(4) Not conforming : Does not fall under any of the above.

5. Evaluation on relevance to Article 23-22, Paragraph 4, Item 1 of the Act (including the cases where applied mutatis mutandis pursuant to Article 23-24, Paragraph 3); the same shall apply hereinafter) of the Act is as follows:

(1) Manufacturing sites corresponding to "conforming": buildings and facilities shall not be those that fall under Article 23-22, Paragraph 4, Item 1 of the Act.

(2) Manufacturing sites corresponding to "generally conforming": For items that were categorized as B in the evaluation results of conformity status for each Article, instructions for improvement shall be provided in documents to persons subject to conformity inspection, and a report on improvement results or improvement plan shall be required. In this case, the conformity status may be re-evaluated as "conforming" by having the persons subject to conformity inspection submit a detailed report on improvement results or a report on a specific improvement plan within the period until the next renewal of their license (in case of new license application, before disposition upon such application), and may be handled in accordance to the above section "(1)". However, if neither a detailed report on improvement results nor a specific improvement plan is submitted within the period until the next renewal of their license, a detailed report on improvement results shall be submitted within 30 days from the day of completing the improvement. Onsite inspection shall be conducted when necessary if the improvement status requires confirmation.

(3) Manufacturing sites corresponding to "require improvement": For items that were categorized as B in the evaluation results of conformity status for each Article, the provision in section "(2)" shall apply. For items that were categorized as C in the evaluation results of conformity status for each Article, a detailed report on improvement results or a report on a specific improvement plan shall be submitted from the persons subject to inspection. If improvement is completed within the period until the next renewal of their license (in case of new license application, before disposition upon such application), the conformity status may be re-evaluated as "conforming", and the manufacturing site may be handled in accordance to the above section "(1)". However, if improvement is not completed, the conformity status shall, in principle, be re-evaluated as "not conforming", and shall be handled in accordance to the below section "(4)".

(4) Manufacturing site corresponding to "not conforming": Buildings and facilities shall fall under Article 23-22, Paragraph 4, Item 1 of the Act. However, items that were categorized as D in the evaluation results of conformity status for each Article may be handled in the same manner as in items that were categorized as C in the above section "(3)", only if improvement is expected to be completed promptly.

Chapter 3 GCTP Ordinance

Section 1 Summary

1. The GCTP Ordinance is prescribed as the standards for manufacturing control or quality control at manufacturing sites of cellular and tissue-based products pursuant to the provision of Article 23-25, Paragraph 2, Item 4 of the Act (including the cases where applied mutatis mutandis pursuant to Article 23-37, Paragraph 5).

2. Provisions pertaining to buildings and facilities in which their necessity is judged according to each product shall be prescribed in the provisions on buildings and facilities pertaining to Article 10 of the GCTP Ordinance.

3. Matters required by the Articles of GCTP Ordinance shall apply to the extent required as a manufacturing site in appropriately managing the manufacturing process (including storage) conducted at the manufacturing site.

4. For operations pertaining to quality control at manufacturing sites of manufacturers in the category of Article 137-9, Item 2 and Article 137-19, Item 2 of the Ordinance for Enforcement (hereinafter referred to as "manufacturing sites in the category of packaging, etc.") where only storage of products, etc., and packaging and labeling materials pertaining to cellular and tissue-based products of the same manufacturers is conducted, the quality division of other manufacturing sites of the same manufacturers at which the product is manufactured, etc., may conduct this operation as long as there is no impediment.

5. Testing at a manufacturing site shall be conducted on the manufacturing process (including storage) conducted at this manufacturing site. Although products shall, in principle, be released from the manufacturing site after their testing results and product release have been determined, products may be released before testing results have been obtained for those that are released from the manufacturing site to the manufacturing site in the category of packaging, etc. where only storage of products, etc., or packaging and labeling materials of the same manufacturers is conducted. In this case, a comprehensive evaluation shall be made on the two manufacturing sites for release acceptance at the manufacturing site in the category of packaging, etc. For products imported from foreign manufacturing sites, testing (shall not be a substitute of the manufacturing process at the foreign manufacturing site) may be conducted at a domestic manufacturing site to

confirm that the manufacturing process is appropriately conducted at the foreign manufacturing site.

