maintenance work of the Operational Infrastructure, it shall maintain it.

(Working Environment)

Article 25 A Manufacturer, Etc. shall define, manage and supervise the working environment necessary to ensure compliance of the Product with the Product Requirements.

2. When the contact between personnel and the Products, Etc. or the working environment may have an adverse impact on the quality of the Product, a Manufacturer, Etc. shall prepare a document describing the requirements of the health conditions of personnel, the degree of cleanness, and the work clothes, shoes, caps and masks, provided that when the Products are cleaned according to Article 41, Paragraph 1, Item (1) or (2), this provision shall not apply to the Process prior to the cleaning process concerned.

3. When conditions of the working environment may have an adverse impact on the quality of the Product, a Manufacturer, Etc., shall prepare a document describing the requirements of conditions of the working environment concerned, and prepare a protocol or a task instruction for inspection and management of the conditions of the working environment concerned, provided that when the Products are cleaned according to Article 41, Paragraph 1, Item (1) or (2), this provision shall not apply to the Process prior to the cleaning process concerned.

4. A Manufacturer, Etc. shall require all personnel who work temporarily under special conditions of the working environment to receive education and training under Article 23, Item (3), provided that this provision shall not apply when they are under supervision of personnel who have received education and training.

5. A Manufacturer, Etc. shall prepare an implementation guide on control of contaminated or possibly contaminated Products Etc. (including the classification by proper labeling under Article 47, Paragraph 3), in order to prevent contamination of other Products, Etc., the working environment or personnel, except when the appropriateness of another method can be demonstrated in writing.

Subchapter 5 Product Realization

(Product Realization Plan)

Article 26 A Manufacturer, Etc. shall plan and establish the Process necessary for product realization (a series of duties for realization of Products performed by a Manufacturer, Etc. under the provisions in this Subchapter).

2. A Manufacturer, Etc. shall ensure compliance of the plan under the preceding Paragraph (hereinafter referred to as the “Product Realization Plan”) with the requirements of the Processes other than those related to the product realization.

3. Upon preparing a Product Realization Plan, a Manufacturer, Etc. hall appropriately define the following matters:
(1) The Quality Goal and Product Requirements of the Products concerned;
(2) Necessary Processes, Quality Control Supervision Documents and Resources which are unique to the Products concerned;
(3) Duties related to verification, Validation, supervision and measurement, and inspection which are unique to the Products concerned, and the criteria to determine release of the Product from the manufacturing site (hereinafter referred to as the “Product Release Decision Criteria”);
(4) Necessary records for verification of compliance of the Process related to product realization, and resulting compliance of the Product with the Product Requirements.
4. A Manufacturer, Etc. shall format the Process Output Information related to preparation of a Product Realization Plan in a form compatible with the working method of the manufacturing site.
5. A Manufacturer, Etc. shall prepare a requirements document related to risk management of Products in all Processes related to product realization.
6. A Manufacturer, Etc. shall prepare and maintain records of risk management.

(Clarification of Product Requirements)
Article 27 A Manufacturer, Etc. shall clarify the following matters as the Product Requirements:
(1) Recipient Requirements related to the Product concerned (including those related to release from manufacturing sites and post-release duties);
(2) Requirements necessary for the indicated or intended use or operation methods of the Product concerned, which the Product Recipient has not clearly indicated but are already known;
(3) Those provisions of Laws and Regulations which are related to the Product concerned;
(4) Other requirements that the Manufacturer, Etc. has defined.

(Collation of Product Requirements)
Article 28 Upon participation in the product supply, a Manufacturer, Etc. shall perform the Collation of the Product Requirements in advance.
2. Upon performing the Collation under the preceding Paragraph, a Manufacturer, Etc. shall confirm the following matters:
(1) That the Product Requirements related to the Product concerned are defined and documented;
(2) That when the requirements in the arrangement with a Product Recipient or in instructions from the Product Recipient differ from those indicated before, the differences concerned are clarified;
(3) That the manufacturing sites possesses the ability to meet the requirements under advance.
3. A Manufacturer, Etc. shall prepare and maintain records of results of the Collation under Paragraph 1, and of the measures taken based on the results.

4. When the Product Recipient does not indicate the requirements in writing, a Manufacturer, Etc. shall, on agreeing to supply Products to the Product Recipient, confirm the contents of the Recipient Requirements in advance.
5. When the Product Requirements are changed, a Manufacturer, Etc. shall have the related documents revised, and ensure that related personnel are fully informed of the revised Product Requirements changed well-known to the related personnel(s).

(Communicating Information with Product Recipient)

Article 29 A Manufacturer, Etc., shall define and implement an effective implementation guide for the communication with Product Recipient of the information related to the following matters:
(1) Communication of product information;
(2) Management of inquiries, confirmations, instructions, contacts, reports and agreements and any change thereof with a Product Recipient;
(3) Opinion (including complaints) of a Product Recipient;
(4) Issue and implementation of the Notice under Article 62, Paragraph 2.

(Design/Development Plan)

Article 30 A Manufacturer, Etc. shall prepare a protocol for design/development of Products.
2. A Manufacturer, Etc. shall prepare a plan for Design and Development (hereinafter referred to as “Design/Development Plan”) and control the Design and Development.
3. Upon preparing a Design/Development Plan, a Manufacturer, Etc. shall define the items described below:
(1) Steps of Design and Development;
(2) Collation, verification, Validation and design transfer (which shall mean the work to create specifications for the manufacturing process from the Process Output Information related to the Design and Development after completion of verification as to the compatibility of the Information with actual manufacturing) appropriate for each step of the Design and Development;
(3) Responsibilities and authority of the department and personnel of Design and Development.
4. A Manufacturer, Etc. shall manage and supervise the communication among those related to Design and Development in order to ensure effective transmission of information and clear demarcation of responsibilities and authority.
5. A Manufacturer, Etc. shall document the Design/Development Plan and appropriately update it according to the progress of the Design and Development.

(Process Input information on Design and Development)

Article 31 A Manufacturer, Etc. shall define the Input Information for the Process on Design and Development described below and prepare and maintain records of the Information:

(1) Product Requirements on indications, effects, performance and safety according to the intended methods of use or operation;
(2) Information which has been acquired from former and similar Design and Development and is applicable as the Process Input Information for the Design and Development concerned;
(3) Process Output Information on risk management under Article 26, Paragraph 5;
(4) Laws and Regulations;
(5) Any other requirements indispensable for the Design and Development.
2. A Manufacturer, Etc. shall collate and authorize the appropriateness of the Process Input Information on Design and Development.

