demonstrated the validity of using them as materials is equivalent or higher in terms of quality and safety assurance, and such facts are described in approval certificates issued at the time of marketing approval.

(3) The provisions of Items (2) and the Standards for Animal Cell and Tissue Materials, (3) shall apply *mutatis mutandis* to products produced using whole living animals as the starting materials.

(4) Processes to inactivate or eliminate bacteria, fungi, viruses, etc. shall be performed for animal-derived materials during the manufacturing processes, provided, however, that this provision shall not apply to the case where there is a rational reason for not performing such processing and such a fact is described in approval certificates issued at the time of marketing approval.

(5) Records on the following matters shall be prepared and retained so that information necessary for ensuring the quality and safety of animal-derived materials can be verified, provided, however, that materials, which are the origin of materials of drugs, etc. and produced through cell culture using cell banks with use experience and being analyzed for characteristics as the starting materials, are excluded:

A. Name of the laboratory which prepared animal-derived materials;
B. Date of preparation of animal-derived materials;
C. Results of tests of animal-derived materials; and
D. Lot numbers of animal-derived materials.

(6) The provisions of Items (2) to (4) are not applicable to drugs, quasi-drugs, cosmetics or medical devices that are not designated as biological products.

PFSB/CND Notification No. 1009-1
October 9, 2014

To: Prefectural Health Department (Bureau)

Compliance and Narcotics Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare
(official seal omitted)

Handling of "Regulations for Buildings and Facilities of Pharmacies, etc.", "Ministerial Ordinance on Good Gene, Cellular, and Tissue-based Products Manufacturing Practice", and "Ministerial Ordinance on Good Quality Practice for Drugs, Quasi-drugs, Cosmetics, and Cellular and Tissue-based Products" Pertaining to Cellular and Tissue-based Products

With the "Act on Partial Revision of the Pharmaceutical Affairs Act, etc." (Act No. 84 of 2013; hereinafter referred to as the "Revision Act"), in which cellular and tissue-based products were newly defined and their marketing requirements prescribed, a new regulatory system will be applied based on the licensing system for manufacturers and marketing authorization holders of cellular and tissue-based products.

The "Ministerial Ordinance Regarding Development, etc., of Relevant Ministerial Ordinances for Enforcement of the Act on Partial Revision of the Pharmaceutical Affairs Act, etc., and the Cabinet Order on Development, etc., of Relevant Cabinet Orders and Interim Measures for Enforcement of the Act on Partial Revision of the Pharmaceutical Affairs Act, etc." (Ordinance of the Ministry of Health, Labour and Welfare No. 87 of 2014; hereinafter referred to as the "Revision Ordinance") was promulgated, and partial revision was made to the "Regulations for Buildings and Facilities of Pharmacies, etc." (Ordinance of the Ministry of Health and Welfare No. 2 of 1961), which are the standards regarding buildings and facilities for manufacturing cellular and tissue-based products that must be met as the licensing requirements for manufacturers prescribed in Article 23-22, Paragraph 4, Item 1 (including the cases where applied mutatis mutandis pursuant to Article 23-24, Paragraph 3) of the "Act for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices, etc." (Act No. 145 of 1961; hereinafter referred to as the "Act") that was revised by the Revision Act; and partial revision was also made to the "Ministerial Ordinance on Good Quality Practice for Drugs, Quasi-drugs, Cosmetics, and Medical Devices" (Ministerial Ordinance No. 136 of 2004), which is the standards for quality control method of cellular and tissue-based products that must be met as

the licensing requirements for marketing authorization holders prescribed in Article 23-21, Item 1 of the Act. The "Ministerial Ordinance on Good Gene, Cellular, and Tissue-based Products Manufacturing Practice" (Ministerial Ordinance No. 93 of 2014; hereinafter referred to as the "GCTP Ordinance") was also promulgated, which is the standards for manufacturing control and quality control methods of cellular and tissue-based products that must be met as the licensing requirements for marketing approval prescribed in Article 23-25, Paragraph 2, Item 4 (including the cases where applied mutatis mutandis pursuant to Article 23-37, Paragraph 5) of the Act and as compliance matters for manufacturers prescribed in Article 23-35, Paragraph 2 of the Act. The Revision Ordinance and the GCTP Ordinance will both come into effect on November 25, 2014.