6. Other than the GCTP Ordinance, appropriate manufacturing control and quality control at manufacturing sites shall be achieved based on the GQP Ordinance, Regulations for Buildings and Facilities, and other relevant laws and regulations.

Section 2 Commentary

1. Article 1 (Purpose)

(1) This Article shall be a specification to indicate that the GCTP Ordinance has been prescribed as the standards for manufacturing control and quality control methods at manufacturing sites prescribed in Article 23-25, Paragraph 2, Item 4 of the Act (including mutatis mutandis application of Article 23-37, Paragraph 5).

Pursuant to Article 1-2 (attached Table No. 2) of the Order, "cellular and tissue-based products" shall be prescribed as products that are within the extent of those indicated below.

A. Human cell therapy products

(a) Human somatic cell therapy products

(b) Human somatic stem cell therapy products

(c) Human embryonic stem cell therapy products

(d) Human induced pluripotent stem cell therapy products

B. Animal cell therapy products

(a) Animal somatic cell therapy products

(b) Animal somatic stem cell therapy products

(c) Animal embryonic stem cell therapy products

(d) Animal induced pluripotent stem cell therapy products

C. Gene therapy products

(a) Plasmid vector products

(b) Viral vector products

(c) Gene therapy products

2. Article 2 (Definitions)

(1) "Products" shall mean those that have gone through a manufacturing process at manufacturing sites (including those that were manufactured in an intermediate manufacturing process and which will become products by going through a manufacturing process that follows (hereinafter referred to as "intermediate products"); the same shall apply hereinafter).

(2) "Packaging and labeling materials" shall mean the container, package, and labeling (including the package insert; the same shall apply hereinafter) of a product. "Package" shall mean the packaging materials and shall not include the shipping container. "Labeling" shall mean the so-called label and the package insert.

(3) "Lot" shall mean a group of products and raw materials that were manufactured to have homogeneity by going through a series of manufacturing processes within a manufacturing period. "Raw materials" shall mean those used in manufacturing of products pertaining to cellular and tissue-based products (excluding packaging and labeling materials and intermediate products; including those that will not be contained in the product).

(4) "Control unit" shall mean a group of packaging and labeling materials in which their uniformity has been confirmed.

(5) "Validation" shall mean to verify that buildings and facilities, procedures, processes, and other manufacturing control and quality control methods at a manufacturing site (hereinafter referred to as "manufacturing procedures, etc.") will provide expected results, and to document these details.

(6) "Verification" shall mean to confirm that a manufacturing procedure has brought about expected results and to document these details.

(7) "Controlled clean area" shall mean the place for conducting manufacturing operations (hereinafter referred to as "work area") where preparation of products, etc., (excluding those that require aseptic handling) is conducted, and where containers, etc., prior to sterilization come in contact with the air within the work area. "Work area" stated here shall include offices that directly connect to, for example, testing rooms and work areas for manufacturing. "Preparation" shall mean such operations as measuring weights, preparing liquids, cultivating, purifying,

filling, and sealing in which products, etc., come in contact with the air within the work area.

(8) "Aseptic operation area" shall mean the place within the work area where preparation is conducted for products, etc., that require aseptic handling; where sterilized containers, etc., come in contact with the air within the work area; and where aseptic operation, such as aseptic studies, is conducted.

(9) "Donor" shall mean the person who offers cells or tissues intended for use as raw materials of cellular and tissue-based products (excluding those pertaining to bodies of persons with brain death prescribed in Article 6, Paragraph 2 of the Organ Transplantation Law (Law No. 104 of 1997).

(10) "Donor animal" shall mean the animal that offers cells or tissues intended for use as raw materials of cellular and tissue-based products.