(Process Output Information for Design and Development)

Article 32 A Manufacturer, Etc. shall retain the Process Output Information on Design and Development in the form which enables verification in reference to the Process Input Information on Design and Development.
2. Prior to authorizing to proceed from Design and Development to the next step of the Process, a Manufacturer, Etc. shall authorize the Process Output Information on Design and Development concerned.
3. A Manufacturer, Etc. shall maintain the Process Output Information on Design and Development in compliance with the conditions described below:
(1) That the Information is in compliance with the requirements as the Process Input Information on Design and Development;
(2) That the Information provides appropriate information for purchase, manufacture, and providing services;
(3) That the Information includes Product Release Decision Criteria;
(4) That the Information sets forth characteristics of the Product concerned which are indispensable for the safe and proper method of use or operation of the Product.
4. A Manufacturer, Etc. shall prepare and maintain records of the Process Output Information on Design and Development.

(Design and Development Collation)

Article 33 A Manufacturer, Etc. shall perform a systematic Collation the purposes of which are described below (hereinafter referred to as “Design and Development Collation”) according to the implementation guide provided for in the Design/Development Plan on appropriate step of the Design and Development:
(1) To assess whether or not the results of Design and Development are compatible with the requirements;
(2) In case were Design and Development encounters problems, to enable identification of the

problems concerned and to propose necessary measures.
2. A Manufacturer, Etc. shall require representatives of the department related to the step in the Design and Development subject to the Collation concerned and professionals in the Design and Development concerned to participate in the Design and Development Collation.
3. A Manufacturer, Etc. shall prepare and maintain records of the results of Design and Development Collation, and if necessary measures are taken on basis of the results of the Collation concerned, the records of those measures.

(Verification of Design and Development)

Article 34 In order to ensure compatibility of the Process Output Information with the requirements in the Process Input Information on the Design and Development concerned, a Manufacturer, Etc. shall perform the verification according to the implementation guide under the Design/Development Plan.
2. A Manufacturer, Etc. shall prepare and maintain the records of the results of the verification described on preceding Paragraph (including the records of the measures, if any, based on the results of the verification).

(Design/Development Validation)

Article 35 A Manufacturer, Etc. shall perform Validation of the Design and Development (hereinafter referred to as "Design/Development Validation" in this Article) according to the implementation guide provided on the Design/Development Plan in order to prepare the Products compliant with the requirements of performance, purpose of use, indications, effects, or intended methods of use or operation.
2. A Manufacturer, Etc. shall complete the Design/Development Validation prior to release the Products from the manufacturing site, provided, however, that when the Validation is possible only after the assembly or installation for use of the medical devices related to the Product concerned, it shall complete the Design/Development Validation by the delivery of the medical devise concerned to the user.
3. A Manufacturer, Etc. shall prepare and maintain records of the results of Design/Development Validation, and if necessary measures are taken on the results of the Validation concerned, the records of those measures.

(Control of Changes of Design and Development)

Article 36 When a Manufacturer, Etc. has changed Design and Development, it shall prepare the change identifiable and prepare and maintain records of that change.
2. Upon undertaking a change of Design and Development, a Manufacturer, Etc. shall appropriately perform and permit the Collation, verification and Validation in advance.

3. A Manufacturer, Etc. shall include in the extent of the Collation for a change of Design and Development assessment of the impact that the change may have on the Components, Etc. and the Products already from the manufacturing sites.
4. A Manufacturer, Etc. shall prepare and maintain records of the results of the Collation of the change under Paragraph 2, and if necessary measures are taken on the results of the Collation concerned, the records of those measures.

(Purchase Process)

Article 37 A Manufacturer, Etc. shall prepare a protocol to bring the purchased goods in compliance with the requirements for such goods (hereinafter referred to as the "Purchase Requirement").
2. A Manufacturer, Etc. shall provide for the method and degree of control applicable to the suppliers and purchased goods corresponding to the impact that the purchased goods concerned may have on the Process of Product Realization following the purchase, and the on Products.
3. A Manufacturer, Etc. shall assess and select suppliers of the purchased goods on the basis of the ability to supply the purchase goods according to the Purchase Requirements.
4. A Manufacturer, Etc. shall establish criteria for selection, evaluation and reevaluation of suppliers of purchase goods.
5. A Manufacturer, Etc. shall prepare and maintain records of the results of the assessment under Paragraph 3, and if necessary measures are taken based on the results of the assessment concerned, the records of those measures.

(Purchase Information)

Article 38 A Manufacturer, Etc. shall include in the information on purchase goods (hereinafter referred to as "Purchase Information") the following Purchase Requirements, unless it is able to show in writing that another method is appropriate:
(1) Requirements relating to release decision of purchased goods, protocols, processes and facilities and tools at the locations of the suppliers of the purchased goods;
(2) Requirements for confirming the staff qualification of the suppliers of the purchased goods;
(3) Requirements for Quality Control and Supervision System of the suppliers of the purchased goods;
(4) Any other matters necessary for purchase of goods.
2. On providing the Purchase Information to suppliers of the goods to be purchased, a Manufacturer, Etc. shall confirm the appropriateness of the Purchase Requirements concerned in advance.
3. A Manufacturer, Etc. shall ensure Traceability set forth in the protocol, in accordance with the provision of Article 48, Paragraph 2prepare and maintain documents and records describing

relevant Purchase Information after.

(Verification of Purchased Goods)

Article 39 A Manufacturer, Etc. shall define and perform testing and inspection and other measures necessary to ensure compliance of the purchased goods with the Purchase Requirements.

2. When verification of the purchased goods is to be performed at the location of supplier of purchased goods by a Manufacturer, Etc. or a Product Recipient, the Manufacturer, Etc. shall define the implementation guide on the verification concerned and methods release decisions by a supplier of purchased goods in the Purchase Information referred in the preceding article.

3. A Manufacturer, Etc. shall prepare and maintain records of the verification in the preceding Paragraph.

(Manufacture and Service Management)

Article 40 A Manufacturer, Etc. shall prepare and implement a plan of manufacture and service under the following control conditions, except for those which do not apply because of the characteristics at the relevant manufacturing site:

(1) That the information describing the specifics of the Products is available;

(2) That the protocols, requirements documents, statement of works, and protocols for reference samples required and measurement of reference samples are available;

(3) That facilities and tools are appropriate for the manufacture concerned;

(4) That facilities and tools for monitoring and measurement are available and such facilities and tools are used;

(5) That monitoring and measurement are implemented according to the provisions of Articles 57 to 59;

(6) That permit to proceed to the next Process stage, release decisions of the Products from the manufacturing site, shipment and post-shipment duties are made or performed according to the provisions of this Chapter;

(7) That tasks of packaging and labeling are performed in accordance with the protocols and other documents.

2. A Manufacturer, Etc. shall prepare and maintain records which enable tracing each Lot of the Products to the degree provided for in the protocol under the provision of Article 48, Paragraph 2, and identification of the produced quantity and the Products ready for release from the manufacturing site.

3. A Manufacturer, Etc. shall verify and approve records of each Lot prepared in accordance to the provision of preceding Paragraph.