With this, the PFSB Notification No. 0812-11, dated August 12, 2014 ("Regulations for Buildings and Facilities of Pharmacies, etc.", "Ministerial Ordinance on Good Gene, Cellular, and Tissue-based Products Manufacturing Practice", and "Ministerial Ordinance on Good Quality Practice for Drugs, Quasi-drugs, Cosmetics, and Cellular and Tissue-based Products" Pertaining to Cellular and Tissue-based Products) has been issued. With the following considerations on its specific operation, etc., we ask you to thoroughly inform relevant parties and organizations regarding this notification and provide appropriate guidance for the purpose of its thorough implementation.

This notification will abbreviate the "Pharmaceutical Affairs Act" (Act No. 145 of 1961) prior to revision by the Revision Act as the "Former Act"; the "Order for Enforcement of the Act for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices, etc." (Order No. 11 of 1961) after revision by the "Cabinet Order on Development, etc., of Relevant Cabinet Order and Interim Measures for Enforcement of the Act on Partial Revision of the Pharmaceutical Affairs Act, etc." (Cabinet Order No. 269 of 2014) as the "Order"; the "Ordinance for Enforcement of the Act for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices, etc." (MHW Ordinance No. 1 of 1961) after revision by the Revision Ordinance as the "Ordinance for Enforcement"; the "Ministerial Ordinance on Good Vigilance Practice for Drugs, Quasi-drugs, Cosmetics, Medical Devices, and Cellular and Tissue-based Products" (Ministerial Ordinance No. 135 of 2004) after revision by the Revision Ordinance as the "GVP Ordinance"; and the "Ministerial Ordinance on Good Quality Practice for Drugs, Quasi-drugs, Cosmetics, and Cellular and Tissue-based Products" (Ministerial Ordinance No. 136 of 2004) after revision by the Revision Ordinance as the "GQP Ordinance".

Table of Contents

Chapter 1 General

Section 1 General Matters

1. This notification shall be applied from November 25, 2014.

2. Recent Ministerial Ordinances that were promulgated regarding manufacturing control and quality control of cellular and tissue-based products are as follows:

   (1) Promulgated on July 30, 2014

      A. Ministerial Ordinance Regarding Development, etc., of Relevant Ministerial Ordinances for Enforcement of the Act on Partial Revision of the Pharmaceutical Affairs Act, etc., and the Cabinet Order on Development, etc., of Relevant Cabinet Orders and Interim Measures for Enforcement of the Act on Partial Revision of the Pharmaceutical Affairs Act, etc." (Ministerial Ordinance No. 87 of 2014)

   (2) Promulgated on August 6, 2014

      A. Ministerial Ordinance on Good Gene, Cellular, and Tissue-based Products Manufacturing Practice" (Ministerial Ordinance No. 93 of 2014)

Section 2 Marketing Approval

1. Compliance of manufacturing control and quality control methods at manufacturing sites to the GCTP Ordinance is prescribed in Article 23-25, Paragraph 2, Item 4 of the Act to be the requirement of marketing approval of Cellular, and Tissue-based Products (including the cases where applied mutatis mutandis pursuant to Article 23-37, Paragraph 5), and therefore, conformity inspection shall be conducted as a procedure other than the procedure for product application when intending to obtain marketing approval (including conditional and time-restricted approval prescribed in Article 23-26 of the Act; the same shall apply hereinafter), when intending to obtain approval of partial change (hereinafter referred to as "partial change approval") (excluding those that do not require conformity inspection), and once every 5 years after marketing approval.

2. Facilities subject to conformity inspection that is required when obtaining marketing approval and required once every 5 years after receiving marketing approval shall, in

principle, be all domestic and foreign manufacturing sites pertaining to marketing approval.