(11) "Quality risk management" shall mean to conduct evaluations, controls, etc., in accordance to appropriate procedures on the risk of product quality (hereinafter referred to as "quality risk") for the entire process from initial product development to termination of marketing.

(12) "Review" shall mean to determine the validity and efficacy in terms of achieving established targets.

(13) The meanings of other terms in this Ministerial Ordinance shall be as follows:
"Calibration of measuring equipment" shall mean to determine the relationship between the true value and the value indicated on an instrument using an appropriate standard device, standard sample, etc., with the consideration of necessary precision.

3. Article 3 (Scope)

(1) Paragraph 1 prescribes that marketing authorization holders of cellular and tissue-based products or the appointed foreign marketing authorization holders of cellular and tissue-based products are required to have manufacturers conduct manufacturing control and quality control at their manufacturing sites, pursuant to the provisions of this Ministerial Ordinance as a requirement for marketing approval of cellular and tissue-based products.

(2) Paragraph 2 prescribes that manufacturers of products pertaining to cellular and tissue-based products are required to conduct manufacturing control and quality control prescribed in Article 137-58 of the Ordinance for Enforcement at their manufacturing sites, pursuant to the provisions of this Ministerial Ordinance.

(3) Paragraph 3 prescribes that manufacturers of products pertaining to cellular and tissue-based products for export prescribed in Article 80, Paragraph 3 of the Act are required to conduct manufacturing control and quality control at their manufacturing sites, pursuant to the provisions of this Ministerial Ordinance.

4. Article 4 (Quality Risk Management)

(1) This Article prescribes that manufacturers are required to consider using quality risk management in their manufacturing control and quality control.

(2) Quality risk management shall be considered for its proactive use in identifying, analyzing, evaluating, reducing, etc., quality risks as one of the factors that compose appropriate manufacturing control and quality control of products pertaining to cellular and tissue-based products.

(3) Methodology, utility, etc., of quality risk management shall be in reference to such as those indicated in the "Quality Risk Management" (PFSB/ELD Notification No. 0901004 and PFSB/CND Notification No. 0901005, dated September 1, 2006).

5. Article 5 (Manufacturing Division and Quality Division)

(1) This Article prescribes that manufacturers are required to place a manufacturing division and a quality division at each manufacturing site, under the supervision of the manufacturing supervisor of cellular and tissue-based products prescribed in Article 23-34, Paragraph 3 of the Act (or the responsible person at the manufacturing site of a foreign manufacturer of regenerative medicine products that has received accreditation pursuant to Article 23-24, Paragraph 1 of the Act, or the person that has been designated in advance by the foreign manufacturer of regenerative medicine products) (hereinafter collectively referred to as the "manufacturing supervisor").

(2) The quality division shall be independent from the manufacturing division. The manufacturing supervisor shall not concurrently serve as the person responsible for

the manufacturing division, but may concurrently serve as the person responsible for the quality division.

(3) For operations pertaining to quality control at manufacturing sites in the category of packaging, etc. where only storage of products, etc., and packaging and labeling materials pertaining to cellular and tissue-based products of the same manufacturers is conducted, the quality division of other manufacturing sites of the same manufacturers at which the product is manufactured, etc., may conduct this operation as long as there is no impediment.

6. Article 6 (Manufacturing Supervisor)

(1) This Article shall prescribe matters regarding operations that manufacturing supervisors are required to conduct.

(2) The phrase "to supervise activities for manufacturing control and quality control (hereinafter referred to as the "manufacturing and quality control duties")" indicated in Paragraph 1, Item 1 shall mean that manufacturing supervisors have the final authority and responsibility regarding manufacturing/quality control operations and shall supervise these operations.