(Management of Cleansing Products)

Article 41 A Manufacturer, Etc. shall prepare a requirements document for cleansing of the Products which fall either of the categories below:
(1) Those which are sterilized or used or operated after cleansing by the Manufacturer, Etc.;
(2) Those which are supplied without sterilization by the Manufacturer, Etc. concerned, and are sterilized or used or operated after the cleansing process;
(3) Those which are supplied by the Manufacturer, Etc. to be used or operated without sterilization, and for which cleansing during use or operation is important;
(4) Those for which the Manufacturer, Etc. remove Manufacturing Materials in the manufacturing process.

(Installation)
Article 42 When manufacturing the Products related to installation control-required medical devices under Article 93, Paragraph 1 of the Enforcement Rules, the Manufacturer, Etc. shall prepare a requirements document including the criteria for decisions of installation of the medical devices and verification of the installation concerned, except when it is able to demonstrate in writing that another method is appropriate.
2. A Manufacturer, Etc. shall provide the requirements document under the preceding Paragraph to the Manufacturer/Distributor, Etc.

(Ancillary Services)
Article 43 When performing the service ancillary to the manufacture of the Product (hereinafter referred to as “Ancillary Services”) is one of the requirements, a Manufacturer, Etc. shall prepare a protocol, a statement of work and a protocol for reference samples required and for measurement of the samples, in order to verify the compliance with the requirements concerned and for performance of the Services.
2. A Manufacturer, Etc. shall prepare and maintain records of the Ancillary Services performed.

(Manufacturing Control of Sterilized Products)
Article 44 A Manufacturer as defined under the Article 26, Paragraph 5, Item (2) or of a Foreign Manufacturer as defined under the Article 36, Paragraph 4, Item (2) of the Enforcement Rules (hereinafter referred to as the “Sterilized Medical Device Manufacturer, Etc.”) shall prepare and maintain records of process indices of that sterilization process for each sterilized Lot.
2. A Sterilized Medical Device Manufacturer, Etc. shall ensure that the records under the preceding Paragraph enable Traceability to each manufacturing Lot of the Products.
3. A Sterilized Medical Device Manufacturer, Etc. shall retain and maintain, in addition to those under Article 24, Paragraphs 1 and 2, the following Operational Infrastructure:
(1) Structures and facilities for prevention of contamination by dust or microorganisms, required

for corresponding to the manufacturing process of the Product, provided that this provision shall not apply so long as the equivalent effects are obtained from the functionalities of the manufacturing facilities, etc.;
(2) Adequate structures and facilities to maintain and control the degree of cleanness according to the manufacturing process of the Product for work rooms or working control areas (consisting of work rooms and passages, etc., which are controlled so as to maintain a consistent level of cleanness; the same hereinafter) for assembling and packaging the Products;
(3) Adequate facilities for water supplies for manufacturing of the quality and quantity needed corresponding to the manufacturing process of the Product for work rooms or working control areas for assembling and packaging the Products;
(4) Sterilizing devices needed for manufacturing corresponding to the type of the Product;
(5)Facilities and tools needed for controlling the sterilizing process corresponding to the type of the Product.

(Validation of Manufacturing Process, Etc.)

Article 45 A Manufacturer, Etc. shall perform the Validation of the Process of manufacturing and services, when the Process Output Information from the results of the relevant Process may not be verified by the subsequent monitoring and measurement, including the cases where defects can be found only after the Products are used or operated, or after the service is provided.
2. A Manufacturer, Etc. shall prove by the Validation that the results under the plan under Article 14, Paragraph 1 can be achieved through the Process of the preceding Paragraph.
3. A Manufacturer, Etc. shall establish an implementation guide on the following matters of the Process subject to the Validation under Paragraph 1, except for the matters which are not applicable because of the characteristics of the Process concerned:
(1) Criteria for Collation and authorization of the Process concerned;
(2) Authorization of the facilities and tools, and confirmation of the staff's qualifications;
(3) Methods and procedure;
(4) Requirements of the record under Article 9;
(5) Re-validation (Validation performed again when the manufacturing procedure is changed)
4. A Manufacturer, Etc. shall prepare a protocol for Validation of application of software to the manufacturing and service (including the change of the software or the change of the application) which may impact on the compliance of the Product without the Product Requirements.
5. A Manufacturer, Etc. shall perform Validation of application of the software under preceding Paragraph in advance of the initial use of the software concerned.
6. A Manufacturer, Etc. shall prepare and maintain records of Validation under Paragraph 1 through the preceding Paragraph.

(Validation of Sterilization Process)

Article 46 A Sterilized Medical Device Manufacturer, Etc. shall prepare a protocol for Validation of the sterilization process.

2. A Sterilized Medical Device Manufacturer, Etc. shall perform the Validation of the sterilizing process in advance of its initial use.

3. A Sterilized Medical Device Manufacturer, Etc. shall prepare and maintain records of the results of the Validation of the sterilizing process.

(Identification)

Article 47 A Manufacturer, Etc. shall classify Products through identification labeling by proper methods for all Processes of product realization.

2. A Manufacturer, Etc. shall prepare a protocol for classification by identification labeling under the preceding Paragraph.

3. A Manufacturer, Etc. shall prepare a protocol for the purpose of separating the Products returned to the Manufacturer, Etc. from compliant Products.

(Ensuring Traceability)

Article 48 A Manufacturer, Etc. shall prepare a protocol for ensuring the Traceability.

2. A Manufacturer, Etc. shall set forth the requirements for each Product of the extent of the Traceability and the required records necessary in the protocol under the preceding Paragraph.

3. When ensuring the Traceability is one of the Product Requirements, a Manufacturer, Etc. shall control, and prepare and maintain records of, classification by proper identification labeling.

(Ensuring the Traceability of Products Related to Designated Medical Devices)

Article 49 In cases where, because of the conditions of the Components, Etc. or the working environment, the Products related to designated medical devices may not be compliant with the Product Requirements, a Manufacturer, Etc. shall ensure the Traceability of the records of the conditions of the Components, Etc. and the working environment.

2. A Manufacturer, Etc. shall record the name and address of consignees of the Products related to designated medical devices.

(Identification of the Products' Conditions)

Article 50 A Manufacturer, Etc. shall classify Products by its conditions according to the requirements of monitoring and measurement, by identification labeling

2. A Manufacturer, Etc. shall maintain the classification of Products according to the conditions by identification labeling in all Processes of manufacturing, storage, installation and Ancillary Services of the Products, so that only the Products which passed the testing and inspection

(including the Products approved for release from the manufacturing site under special adoption (which shall mean to permit to use or operate, to permit to proceed to the following step of a Process, or to decide for release from the manufacturing site a Product not in compliance with the Product Requirements, after properly confirming that the Product does not prevent the manufacturing control or quality control) which are from the manufacturing sites, used or operated, or installed.

(Goods of Product Recipient)

Article 51 A Manufacturer, Etc. shall classify with identification labeling, verify and protect the goods which a Product Recipient to be used for or integrated to the Products, Etc..

2. In case that the goods the in preceding Paragraph are lost or damaged, or are found not appropriate for use, the Manufacturer, Etc. shall report to the Product Recipient, and prepare and maintain records.