3. If conformity inspection is not conducted once every 5 years after marketing approval, this marketing approval may be withdrawn, or a part of its approved matters may be required to be changed.

4. Conformity inspection shall also be conducted, in principle, when intending to obtain partial change approval. However, pursuant to the provision of Article 137-34 of the Ordinance for Enforcement, conformity inspection shall not be a requirement for addition, change, or deletion of dosage or indications of the item, or for any other changes that will have no influence on manufacturing control or quality control method of the item. For changes that will influence the manufacturing control or quality control method, conformity inspection shall be conducted only on the manufacturing site pertaining to marketing approval among which pertain to the relevant change. For other manufacturing sites, their state of change control shall be confirmed, etc., at conformity inspections conducted once every 5 years after marketing approval.

5. For changes other than "for addition, change, or deletion of dosage or indications of the item, or for any other changes that will have no influence on manufacturing control or quality control method of the item", i.e., changes that will require conformity inspection for when obtaining partial change approval, shall be such changes as the following:

   (1) Change of manufacturing site

   (2) Fundamental change of essential process

Section 3 Conformity Inspection

1. GCTP conformity inspections shall be classified into either conformity inspections based on conformity inspection application, or inspections pursuant to Article 69 of the Act (hereinafter referred to as the "Article 69 inspection").

2. Although conformity inspections are required when intending to obtain marketing approval, when intending to obtain partial change approval (excluding those pertaining to partial change approval that do not require conformity inspection), once every 5 years after marketing approval, etc., conformity inspection application may be submitted as

necessary based on the judgment of the applicant upon consulting the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as the "PMDA").

3. Article 69 inspection shall, in principle, be conducted by the PMDA.

4. The PMDA shall basically be responsible for determining whether the conformity inspection should be conducted on-site or be document-based. When making the actual decision of whether to be conducted on-site or be document-based, the priority of the inspection shall be determined with such consideration of the extent of caution required in manufacturing control or quality control (complexity of manufacturing process, extent of risk when using the product, etc.), past on-site inspection results, and past non-conformities, recalls, etc., and their content; and inspections of high priority shall be conducted on-site.

5. For domestic manufacturing sites, on-site conformity inspections shall be conducted on those manufacturing processes equivalent to the subject product, in principle, if on-site GCTP inspection has not been conducted within the past 2 years from the day the conformity inspection application has been submitted.

6. For foreign manufacturing sites, whether to be conducted on-site or document-based shall be determined as necessary with consideration of inspection status of manufacturing control and quality control at the foreign manufacturing site of that country.

7. Submission data for conformity inspection application is prescribed in Article 137-31, Paragraph 2 of the Ordinance for Enforcement as "data related to manufacturing control and quality control of items pertaining to conformity inspection of cellular and tissue-based products" and "data related to manufacturing control and quality control of the manufacturing sites pertaining to conformity inspection of cellular and tissue-based products", and matters regarding handling of these data are as follows:

   (1) Data necessary in conformity inspections for product application, application for partial change approval, and export notification of cellular and tissue-based products for exports

      A. A copy of notification on conformity inspection results or of inspection report pertaining to GCTP inspection conducted within 2 years from the day of the relevant conformity inspection application (shall be limited to cases where inspection has been conducted)

B. A copy of product application or of application for partial change approval of the product whose application will be submitted (or manufacturing notification of cellular and tissue-based products for export if based on this notification)

C. Other data required by the PMDA

(2) Data necessary in conformity inspections conducted once every 5 years after receiving marketing approval and once every 5 years after submitting export notification of cellular and tissue-based products for export.