(3) The phrase "make efforts for the effective performance of the duties" indicated in Paragraph 2 means that manufacturers must not disturb the operation regarding the manufacturing supervisor and are required to provide necessary support for the manufacturing supervisor to execute his/her operation. This support shall include provisions of resources and other support necessary for the manufacturing supervisor to integrate manufacturing/quality control operations based on quality risk management and product quality review. These supports shall be those that may be in reference to the "Guideline on Pharmaceutical Quality System" (PFSB/ELD Notification No. 0219-1 and PFSB/CND Notification. No. 0219-1, dated February 19, 2010).

7. Article 7 (Personnel)

(1) This Article shall prescribe such matters as allocation of responsible persons, securing of personnel, etc.

(2) The phrase "a responsible person who is capable of properly and smoothly carrying out the manufacturing and quality control duties" indicated in Paragraph 1 is a

person who was judged by the manufacturers to have the capacity to enable appropriate and smooth conduct of operations upon comparing the type, etc., of operation he/she is responsible for and his/her operational experience, training experience, etc.

(3) Provisions in Paragraph 3 prescribe that a sufficient number of personnel with capacity is required to have been secured in all divisions, etc., that conduct manufacturing/quality operations.

(4) A method of appropriately stipulating in the document, indicated in Paragraph 4, may be, for example, to establish an organization chart that appropriately indicates the responsibility, authority and the management system of personnel engaged in manufacturing/quality control operations. The document creation date shall be indicated when this document has been created, or the revision date, revised matters, and the reason for the revision when this document has been revised.

8. Article 8 (Product Master Formula)

(1) This Article shall prescribe matters regarding creation, storage, and handling of the product master formula according to each product (excluding intermediate products) and each manufacturing site.

(2) The content of the product master formula shall be one that is consistent with the content of the agreement that has been concluded with the marketing authorization holder that markets cellular and tissue-based products pertaining to the relevant product.

(3) Matters that shall be included in the product master formula shall be to the extent in which there is no impediment in appropriate product/quality control operations pertaining to the manufacturing process (including storage) that the relevant manufacturers conduct, and are not necessarily required to have included the entire manufacturing process pertaining to the product.

(4) The "approved product information" indicated in Item 1, "manufacturing procedures (excluding the matter set forth in Item (1))" indicated in Item 3, and "other necessary matters" indicated in Item 6 shall be the following matters:

A. Generic name and brand name of the product

B. Date of marketing approval (or the approval date of conditional and time-restricted approval) and marketing approval number

C. Component cell or transgene

D. Specifications of the products and container, and testing method (including the following matters)

(a) Specifications, testing methods, and rationale for those testing methods, if more strict specifications and more precise testing methods are used compared to those specified in the marketing approval document or the official compendium

(b) Independent specifications, testing methods, and rationale for those testing methods that were established judging from their necessity in terms of quality control, if specifications and testing methods of products or containers are not specified in the marketing approval document or the official compendium, or if the specified details may not necessarily be regarded sufficient in the actual manufacturing

(c) Testing items and their specifications and testing methods if testing of products or containers is conducted using external testing agencies, etc.

E. Specification and print sample of labeling material, and specification of packaging material

F. Shipping method of cells and tissues intended for use as raw materials

G. Manufacturing method and manufacturing procedure (including testing method and testing procedure pertaining to process control)

H. Standard amount of preparation and rationale for this amount

I. Storage condition of raw materials and intermediate products

J. Storage condition and shelf life or expiration date of products (excluding intermediate products) (including stability testing results that became the rationale for this)

K. Shipping method of products

L. Dosage or directions for use, indications or performance, and precautions or precautions for handling

M. Document indicating the details of agreements concluded with the marketing authorization holders (a copy of the contract for the agreement, etc.)

(5) Matters indicated in Item 2 shall be the Standards for Biological Materials (MHLW Ministerial Announcement No. 210 of 2003), related matters from the approved product information, related matters from improvement orders, related matters from the conditions applied to marketing approval, etc.