(Storage of the Products)

Article 52 A Manufacturer, Etc. shall prepare a protocol or a statement of work for maintaining Products' compliance (including classification by identification labeling, handling, packaging, storage and protection) during the process from manufacturing to release from the manufacturing site.

2. A Manufacturer, Etc. shall prepare protocol or a statement of work for management of the Products whose expiration date is limited or those which need to be kept under special conditions.

3. A Manufacturer, Etc. shall control, and prepare and maintain records of, the special storage conditions under the preceding Paragraph.

(Management of Facilities and Tools)

Article 53 A Manufacturer, Etc. shall identify the monitoring and measurement necessary for verification of the Products' compliance with the Product Requirements, and facilities and tools for that monitoring and measurement.

2. A Manufacturer, Etc. shall prepare a practical protocol which enables the monitoring and measurement to be performed by a method compatible with the relevant requirements.

3. When necessary for ensuring the appropriateness of the results of the monitoring and measurement, a Manufacturer, Etc. shall, maintain the facilities and tools for the monitoring and measurement compliant with the following conditions:

(1) To be corrected or verified, at intervals designated in advance or before their use, by the method which ensures Traceability of the measurement standards (when there is no such standard, the basis for the correction or verification shall be recorded);

(2) That necessary adjustments or re-adjustments have been completed;

(3) To be classified with identification labeling which clearly shows stages of corrections;
(4) To be protected from the operation which might invalidate the results of the monitoring and measurement;
(5) To be protected from damage and deterioration during handling, maintenance and storage.
4. When the facilities and tools for the monitoring and measurement are found not compliant with the requirements of monitoring and measurement, a Manufacturer, Etc. shall assess and record the appropriateness of the results of such monitoring and measurement.
5. In the case of the preceding Paragraph, a Manufacturer, Etc. shall take appropriate measures for such facilities and tools for the monitoring and measurement and the Products affected by the non-compliance referred to in the preceding Paragraph.
6. A Manufacturer, Etc. shall prepare and maintain records of the results of correction and verification of the facilities and tools for the monitoring and measurement.
7. When software is used in the monitoring and measurement of the Product Requirements, a Manufacturer, Etc. shall, prior to its initial use, confirm, and reconfirm in necessary, that such software is applied to the monitoring and measurement as intended.

Subchapter 6 Measurement, Analysis and Improvement

(Monitoring and Measurement, Analysis and Improvement)

Article 54 A Manufacturer, Etc. shall prepare and implement a plan (including method of testing and inspection (including statistical methods for Product sampling) to be applied and the definition of the extent of its application) for the Process of monitoring and measurement, analysis and improvement for the following matters:
(1) Verification of the compliance of the Products;
(2) Ensuring and maintaining the compatibility and effectiveness of the Quality Control and Supervision System.

(Product Recipient's Opinion)

Article 55 A Manufacturer, Etc. shall monitor the information in respect of whether or not the manufacturing sites are in compliance with the Recipient Requirements as a part of monitoring and measurement of the implementation results of the Quality Control and Supervision System.
2. A Manufacturer, Etc. shall define the method of obtaining and using of the information of the preceding Paragraph.
3. A Manufacturer, Etc. shall prepare a protocol of a mechanism for collecting information from a Product Recipient for any early warning, and a protocol for providing Process Input Information concerning corrections and preventative measures, in respect of Product quality problems.
4. A Manufacturer, Etc. shall include the Collation of intelligence acquired after the release of the

Products from the manufacturing site in the information collection mechanism under the preceding Paragraph.

(Internal Audit)

Article 56 A Manufacturer, Etc. shall perform internal audit at intervals set forth in advance, for the purpose of determining whether the Quality Control and Supervision System is incompliance with the following requirements:

(1) That the System is compliant with the implementation guide under the Product Realization Plan, provisions of this Ordinance, and the requirements of such Quality Control and Supervision System;

(2) That the System is effectively implemented and maintained.

2. A Manufacturer, Etc. shall prepare a plan for implementing the internal audit considering the results and importance of the Process and areas subject to the audit, and the results of the preceding audit.

3. A Manufacturer, Etc. shall set forth the criteria, extent, frequency, and method of the internal audit.

4. A Manufacturer, Etc. shall ensure the objectivity and fairness in selecting the staff for the internal audit (hereinafter referred to as the “Internal Auditor”) and in performing the internal audit.

5. A Manufacturer, Etc. shall not allow an Internal Auditor audit his own work.

6. A Manufacturer, Etc. shall set forth in a relevant protocol the responsibilities, authority and requirements for planning and implementing a plan for the internal audit, reports of results of the internal audit, and for retention of the record.

7. A Manufacturer, Etc. shall require the Controller/Manager responsible for the area subject to the audit to take the measures without delay to remedy the non-compliance found and to remove causes of such non-compliance, to verify such measures, and to report the results of the verification.

(Monitoring and Measurement of the Process)

Article 57 For monitoring and measurement of a Process, a Manufacturer, Etc. shall apply a method of monitoring and measurement commensurate with the monitoring and measurement of such process.

2. A Manufacturer, Etc. shall demonstrate using the method of monitoring and measurement under the preceding Paragraph that the Process adverse achieve the goal of the plan under Article 14, Paragraph 1.

3. When the goal of the plan under Article 14, Paragraph 1 cannot be achieved, a Manufacturer, Etc. shall take appropriate measures for modification and rectification in order to ensure the

compliance of the Products.

(Monitoring and Measurement of the Products)

Article 58 A Manufacturer, Etc. shall monitor and measure characteristics of the Products in order to verify the compliance of the Products with the Product Requirements.

2. A Manufacturer, Etc. shall perform the monitoring and measurement under the preceding Paragraph at an appropriate step of the product realization process in accordance with the implementation guide under the Product Realization Plan and the protocol. under Article 40 Paragraph 1 Item (2).

3. A Manufacturer, Etc. shall prepare and maintain records of the results of the monitoring and measurement as evidence of the compliance with the Product Release Decision Criteria.

4. A Manufacturer, Etc. shall prepare and maintain records which identify the personnel who permit to proceed to the following step of a Process or who determine to release the Products.

5. Prior to completion of the monitoring and measurement based on the implementation guide under Product Realization Plan, a Manufacturer, Etc. may not permit to proceed to the following step, determine to release the Product from the manufacturing site, nor provide any service.

(Monitoring and Measurement of the Products Related to Designated Medical Devices)

Article 59 When monitoring and measurement under the preceding Article is performed for a Product related to designated medical devices, a Manufacturer, Etc. shall prepare and maintain records identifying the staff who performed the testing and inspection.

(Control of Non-Compliant Products)

Article 60 A Manufacturer, Etc. shall have the Products which are not compliant with the Product Requirements (hereinafter referred to as a “Non-Compliant Product”) classified by identification labeling and controlled so as to prevent unintentional use or operation or release from the manufacturing sites of such Non-Compliant Products.

2. A Manufacturer, Etc. shall provide, in a relevant protocol, for management of disposal of Non-Compliant Products and for related responsibilities and authority.