A. Data specified in "(1) A"

B. A copy of submission data (or manufacturing notification of cellular and tissue-based products for export if based on this notification) from the marketing approval document

C. A copy of application for partial change approval in the past 5 years

D. A copy of minor change notification in the past 5 years

E. Data that indicates the rationale for the classification according to work area, work room, area, facility, etc., and for the selection of a representative product according to this classification, when submitting application pertaining to 2 or more items (data may be confined to only those data specified in "A" and "B" that pertain to the representative product if the representative product is selected pursuant to this provision)

F. Recalls within the past 5 years pertaining to the product whose application will be submitted (summary of the recall)

G. Declaration (Attachment 1-3-1)

H. Other data required by the PMDA

8. Conformity inspection for marketing approval or partial change approval shall basically be conducted for one item per application and shall be conducted on all manufacturing sites indicated in the product application. However, for conformity inspections conducted once every 5 years after marketing approval, multiple applications pertaining to multiple items may be submitted together simultaneously for the purpose of convenience, including application of items that are within 5 years after receiving their marketing approval. For conformity inspections conducted once every 5 years after marketing approval, applications for items pertaining to the manufacturing site may be submitted together according to each marketing authorization holder at the timing of renewal of its

license for manufacturer, given that the item is within 5 years after marketing approval. Application for conformity inspection pertaining to cellular and tissue-based products for export shall also be submitted according to this same procedure.

9. Conformity inspection for review of partial change approval shall not influence the timing of conformity inspection conducted once every 5 years after marketing approval.

10. When submitting anew an application for marketing approval within the deadline of conditional and time-restricted approval and if this change from conditional and time-restricted approval to an item intended for product application does not influence the manufacturing control or quality control method, conformity inspection for product application shall not be required. Approval obtained after submitting anew an application for marketing approval within the deadline of conditional and time-restricted approval shall also have no influence on the timing of conformity inspections conducted once every 5 years after marketing approval.

11. Attention shall be given to the fact that marketing approval may be withdrawn if inspection application is omitted for those that are required once every 5 years after marketing approval.

12. Conformity inspection application shall be submitted at an appropriate timing with sufficient consideration of the review progress and putting into account the effect on the standard processing time pertaining to the marketing approval review. When submitting conformity inspection application for product application or for application for partial change approval, the product application date shall have the standard processing period for marketing approval review added and then have the period required for the PMDA conformity inspection dated back, which shall be the desirable date for the conformity inspection application to be submitted by.

13. Matters that have been registered in the drug master file shall also be similarly subject to conformity inspections.

14. Changes pertaining to minor change notification shall together be subject to conformity inspections, etc., conducted once every 5 years after marketing approval.

15. The PMDA shall send a notification of conformity inspection results to the authorizer for licensing marketing authorization holders, i.e. the prefectural governor, pertaining to the item that underwent inspection, and shall issue a copy of this notification of conformity inspection results to the marketing authorization holder. Based on the qualification

criteria results, "conforming" or "non-conforming" shall be clearly indicated in the "Inspection Results" column of the Ordinance for Enforcement Form No. 75-6, which is the "Notification of Conformity Inspection Results of Cellular and Tissue-based Products".

16. The PMDA shall conduct conformity inspections, evaluate relevance based on qualification criteria at the time of notification of conformity inspection results or after this notification, and prepare reports on conformity inspection results that include details for improvements, etc. A copy of this report shall be issued to the manufacturing site that was subject to conformity inspection (limited to those pertaining to on-site conformity inspection).

17. The PMDA shall notify the authorizer for licensing marketing authorization holders any violation against pharmaceutical affairs found at conformity inspection. After receiving this notification, the authorizer for licensing marketing authorization holders shall take measures together with relevant authorizers for licensing manufacturers.

18. If the marketing approval review is in a state where only the notification of conformity inspection results is being awaited due to reasons attributable to the applicant, the time from suspension of the review procedure until receipt of notification may be excluded from the total review time.

19. Even if the application pertains to foreign manufacturing sites, application forms and submission data shall, in principle, be prepared in Japanese. If the text of the submission data is comprised of mostly data written in a foreign language, only its main summary may be prepared in Japanese.