(6) "Other specifications" indicated in Item 4 shall include matters pertaining to the origin, place of production, manufacturing control and quality control methods, etc., that are necessary for confirming the quality of raw materials, and as matters that fall under this, necessary matters pertaining to raw materials specified in the Standards for Biological Materials shall be included in the product master formula. In cases of cellular and tissue-based products that use human blood or a substance obtained from human blood as the active raw material and in other cases of specified regenerative medicine products that are manufactured using human blood as raw material (anything that will be the origin of the raw material or material for use in manufacturing (including those used in the manufacturing process); the same shall apply hereinafter), the name of the country where blood used as raw material was obtained and whether the blood is donated blood or not shall also be included in this (provided, however, that this shall not apply to cases where the origin of the blood used as raw material is only from the person who will use this cellular and tissue-based product and specified cellular and tissue-based product).

(7) "Other necessary matters" indicated in Item 6 shall mean, for example, matters regarding suppliers of raw materials or packaging and labeling materials that were authorized by the quality division, and matters regarding measures for expected deviations (those due to donor age, sex, medical history, such individual differences as physical constitution, etc.).

9. Article 9 (Operating Procedures, etc.)

(1) This Article prescribes that manufacturers are required to create, store, and furnish sanitation control standard code, manufacturing control standard code, quality control standard code and operation procedures according to each manufacturing site in order to appropriately and smoothly conduct manufacturing/quality control operations.

(2) "Sanitation control standard code" indicated in Paragraph 1 shall not be limited to matters pertaining to manufacturing sanitation, but shall also include matters on sanitary control in testing operations (including testing operations pertaining to

process control and testing operations pertaining to quality control), etc., in order to enable appropriate execution of manufacturing/quality control operations.

(3) "Sanitary control of" "personnel" indicated in Paragraph 1 shall be for the purpose of preventing personnel from contaminating products, etc., with microorganisms, etc.

(4) "Sanitary control of buildings and facilities as well as personnel and other necessary matters" indicated in Paragraph 1 shall be those that fall under either of the following matters:

A. The following matters regarding sanitary control of personnel:

(a) Matters regarding change of personnel's clothes, etc.

(b) Matters regarding knowledge of personnel's health condition, etc.

(c) Matters regarding method of hand washing

(d) Matters regarding measures for preventing infections in personnel due to pathogenic microorganisms, etc.

(e) Other matters necessary for sanitary control of personnel

B. The following matters regarding sanitary control of buildings and facilities

(a) Matters regarding buildings and facilities that require cleanliness to be ensured

(b) Matters regarding cleaning interval of buildings and facilities

(c) Matters regarding cleaning procedure of buildings and facilities

(d) Matters regarding confirmation of cleanliness in buildings and facilities

(e) Matters regarding measures for preventing contamination of buildings and facilities (excluding those related to testing) due to microorganisms

(f) Other matters necessary for sanitary control of buildings and facilities

C. Matters regarding environmental monitoring

D. Other matters necessary for sanitary control

(5) "Manufacturing control standard code" indicated in Paragraph 2 shall be one that enables appropriate execution of operations prescribed in Article 11.

(6) "Storage of products, etc., the control of manufacturing processes and other necessary matters" indicated in Paragraph 2 shall be those that fall under either of the following matters:

A. Matters regarding engagement restriction and other operational control of personnel

B. Matters regarding entry restriction of personnel into work areas or working control areas

C. Matters regarding inspection and maintenance of buildings and facilities, calibration of measuring equipment, etc.

D. Matters regarding control of water for manufacturing

E. Matters regarding setting and control of control level for operation environment, such as cleanliness level

F. Matters regarding control of cell lines for manufacturing, etc. (excluding those used for testing)

G. Matters regarding measures for preventing contamination of cells and tissues intended for use as raw materials due to microorganisms, etc.