3. A Manufacturer, Etc. shall dispose Non-Compliant Products by any of the following way:

(1) To take measures to remove the non-compliance found;

(2) To permit use or operation, to permit to proceed to the next step of the Process, or to make a release decision from the manufacturing sit, as a case of special adoption;

(3) To take measures to disable the intended use, operation or application.

4. A Manufacturer, Etc. shall release the Product from the manufacturing site as a case of special adoption only when it is compliant with provisions of Laws and Regulations.

5. When a Non-Compliant Product is adopted as a case of special adoption, a Manufacturer, Etc.

shall prepare and maintain records which identify the staff who authorized such special adoption.
6. A Manufacturer, Etc. shall prepare and maintain records of details of the non-compliance and the measures taken for such non-compliance, including special adoption.
7. When a Non-Compliant Product is modified, a Manufacturer, Etc. shall re-verify the Product in order to demonstrate the compliance of such modified Product with the Product Requirements.
8. When any Non-Compliant Product is found after the delivery, or use or operation, a Manufacturer, Etc. shall take appropriate measures for the actual and possible effects.
9. If a Product needs to be re-processed, a Manufacturer, Etc. shall prepare a new statement of work for the Process under the same permission and approval mechanism as the preceding statement of work.
10. A Manufacturer, Etc. shall, upon granting the permission and approval in the preceding Paragraph, identify and document in advance all adverse effects to the Product from re-processing.

(Analysis of the Data)

Article 61 A Manufacturer, Etc. shall prepare a protocol to identify, collect and analyze the appropriate data (including data acquired from the monitoring and measurement and any other data from related sources), in order to demonstrate that the Quality Control and Supervision System is appropriate and effective, and to assess possible improvement of the effectiveness of such Quality Control and Supervision System.
2. A Manufacturer, Etc. shall obtain information related to the following matters from the analysis of the data of preceding Paragraph:
(1) Opinions of Product Recipients collected by the protocol prepared in accordance to the provision of Article 55 Paragraph 3;
(2) Compliance with the Product Requirements;
(3) Characteristics and tendency of Processes and Products, including those which may trigger any preventative measures;
(4) Suppliers of the purchased goods, etc.
3. A Manufacturer, Etc. shall prepare and maintain records of the result of the data analysis under the preceding two Paragraphs.

(Improvement)

Article 62 A Manufacturer, Etc. shall identify all matters which require any change, and shall implement such change, in order to maintain the appropriateness and effectiveness of the Quality Control and Supervision System, by making use of the Quality Policy, Quality Goal, results of the internal audit, data analysis, corrections, preventative measures and Collation by Controller/Manager.

2. A Manufacturer, Etc. shall prepare for ready use from time to time a protocol for issue and implementation of Notices, except when a Product Recipient issues and implements Notices and the Manufacturer, Etc. provides necessary information to the Recipient.
3. When a Manufacturer, Etc. investigated any complaint from a Product Recipient, it shall prepare and maintain records of anything related to such investigation.
4. When the investigation under the preceding Paragraph shows that one of the causes of the Product Recipient's complaint is the work done by a party other than the Manufacturer, Etc., it shall mutually communicate relevant information with such related party.
5. When a Manufacturer, Etc. decides not to take any corrective or preventative measures in respect of a complaint by a Product Recipient, it shall approve and record the reasons therefor.
6. A Manufacturer, Etc. shall prepare a protocol for Notifications to be issued to a Product Recipient when it is aware of any matter under Items of Article 253, Paragraph 2 of the Enforcement Rules.

(Corrections)

Article 63 A Manufacturer, Etc. shall take appropriate corrections corresponding to the impact of the non-compliance found.
2. A Manufacturer, Etc. shall prepare protocol for corrections which provides for the following requirements:
(1) Collation of non-compliance including complaints from a Product Recipient;
(2) Identification of causes of the non-compliance;
(3) Assessment of the necessity of the measures to ensure that the non-compliance do not recur;
(4) Identification and implementation of the necessary corrections including any update of the documents;
(5) Records of the results of, and the results of the corrections taken based on, any study of corrections;
(6) Collation of the corrections taken and their effectiveness.

(Preventative Measures)

Article 64 A Manufacturer, Etc. shall identify and take appropriate preventative measures according to the effect of possible problems.
2. A Manufacturer, Etc. shall prepare a protocol for preventative measures which provides for the following requirements:
(1) Identification of the possible non-compliance and its cause;
(2) Assessment of the necessity of preventative measures;
(3) Identification and implementation of the necessary preventative measures;
(4) Records of the results of, and of the preventative measures taken, of any study of preventative

measures;
(5) Collation of the preventative measures taken and their effectiveness.

Chapter 3 Manufacturing Control and Quality Control in Manufacturing Sites of a Medical Device Custodian/Manufacturer. Etc.

(Responsible Engineer)

Article 65 A responsible engineer shall perform the following duties:
(1) To supervise the duties of manufacturing control and quality control, to properly assess the results of manufacturing control and quality control, and to determine the release of Products from the manufacturing sites;
(2) Duties under Articles 68 and 71;
(3) To confirm that an internal audit is properly performed by the document provided in accordance with the provision of Article 70, Paragraph 1, Item (2).
2. A Medical Device Custodian/Manufacturer, Etc. shall ensure that a responsible engineer's work is not impeded.

(Documents on Manufacturing Control and Quality Control)

Article 66 A Medical Device Custodian/Manufacturer, Etc. shall prepare a Product Document stating the following matters for each Product and for each manufacturing sites:
(1) Storage;
(2) Packaging and labeling;
(3) Testing and inspection;
(4) Any other necessary matters.
2. A Medical Device Custodian/Manufacturer, Etc. shall prepare a protocol for manufacturing control, quality control, control of Non-Compliant Products, corrections, internal audit, education and training, and management of documents and records for each manufacturing site, in order to appropriately perform the duties under the following Article through Article 72.

(Manufacturing Control and Quality Control)

Article 67 A Medical Device Custodian/Manufacturer, Etc. shall perform appropriately the following duties in accordance with the Product Document and the protocol of manufacturing control and quality control:
(1) To prepare a statement of work that provides for instructions, warnings and any necessary matters for manufacturing control;
(2) To perform the work according to the statement of work under the preceding Item;
(3) To prepare records of manufacturing for each Testing and Inspection Unit;

(4) To confirm for each Testing and Inspection Unit that the packaging and labeling of the Product is appropriate, and to prepare and maintain records of the results of such confirmation;
(5) To appropriately store and accept/release each Testing and Inspection Unit of the Products and each Control Unit of the Labeling and Packaging Materials, and prepare and maintain the records thereof;
(6) To perform testing and inspection appropriately of each Control Unit of Labeling and Packaging Materials and prepare and maintain the records thereof;
(7) To periodically inspect and service the buildings and facilities (including correction of instruments), and prepare and maintain the records thereof;
(8) To confirm by records of testing and inspection, storage and release/acceptance that the manufacturing control and quality control is appropriately performed, and report the result to the responsible engineer in writing;
(9) To prepare and maintain records of manufacturing, testing and inspections, storage and release/acceptance;
(10) Any other necessary work.