Attachment 1-3-1

Declaration

To: Pharmaceuticals and Medical Devices Agency

I, (applicant), hereby declare that no inconsistency exists between the truth and the content of the application pertaining to conformity inspection of the below item; that manufacturing control and quality control methods of the manufacturing site do not fall under Article 23-25, Paragraph 2, Item 4 of the Act (Article 23-25, Paragraph 2, Item 4 of the Act applied mutatis mutandis pursuant to Article 23-37, Paragraph 5 of the Act); and that items that satisfy the marketing approval standards are being manufactured.

Date:

Address:
Name: (name of the marketing supervisor-general) Seal

Section 4 License for Marketing Authorization Holders

1. "Document on the system pertaining to quality control" indicated in Article 137-2, Paragraph 2, Item 7 of the Ordinance for Enforcement shall be the following data:

   (1) A copy of data prescribed in Article 4, Paragraph 4 as applied mutatis mutandis pursuant to Article 21 of the GQP Ordinance

   (2) A document that indicates the location of the responsible person for quality assurance if located at a different place from the office that possesses the main function of the marketing authorization holder

   (3) A floor plan of the facility for storage, etc., if products (excluding intermediate products) are stored, etc., pursuant to Article 15 as applied mutatis mutandis pursuant to Article 21 of the GQP Ordinance at the office that possesses the main function of the marketing authorization holder

Section 5 License for Manufacturers/Foreign Manufacturer Accreditation

1. Pursuant to Article 137-58 of the Ordinance for Enforcement, manufacturers and accredited foreign manufacturers of cellular and tissue-based products shall comply with the provisions in the GCTP Ordinance regarding manufacturing control and quality control methods at their manufacturing sites.

2. Application of license for manufacturer and of accreditation for foreign manufacturer shall be submitted to the PMDA.

3. When conducting inspections for renewal of license for manufacturer and of accreditation for foreign manufacturer, attention shall also be given to conformity to compliance matters and to licensing (accreditation) requirements.

4. Submission data that are to be submitted with the application of license for manufacturer and of accreditation (renewal) for foreign manufacturer are prescribed in Article 137-8, Paragraph 2 of the Ordinance for Enforcement, and their handlings shall be as follows:

   (1) "Document on buildings and facilities of the manufacturing site" shall be pre-submitted documents that will be useful in licensing (accreditation) inspection, such as the floor plan of the manufacturing site.

(2) "A list of items intended to be manufactured" shall be indicated to the extent determined at the time of licensing (accreditation) application.

(3) "Document on manufacturing process" shall indicate details that enable recognition of which process of the product intended to be manufactured is indicated in that document.

Section 6 Cellular and Tissue-based Products for Export

1. Manufacturers of cellular and tissue-based products for export shall have conformity inspections conducted when intending to manufacture cellular and tissue-based products and once every 5 years after initiating manufacturing. Products shall not be released from manufacturing sites if the product was not considered to be conforming in the conformity inspection.

2. Subject institutions that require conformity inspections when intending to manufacture products and once every 5 years shall be all manufacturing sites pertaining to the manufacturing notification of cellular and tissue-based products for export.

Chapter 2 Regulations for Buildings and Facilities (Related to Cellular and Tissue-based Products)

Section 1 Summary

1. Article 14 and Article 15 of the Regulations for Buildings and Facilities were prescribed as standards on buildings and facilities at manufacturing sites of cellular and tissue-based products prescribed in Article 23-22, Paragraph 4, Item 1 of the Act.

2. Buildings and facilities according to products for manufacturing (including intermediate products; the same shall apply hereinafter) shall be prescribed in the GCTP Ordinance.

Section 2 Commentary

1. Article 14 (Buildings and facilities at manufacturing sites of manufacturers of cellular and tissue-based products)

   (1) This Article shall be the standards for buildings and facilities at manufacturing sites of manufacturers of cellular and tissue-based products in the general category and foreign manufacturers of cellular and tissue-based products (hereinafter referred to as "manufacturers of cellular and tissue-based products"), which fall under the category prescribed in Article 137-9, Item 1 and Article 137-19, Item 1 of the Ordinance for Enforcement.