H. Matters regarding confirmation, etc., of cells and tissues intended for use as raw materials (including confirmation of shipping process)

I. Matters regarding creation and storage of records on biological raw materials of cellular and tissue-based products

J. Matters regarding storage and receipt/distribution of products, etc., and packaging and labeling materials

K. Matters regarding setting and control of control items for products, etc., and packaging and labeling materials

L. Matters regarding setting and control of control level necessary for process control

M. Matters regarding necessary measures for maintaining culture condition

N. Matters regarding measures for preventing confusion and cross-contamination of cells and tissues

O. Matters regarding measures for preventing contamination of products, etc., due to microorganisms, etc.

P. Matters regarding measures for preventing contamination due to products, etc., whose microorganisms, etc., have not been inactivated or eliminated

Q. Matters regarding disposal of articles, etc., that have been contaminated with microorganisms, etc.

R. Matters regarding necessary measures, etc., for ensuring product quality when shipping

S. Matters regarding knowledge, etc., of shipping destination (institution name), shipping date, and lot number or manufacturing number according to each product

T. Matters regarding confirmation of whether manufacturing control is appropriately conducted and reporting of this result to the quality division

U. Other matters regarding necessary operations for manufacturing control

(a) Matters regarding measures necessary for preventing confusion in manufacturing control

(b) Matters regarding rearing control (including identification control) of donor animals after obtaining them

(c) Matters regarding measures for when an accident occurs

(d) Matters regarding notification of testing results reported from the quality division

(7) "Quality control standard code" indicated in Paragraph 3 shall be one that enables appropriate execution of operations prescribed in Article 12.

(8) "Method for sample collection, a method for assessing inspection and testing results, and other necessary matters" indicated in Paragraph 3 shall be those that fall under either of the following matters. If products, etc., or packaging and labeling materials are tested at an external testing institution, etc., shipping method of the samples and assessment method, etc., of their testing results shall be indicated in the quality control standard code.

A. Matters regarding storage of sample products

B. Matters regarding inspection and maintenance of facilities and equipment for testings, calibration of measuring equipment, etc.

C. Matters regarding control of cell lines, etc., for testing (limited to those used for testings)

D. Matters regarding testing, etc., of donor animals at the time of receipt and after receipt

E. Matters regarding sampling, etc., at testing of products, etc., and packaging and labeling materials (including specification of the place for sampling)

F. Matters regarding identification and categorization method of the samples

G. Matters regarding testing of collected samples

H. Matters regarding testing conducted at an appropriate stage of the manufacturing process that cannot be conducted on the product

I. Matters regarding disposal of articles, etc., that have been contaminated with microorganisms, etc.

J. Matters regarding assessment, etc., of testing results

K. Matters regarding creation and storage of records on testing results

L. Other matters regarding operations necessary for quality control

(a) Matters regarding measures necessary for preventing confusion in quality control

(b) Matters regarding control of raw material and material suppliers

(c) Matters regarding storage of sample products for those packaging and labeling materials, etc., that may influence the quality of raw materials and of products released into the market in which storage is necessary for ensuring product quality

(d) Matters regarding quality assurance of reference standards and reagents/reagent solutions, etc., used in testings

(e) Matters regarding re-testing

(f) Matters regarding stability monitoring (including subject products, etc., and packaging and labeling materials, and their sampling methods; excluding products that do not compose a lot)

(g) Matters regarding storage of retention samples

M. Matters regarding operations of when testings are substituted by records of testings conducted at a foreign manufacturer of regenerative medicine products at the country of origin

N. Matters regarding storage of a series of records, from biological raw materials of cellular and tissue based products that were used in manufacturing, to products that were manufactured using those biological raw materials of cellular and tissue based product.

O. Matters regarding confirmation of results reported from the manufacturing division regarding confirmation pertaining to manufacturing control

(9) A document on "procedures for control of release from a manufacturing site" indicated in Paragraph 4, Item 1 shall be one that enables appropriate execution of operations prescribed in Article 13.

(10) A document on "procedures for validation or verification" (hereinafter referred to as "procedures for validations, etc.") indicated in Paragraph 4, Item 2 shall be one that enables appropriate execution of operations prescribed in Article 14. Specifically, this shall be pursuant to "Section 3 Validation Criteria" of this notification.