(Control of Non-Compliant Products)

Article 68 A Medical Device Custodian/Manufacturer, Etc. shall provide, in the protocol of control of the Non-Compliant Products under Article 66 Paragraph 2, for the control of disposal of Non-Compliant Products, and for responsibilities and authority of the related department and staff.
2. A Medical Device Custodian/Manufacturer, Etc. shall require the responsible engineer to perform the following duties appropriately in accordance with the protocol:
(1) To classify and control the Non-Compliant Products with identification labeling so as to prevent such Non-Compliant Products from erroneous use or handover;
(2) To dispose Non-Compliant Products appropriately;
(3) To prepare and maintain records of the content of the non-compliance and the measures taken of the Non-Compliant Products;
(4) When any Non-Compliant Products is found after the release from the manufacturing site, to take appropriate measures to counter the actual and possible effects of such non-compliance.

(Correction)

Article 69 A Medical Device Custodian/Manufacturer, Etc. shall take appropriate measures for the effect of the non-compliance found.
2. A Medical Device Custodian/Manufacturer, Etc. shall provide, in the protocol of correction of the Non-Compliant Products under Article 66 Paragraph 2, for the following matters:
(1) Collation of non-compliance, including any complaint from a Product Recipient;

(2) Identification of the cause of the non-compliance;
(3) Assessment of the necessity of the measures to ensure such non-compliance does not reoccur;
(4) Identification and implementation of the necessary correction, including update of the documents;
(5) When any correction is studied, the results of such study and the results of the correction taken according to the result of such study;
(6) Collation of the correction taken and its effectiveness.

(Internal Audit)

Article 70 A Medical Device Custodian/Manufacturer, Etc. shall require the personnel designated in advance to perform the following duties in accordance with a relevant protocol:
(1) To perform an periodical internal audit of manufacturing control and quality control of the Products at manufacturing sites;
(2) To report the results of the internal audit to the responsible engineer in writing;
(3) To prepare and maintain records of the results of the internal audit.
2. When the results of the internal audit in the preceding Paragraph show the necessity of the improvement of manufacturing control and quality control, a Medical Device Custodian/Manufacturer, Etc. shall take necessary measures, and prepare and maintain records of such measures.

(Education and Training)

Article 71 A Medical Device Custodian/Manufacturer, Etc. shall require its personnel, designated in advance, to perform the following duties in accordance with a relevant protocol:
(1) To conduct systematically education and training of personnel regarding the manufacturing control and quality control;
(2) To report the results of the training in writing to the responsible engineer;
(3) To prepare and maintain records of the training.

(Management of Documents and Records)

Article 72 A Medical Device Custodian/Manufacturer, Etc. shall maintain at least one original or copy of the documents under this Ordinance for the following period (for documents of education and training, five (5) years) from the repeal of such documents, provided, however, that the documents used for the manufacturing or testing and inspection of Products may be made available only during the period of retention of records of the Products concerned under the following Paragraph:
(1) For the Products related to the designated maintenance/control-required medical devices, fifteen (15) years, provided that, for the medical devices of which the duration of use or the

expiry date (hereinafter referred to as the "Expiry Date") is required, the Expiry Date plus one year if it is longer than 15 years;

(2) For the Products related to the medical devices other than the designated maintenance/control-required medical devices, five (5) years, provided that, for the medical devices of which the Expiry Date is required, the Expiry Date plus one year if it is longer than 5 years.

2. A Medical Device Custodian/Manufacturer, Etc. shall maintain the records under this Chapter for the following period (for those on education and training, five (5) years) from the date of the record:

(1) For the Products related to the designated maintenance/control-required medical devices, fifteen (15) years, provided that, for the medical devices of which the duration of use or the expiry date (hereinafter referred to as the "Expiry Date") is required, the Expiry Date plus one year if it is longer than 15 years;

(2) For the Products related to the medical devices other than the designated maintenance/control-required medical devices, five (5) years, provided that, for the medical devices of which the Expiry Date is required, the Expiry Date plus one year if it is longer than 5 years.

Chapter 4 Manufacturing Control and Quality Control in Manufacturing Sites of Biological Medical Device Manufacturer, Etc.

（Operational Infrastructure of Manufacturing Sites of a Manufacturer, Etc. of Designated Biological Medical Devices, Etc.）

Article 73 A Manufacturer, Etc of Products related to designated biologically derived products under Article 2, Paragraph 10 of the Law (hereinafter referred to as "Designated Biological Medical Devices"), medical devices designated by the Minister of Health, Labor and Welfare pursuant to Article 43, Paragraph 2 of the Law, or Cellular/Tissue Based Medical Devices (hereinafter referred to collectively as "Designated Biological Medical Devices Etc.") shall ensure that the Operational Infrastructure satisfy the following requirements, in addition to those under Article 24 Paragraph1 and 2, and Article 44 Paragraph3:

(1) Facilities to supply distilled water, etc. for manufacturing a Product shall have a structure necessary to prevent contamination of distilled water, etc. by foreign articles or microorganisms;

(2) Work areas satisfy the following requirements:

A. Work rooms or work control areas shall be equipped with structures and facilities which will maintain and control the degree of cleanness according to the manufacturing process of the Product;

B. Work rooms for the drying and sterilization operations of washed containers shall be

used exclusively for that purpose, provided that this provision shall not apply so long as there is no risk of contamination of washed containers;

C. Work areas shall be equipped with the following facilities in a room distinctly separated from others, except for those found unnecessary for manufacturing of the Product depending on the type, manufacturing method, etc. of the Product:

(i) Storage facilities of microorganisms;

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

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

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

(v) Facilities for cultivating microorganisms;

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

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

D. The ceiling, wall and floor of the room with such facilities as indicated in C (ii) through (iv) and (vi) shall be washable and disinfectable structure;

E. Rooms with such facilities as indicated in C (ii) through (iv) and (vi) shall meet the following requirements:

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

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

(3) Work Areas of Products related to Cellular/Tissue Based Medical Device shall satisfy the following requirements;

A. The area for receipt of source materials, processing, storage of Products, etc. shall be separated from other area for manufacturing the Products related to Cellular/Tissue Based Medical Device;

B. The area for receipt of source materials, processing, storage of Products, etc. shall be equipped with structure and facilities necessary for the process.

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

(Documents on Manufacturing Control and Quality Control)

Article 74 When a Biological Medical Device Manufacturer, Etc. manufactures Products related to a Biological Medical Device, Etc., it shall prepare Product Documents for each manufacturing site, setting forth the following items for each Product:

(1) The name, essence, properties, ingredients and their contents, and other specifications of the substance obtained from humans, animals, plants or microorganisms which are used as Components, Etc.;

(2) Specifications of animals (including a Donor Animal; hereinafter referred to as an "Animal Used") to be used in manufacturing or in testing and inspection (including methods of breeding and management);

(3) Other necessary matters.