   (2) Although manufacturing sites of manufacturers of cellular and tissue-based products in the general category shall be subject to provisions of this Article regardless of whether their manufacturing is conducted on the entire process or a part of the process, those that conduct only the packaging, labeling, or storing shall not be subject to provisions of this Article but shall be subject to provisions of Article 15. The manufacturing sites that conduct only the packaging, labeling, or storing stated here shall mean manufacturing sites that put what have completed the process of filling into immediate containers or packages (including inner packages) into outer containers or packages, or that conduct other operations that do not directly influence the quality of the product that has been filled, such as those in a sterilized condition, etc.

(3) The phrase "facilities and equipment necessary for manufacturing products at the manufacturing site" indicated in Item 1 shall be facilities and equipment necessary for manufacturing products if the manufacturing site manufactures products (excluding intermediate products), and facilities and equipment necessary for manufacturing intermediate products if the manufacturing site manufactures intermediate products.

(4) The phrase "shall be positioned so as not to impede smooth and appropriate operation and shall be those that enable easy cleaning and maintenance" indicated in Item 2 shall mean the following:

A. Each work room shall be positioned with consideration of preventing contamination from outside during operation, and of preventing cross-contamination to other products, etc., and packaging and labeling materials. A "work room" shall mean the individual room at which the operation is conducted at the work area.

B. Facilities and equipment within the work room shall be positioned with consideration of preventing confusion and mistakes during operation, and of enabling easy cleaning and maintenance.

C. From the perspective of preventing contamination of products, etc., and packaging and labeling materials, buildings and facilities shall use building materials in the interior that enable cleaning and maintenance depending on their operational conditions, and shall have an area according to their operational conditions. Sections of the manufacturing facility that directly come in contact with the product shall be those that allow easy cleaning and maintenance, and shall use materials that do not allow contamination and cross-contamination.

(5) "Dressing room" indicated in Item 3 does not necessarily require an exclusive room for changing clothes.

(6) Item 4 requires that areas for receiving raw materials, processing, and storing products, etc., shall be divided from other areas for the purpose of preventing confusion of products, etc., and packaging and labeling materials, and of preventing contamination and cross-contamination.

(7) Appropriate "lighting" indicated in Item 6 (a) requires necessary illuminance to be ensured, including natural lighting, depending on the type of operation conducted at that place so as not to impede the operation.

(8) The phrase "entrance doors and windows shall be those that can be closed" indicated in Item 7 (b) shall mean that entrance doors and windows shall be those that can be closed and that are of a structure necessary for preventing contamination via the closed route. For example, a ventilation fan attached to a window shall have such necessary measures be taken for protecting against solvents and particulates, and for preventing contamination from outdoors.

(9) The phrase "if easy cleaning is possible" indicated in Item 7 (e) shall be cases of facilities with a structure that enables sufficient cleaning within the extent of regular cleaning. For example, even if pipes, ducts, etc., are horizontally installed, they may be regarded as a case of "easy cleaning is possible" if their surface dust can be easily removed via regular cleaning and if they are of a structure that does not allow accumulation of dust.

(10) "Passageway, etc." that compose the "working control area" indicated in Item 8 shall include, for example, a storage place for intermediate products.

(11) The phrase "buildings and facilities that enable maintenance of temperature and humidity (humidity is limited to when its maintenance is necessary)" indicated in Item 8 shall be buildings and facilities that enable maintenance of temperature and humidity generally necessary for manufacturing cellular and tissue-based products.

(12) "Preparation" indicated in Item 9 shall mean such operations as measuring weights, preparing liquids, cultivating, purifying, filling, and sealing in which the products, etc., come in contact with the air within the work area.

(13) The drainage facility with "appropriate structure" indicated in Item 9 (c) shall be, for example, drainage outlets with drainage traps or with a device, etc., for preventing reflux (including reflux of contaminated air). "Harmful waste water" shall be waste fluid that includes pathogenic microorganisms, etc., that have not been inactivated (BSL 2 or above) or other waste water that will influence the human body and environment.