(11) A document on "procedures for review of product quality" indicated in Paragraph 4, Item 3 shall be one that enables appropriate execution of operations prescribed in Article 15.

(12) A document on "procedures for change control set forth in Article 16" indicated in Paragraph 4, Item 4 shall be one that enables appropriate execution of operations prescribed in Article 16.

(13) A document on "procedures for deviation control set forth in Article 17" indicated in Paragraph 4, Item 5 shall be one that enables appropriate execution of operations prescribed in Article 17.

(14) A document on "procedures for handling quality information and quality defects" indicated in Paragraph 4, Item 6 shall be one that enables appropriate execution of operations prescribed in Article 18.

(15) A document on "procedures for recall action" indicated in Paragraph 4, Item 7 shall be one that enables appropriate execution of operations prescribed in Article 19.

(16) A document on "procedures for self-inspections" indicated in Paragraph 4, Item 8 shall be one that enables appropriate execution of operations prescribed in Article 20.

(17) A document on "procedures for training" indicated in Paragraph 4, Item 9 shall be one that enables appropriate execution of operations prescribed in Article 21.

(18) A document on "procedures for document and record control" indicated in Paragraph 4, Item 10 shall be one that enables appropriate execution of operations prescribed in Article 22 and Article 23.

(19) Documents on "other procedures necessary for properly and smoothly implementing manufacturing control and quality control" indicated in Paragraph 4, Item 11 shall be expected to be those that are required to be created separately from the following and separately from documents on procedures indicated from Item 1 to Item 10.

Documents on procedures pertaining to cooperation with marketing authorization holders, manufacturers, etc. (including procedures pertaining to notification method of information prescribed in Article 7, Item 6 (a) and 6 (b) as applied mutatis mutandis to Article 21 of the GQP Ordinance, and procedures pertaining to conduct of necessary measures and report on those results prescribed in Article 10, Paragraph 2, Item 1 and Item 2 as applied mutatis mutandis to Article 21 of the GQP Ordinance).

10. Article 10 (Buildings and Facilities)

(1) This Article shall prescribe matters regarding requirements that buildings and facilities at manufacturing sites should conform to according to each product.

(2) Use of quality risk management shall be put into consideration as necessary for judging the propriety of buildings and facilities.

(3) Buildings and facilities at manufacturing sites, in principle, shall not be shared with the research division, development division, or any other divisions that are not relevant to manufacturing/quality control operations; provided, however, this shall not apply to cases where measures are taken to prevent contamination, cross-contamination, and confusion, to ensure traceability, and other appropriate measures that will allow buildings and facilities to be shared.

(4) The phrase "with adequate buildings and facilities for maintaining and controlling cleanliness" indicated in Item 3 shall mean that work rooms or working control areas for manufacturing products are required to possess buildings and facilities that enable necessary cleanliness level to be maintained and controlled depending on the manufacturing process, etc.

(5) The sentence "The work room shall be provided with buildings and facilities for preventing contamination by dust or microorganisms according to the types, structures and manufacturing processes of products" indicated in Item 4 (a) shall mean:

A. A dust elimination device shall be equipped as necessary in work rooms for weight measurement of products, etc., work rooms for preparation, etc., in which dust may develop, and work rooms for filling and sealing in which dust may develop, and an individual room shall be applied to these work rooms. However, in manufacturing operation regarding products of the same type (products of the same type in which appropriate risk control of cross-contamination is possible; the same shall apply hereinafter), the operations of weight measurement, preparation, and filling and sealing may be conducted in the same work room given that they are individually conducted in divided areas and that they are equipped with a dust elimination device as necessary.

B. When conducting manufacturing operations for products of different type at the same time in the work rooms indicated in the first sentence of the above section "A.", those rooms shall be equipped with facilities to prevent contamination with other products.