(Process Control)

Article 75 A Biological Medical Device Manufacturer, Etc. shall, when it manufactures Products related to a Biological Medical Device, Etc., manage appropriately the following duties for process control of Products related to a Biological Medical Devices, Etc., in accordance with the Product Documents and a relevant protocol, in addition to the duties under the preceding Article:

(1) To require personnel, who have been designated according to the type of duties in advance, to perform the following duties:

A. When the source material or a Product is inactivated, or microorganisms, etc. contained in the source materials or the Product are inactivated or eliminated during the manufacturing process, to take measures necessary to prevent contamination from the source material or the Product that has not been inactivated or virus-eliminated;

B. When biochemical technology such as fermentation, etc. is used during the manufacturing process, to monitor continuously the temperature, hydrogen-ion index and other items which are necessary for the control of manufacturing process;

C. When column chromatography equipment, etc. is used during the manufacturing process, to take any measures required to prevent contamination of the equipment by microorganisms, etc., and to measure end toxins, as necessary;

D. When a culture method is used whereby culture media are continuously supplied to an incubation tank and culture liquid is continuously discharged during the manufacturing process, to take any measures required to maintain culture conditions in the incubation tank during the incubation period;

E. To perform Validation in the following cases and prepare and maintain the records thereof:

(i) When the Biological Medical Device Manufacturer, Etc. commences manufacturing of Products related to a Biological Medical Device, Etc. at the manufacturing site;

(ii) When there are changes made in Operating Procedures, Etc., which have a significant impact on the quality of Product related to a Biological Medical Device, Etc.;

(iii) When Validation is otherwise necessary in order to perform properly the manufacturing control and the quality control of a Product related to a Biological Medical Device, Etc.

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

G. To perform the following duties related to the sanitation control of personnel:

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

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

H. To perform the following duties related to the sanitation control of personnel working in the Clean Area or in the Aseptic Area:

(i) To require personnel engaged in manufacturing to wear work clothes, shoes, caps and masks that have been disinfected;

(ii) To require personnel to undergo medical checkups at intervals not exceeding six (6) months in order to confirm that they do not have diseases that are suspected to contaminate source materials or a Product by microorganisms, etc.;

(iii) When personnel are under such conditions that are suspected to contaminate source materials or a Product with microorganisms, etc. (including infectious diseases of skin or hair, common cold, injuries, or symptoms such as diarrhea or fever for unidentified causes), to require them to report to that effect.

I. To breed a Animal Used (only those used in manufacturing) under constant and proper care, and not to use an animal with infectious diseases or otherwise not appropriate for use in manufacturing through monitoring of their physical conditions;

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

K. To prepare and maintain the following records in handling of microbial strains for use in manufacturing:

(i) Name of microorganisms and the number assigned to each container;

(ii) Date of assignment, the name and address of a person who assigned (in case of corporations, the name and address);

(iii) Biological properties and date of testing;

(iv) Status of subculture.

L. To confirm that source materials derived from organisms (excluding plants) for use in manufacturing of a Biological Medical Device (hereinafter referred to as "Biologically Derived Source Materials") appropriately satisfy the Product Documents of the Product, and prepare and maintain the records of confirmation;

M. To retain records of the matters which the Minister of Health, Labor and Welfare requires to be recorded, either by itself or conclude an arrangement with an enterprise, etc. who collects materials of the Biologically Derived Source Materials (hereinafter referred to as a "Source Material Collecting Enterprise, Etc.") so that the records shall be maintained appropriately by the Source Material Collecting Enterprise, Etc., in respect of the Biologically Derived Source Material for use in manufacturing of a Biological Medical Device.

(2) To prepare and maintain the records under items E, L and M for each Lot.

2. A Biological Medical Device Manufacturer, Etc. shall, when it manufactures a Product related to a Cellular/Tissue Based Medical Device, manage appropriately the following duties related to the process control of the Product in accordance with the Product Document and a relevant protocol, in addition to the duties as defined under the preceding Paragraph:

(1) To require personnel who have been designated in advance to perform the following duties:

A. To take necessary measures to prevent mixture and cross-contamination of the cells or tissues collected from different Donors or Donor Animals;

B. To confirm, at the time of receipt of cells or tissues which will be used as source materials, from records of the following matters that the cells or tissues appropriately satisfy the Product Document of the Product, and prepare and maintain the records of the confirmation:

(i) Facilities where the cells or tissues were collected;

(ii) Date on which the cells or tissues were collected;

(iii) When the cells or tissues are derived from humans, the diagnosis of the Donor through their health check-up or testing for the Donor screening (the decision as to, from the results of the health check-up and testing of a Donor, whether or not such Donor is fully eligible to provide their cells or tissues as source materials of the Cellular/Tissue Based Medical Device);

(iv) When the cells or tissues are derived from animals, the receipt of the Donor Animal, as well as conditions of the testing and inspection and breeding and management of such animals for the Donor screening (the decision as to, from the results of the testing and inspection, and breeding and management of the Donor Animal, whether or not such Donor Animal is fully eligible to provide their cells or tissues as source materials of the Cellular/Tissue Based Medical Device);

(v) History of collecting the cells or tissues;

(vi) Matters necessary for ensuring the quality of Products related to the

Cellular/Tissue Based Medical Device, in addition to those in Sub-items A through E. above.

C. To take necessary measures to prevent contamination by microorganisms during the collection, and to prepare records of the measures, in collecting the cells or tissues as source materials from a Donor Animal;

D. When personnel are under any of the following conditions, not to allow the personnel to work in the Clean Area or in the Aseptic Area:

(i) When personnel are under physical conditions which may lead to contamination of a source material or a Product with microorganisms, etc.;

(ii) When personnel have treated microorganisms which may contaminate cells or tissues immediately prior to their collecting or processing.

E. To collect information, for each Product, the name of the destination facilities, the date of release and Lots, and to prepare records thereof;

F. To take necessary measures of delivery to ensure the quality of a Product, and to prepare records of the measures taken;

G. To prepare records of breeding and management of Donor Animals after their acceptance.

(2) To prepare and maintain records in Sub-items B, C, F and G in the preceding Paragraph by Lot, and by Product for the records of Sub-item E.

3. A Biological Medical Device Manufacturer, Etc. shall maintain records of a Biological Medical Device in the preceding two Paragraphs so as to enable confirmation of a series of records, from those of Biologically Derived Source Materials used in manufacturing to those of a Product manufactured therefrom.

(Testing and Inspection)

Article 76 A Biological Medical Device Manufacturer, Etc. shall, when it manufactures a Product related to Biological Medical Devices, Etc., manage appropriately the following duties related to the testing and inspection of the Product in accordance with the Product Document and a relevant protocol, in addition to the duties under the preceding Article, :

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

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

(3) To breed Animals Used (for testing and inspection) under constant and proper care, and not to use an animal with infectious diseases or otherwise not appropriate for use through monitoring of their physical conditions;

(4) To dispose of all articles (limited to those contaminated during the testing and inspection) that

have been contaminated by microorganisms and animal carcasses so as not to cause hazards to the health and hygiene;

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

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

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

C. Biological properties and date of testing;

D. Status of subculture.

(6) With respect to Products related to a Designated Biological Medical Devices, Etc. under Article 2, Paragraph 10 of the Law, to retain as reference samples from each Lot of the Product (in the case of a Designated Biological Medical Device, Etc. not constituting a Lot, from the Biologically Derived Source Materials used in manufacturing of the Product by each manufacturing number of the Product or by Lot of such Biologically Derived Source Materials), at least twice the quantity needed for all required testing and inspection, for an appropriate period from the date of manufacturing (in the case of the Product related to a Designated Biological Medical Devices, for ten (10) years from the Expiry date), under proper conditions, provided that this provision shall not apply to a Product related to a Designated Biological Medical Device not constituting a Lot under, for which the Manufacturer, Etc. has concluded an arrangement with the Source Material Collecting Enterprise, Etc., that the Enterprise, Etc. shall retain the reference samples for that period, or a Product related to a medical device other than Designated Biological Devices which does not constitute a Lot, and that, for Products related to Designated Biological Medical Devices, Etc. which constitute Lots, retention of the Products may be substituted by retention of the Biologically Derived Source Materials which were used to manufacture the Products after three (3) years (or the Expiry Date plus one year if it is longer than 3 years for Products related to medical devices for which an Expiry Date is mandatory).

2. A Biological Medical Device Manufacturer, Etc. shall, when it manufactures Products related to a Cellular/Tissue Based Medical Device, manage the following duties of testing and inspection of the Products in accordance with the Product Document and a relevant protocol, in addition to the duties as defined under the preceding Paragraph:

(1) To require personnel designated in advance to perform testing and inspection at the time of or after receipt of Donor Animals and other necessary duties, according to the type of duties;

(2) To prepare and maintain records of duties under the preceding Paragraph.

3. A Biological Medical Device Manufacturer, Etc. shall maintain the records in the preceding two Paragraphs so as to enable confirmation of a series of records, from those of Biologically Derived Source Materials used in manufacturing to those of a Product manufactured with such Materials.

(Education and Training)

Article 77 A Biological Medical Device Manufacturer, Etc. shall, when it manufactures a Product related to a Biological Medical Devices, perform the following duties in accordance with a relevant protocol, in addition to the duties as defined under other provisions:

(1) To conduct education and training of personnel engaged in the manufacturing or testing and inspection of a Product related to Biological Medical Devices in respect of microbiology, medicine and veterinary medicine, etc.;

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

(Management of Documents and Records)

Article 78 A Biological Medical Device Manufacturer, Etc. shall maintain at least one original or copy of documents and records under this Chapter for the following period (for documents of education and training, five (5) years) from the date of repeal, provided, however, that the documents used for the manufacturing or testing and inspection of Products may be made available only during the period of retention of records of the Products concerned under the following Paragraph:

(1) For the Products related to a Designated Biological Medical Device or a Biological Medical Device manufactured from human blood as raw materials (those materials from which source materials sued for manufacturing (including those used in the manufacturing process) are derived), a period of the Expiry Date plus thirty (30) years;

(2) For the Products related to a Biological Medical Device (excluding those under Item (1) above) or a Cellular/Tissue Based Medical Device (excluding those under Item (1) above), a period of the Expiry Date plus ten (10) years.

2. A Biological Medical Device Manufacturer, Etc. shall maintain records under this Chapter for the period defined under the preceding Paragraph, Item (1) or (2), from the date of the records (for the documents of education and training, five (5) years).

(Exceptions of Retention of Records)

Article 79 Notwithstanding the provisions in this Chapter, a Biological Medical Device Manufacturer, Etc. , Etc shall maintain records of Products related to Biological Medical Devices designated by the Minister of Health, Labor and Welfare, for a period designated by the Minister of Health, Labor and Welfare, provided, however that this provision shall not apply where an arrangement is concluded with a Source Material Collecting Enterprise, Etc. under which the records shall be maintained appropriately by the Enterprise, Etc., for the required period.

Chapter 5 Manufacturing Control and Quality Control in Manufacturing Sites of In Vitro Diagnostics Manufacturer, Etc.

(Application Mutates mutandis)

Article 80 The provisions in Chapters 2 and 3 (excluding Article 8, Paragraph 4, Item (1) and (2), Article 9, Paragraph 3, Items (1) and (2), Article 24 Paragraph 2, Article 42, Article 44, Article 46, Article 49, Article 59, Article 72, Paragraph 1, Items (1) and (2), and Paragraph 2, Items (1) and (2)) shall apply mutates mutandis to manufacturing control and quality control of an In Vitro Diagnostic Manufacturer, Etc. In this case, a "manufacturing control of designated medical devices as defined under Article 77-5, Paragraph 1 of the Law" in Article 4, Paragraph 1 shall read "manufacturing control," and "the details of the duties, if applicable" in Article 6, Paragraph 3 shall read "the details of the duties," and "the following period (for the documents of education and training, five (5) years)" in Article 8, Paragraph 4 shall read "five (5) years (the Expiry Date plus one year if the Expiry Date is required of such in vitro diagnostic drug and the Expiry Date plus one year is longer than 5 years, except for those on education and training)," and "for the following period (for records of education and training, five (5) years)" in Article 9, Paragraph 3 shall read "five (5) years (the Expiry Date plus one year if the Expiry Date is required of such in vitro diagnostic drug and the Expiry Date plus one year is longer than 5 years, except for those on education and training)," a "responsible engineer under Paragraph 5 of Article 17 of the Law" in Article 16 shall read a "drug manufacturing manager under Paragraph 3 of Article 17 of the Law," a "responsible engineer" in Article 16 shall read a "manufacturing manager," "Paragraph 2" in Article 62, Paragraph 6 shall read "Paragraph 1," a "responsible engineer" in Article 65 shall read a "manufacturing manager," a "responsible engineer" in Article 67 shall read a "manufacturing manager," a "responsible engineer" in Article 68 shall read a "manufacturing manager," a "responsible engineer" in Article 70 shall read a "manufacturing manager," a "responsible engineer" in Article 71 shall read a "manufacturing manager," and "the following period (for those on education and training, five (5) years)" in Article 72, Paragraph 1 shall read "five (5) years (the Expiry Date plus one year if the Expiry Date is required of such in vitro diagnostic drug and the Expiry Date plus one year is longer than 5 years, except for those on education and training," and "the following period (for those on education and training, five (5) years)" in Article 72, Paragraph 2 shall read "five (5) years (the Expiry Date plus one year if the Expiry Date is required of such in vitro diagnostic drug and the Expiry Date plus one year is longer than 5 years, except for those on education and training."

Supplementary Rules

(Enforcement Date)

Article 1 This Ordinance shall be enforced as from April 1, 2005.