(6) The phrase "the case where the same effects are obtained from the functions of the manufacturing facilities" indicated in Item 4 (a) shall be, for example, cases that fall under either of the following:

A. If buildings and facilities, etc., are those that are closed and if measures are taken to prevent contamination to products during manufacturing.

B. If measures are taken to prevent contamination to products during manufacturing via streamline flow device, etc., installed in the work rooms or buildings and facilities, etc.

(7) The phrase "the case where there is no risk of contamination of containers after washing" indicated in Item 5 shall be in the cases where, for example, the washed containers are stored in their exclusive boxes with measures taken to prevent contamination.

(8) The phrase "the case where there is no risk of contamination to products by personnel other than those working in the room" indicated in Item 6 shall be in the cases of the following, and in cases where there is no risk of contamination to products via persons other than the personnel in their respective work rooms for weight measurement of raw materials, work rooms for preparation of products, etc., or in which other operations with risk of cross-contamination of products, etc., are conducted, and work rooms for filling and sealing products.

A. In cases where the work room handles only products of the same type

B. In cases of work rooms that handle what are in a state with no possibility of dispersion or cross-contamination (e.g., those that are in a state with no risk of cross-contamination, such as those that have been put in containers in which there is no possibility of their content being dispersed, those that are in the form of solution, etc.), and that are separated from other work rooms that handle what are in a state with possibility of dispersion or cross-contamination, with air handling systems separated according to each work room.

(9) The phrase "shall be separated from work rooms other than these or the working control area but used exclusively for those purposes" indicated in Item 7 shall mean that the work room for preparing products and rooms for filling and sealing products are required to be separated from other work rooms and working control areas, and are required to be an exclusive room; provided, however, that this shall not apply to cases where quality risk management is used as necessary, and contamination and cross-contamination risk is appropriately evaluated and controlled.

If preparation and filling, or if preparation, filling, and sealing are conducted as one coherent operation in a closed facility, those operations can be conducted in the same work room.

(10) The provision in Item 8 shall mean that when manufacturing products, etc., with possible risk of seriously influencing other products via dispersion, etc., of substances with strong sensitization, such as penicillins and cephalosporins, even under appropriate control, the work room associated with this product is required to

be exclusive and is required to have a separate air handling system. This provision shall also mean that when handling an infectious product, etc., or a product, etc., that includes a substance with strong pharmacological effect or toxicity, e.g., some types of steroids or anticancer agents with cytotoxicity, consideration shall be given for the work room to be made exclusive for handling this product, etc., if verified inactivation process and/or cleaning procedure is not established and conducted.

(11) The provision in Item 8 shall not apply to products, etc., that are in a state where dispersion or cross-contamination is impossible, even if those products, etc., contain substances that exhibit hypersensitivity reaction at minute amounts or substances with risk of seriously influencing other products via cross contamination.

(12) When releasing into the atmosphere the air that passed through a work room associated with products, etc., prescribed in Item 8, this must be conducted after the final processing has been completed.

(13) The provision in Item 9 shall not apply to cases where there is no impediment in the operations pertaining to manufacturing control and quality control by, for example, purchasing, etc., water (including water for cleaning facilities, equipment, and containers) at a necessary amount with necessary quality for manufacturing the product, and if manufacturing is not conducted at this manufacturing site, etc.

(14) The phrase "shall be of a structure to prevent contamination of distilled water, etc. by foreign matters or microorganisms" indicated in Item 10 shall mean, for example, appropriate quality, shape, and inclination structure of pipes, etc., and high-temperature circulation system, etc. "Distilled water, etc." shall include distilled water, purified water, water for injection, etc., and also drug solutions.

11. Article 11 (Manufacturing Control)

(1) This Article shall prescribe matters regarding operations pertaining to manufacturing control that the manufacturers have the manufacturing division conduct. When conducting these operations, use of quality risk management shall be put into consideration as necessary.

(2) "Manufacturing order" indicated in Paragraph 1, Item 1 shall, in principle, be issued according to each lot (or according to each manufacturing number for those products that do not compose a lot).