(14) "A structure necessary" indicated in Item 9 (d) shall be structures that conform to the following requirements:

A. The drainage outlet (the drainage destination shall not be connected to the manufacturing area) shall have a trap (shall be of a structure that enables disinfection) that enables easy cleaning and shall have a device for preventing reflux.

B. The floor ditch shall be one that is shallow and enables easy cleaning.

(15) Item 9 (e) (1) prescribes that the drainage outlet shall not be installed in aseptic operation areas, and drainage outlets that have already been installed in existing buildings and facilities shall be removed. However, in cases of difficulty removing them, the drainage outlets may exceptionally be accepted if measures are taken for preventing contamination given that they are of a structure that can be sealed during manufacturing operation, and this procedure shall be prescribed in the sanitation control standard code, etc.

(16) "Area that handles pathogenic microorganisms, etc." indicated in Item 12 shall include areas that handle pathogenic microorganisms, etc., for manufacturing, and areas that handle what may have been contaminated with pathogenic microorganisms, etc., in which there is concern of contamination or cross-contamination of products, etc. unless they are confined. "Buildings and facilities necessary for appropriate negative pressure control" shall be, for example, to have the area be a building structure with a direct vent system, and to have their environment be at a negative pressure against the surrounding anteroom, passageway, etc. (negative pressure is not necessarily required against outside air). Pathogenic microorganisms, etc., shall require handling in accordance to the confinement requirements, and shall be handled with reference to the "National Institute of Infectious Diseases Safety Management Regulations for Pathogens and Toxins" "Handling of Biosafety at Manufacturing Sites of Biological Products, etc. (CND Notification No. 14, dated February 14, 2000)" and other relevant regulations, etc., in their latest version, etc.

(17) Item 13 requires that if there is an area at the work area in which pathogenic microorganisms, etc., are handled, such as aseptic operation areas, this area shall require a facility for washing, disinfecting, and sterilizing instruments that were used in this area, and a facility for disposing waste fluids, etc.

(18) Item 14, which shall not apply limited to the air-handling system of aseptic operation areas, requires that the air-handling system in other areas be of a structure necessary for preventing contamination of products, etc., due to microorganisms, etc.

(19) "Of an appropriate structure" indicated in Item 14 shall be such structures as the following:

A. An appropriate structure for preventing air diffusion of pathogenic microorganisms, etc.

B. A structure that discharges air after eliminating microorganisms, etc., via high-performance air filters from the air that was discharged from the area that handles pathogenic microorganisms (including the area that uses pathogenic microorganisms, etc., in testings).

C. A structure that will not allow recirculation of air discharged from a work room in which there may be leakage of pathogenic microorganisms, etc.; provided, however, that this shall not apply if microorganisms, etc., is sufficiently eliminated via structure indicated in section "B", and recirculation is considered inevitable.

D. A structure exclusive to different systems according to each work room (excluding cases with rationale for no contamination and cross-contamination based on the property of the product and manufacturing process).

(20) Item 16 (a) requires that newly obtained animals shall be isolated from breeding rooms and other areas until results of testing that was conducted at receipt have been obtained, in order to prevent contamination or cross-contamination of products, etc., via bred animals due to infected pathogenic microorganisms, etc.

(21) The phrase"facilities necessary for sanitary and safe storage in which products, etc., and packaging and labeling materials are divided" indicated in Item 17 shall be, for example, such facility as storage shelf, and storehouses. In principle, a section of central corridors or work rooms shall not fall under this "facilities". However, a section of central corridors or work rooms may be exceptionally regarded as "facilities" indicated in Item 17 in cases of temporary use and if necessary measures are taken to prevent confusion with other products and packaging and labeling materials, and to prevent contamination and cross-contamination. This "section" stated here shall mean a specific place partitioned by walls, partition boards, etc., and "to divide" means to divide a certain place or certain things by lines, partitions, etc. How these "sections" and "divisions" should be specifically realized shall be determined depending on individual cases and on their purposes.

(22) "Facilities and equipment for testings" indicated in Item 19 shall mean facilities and equipment necessary for conducting testings pertaining to marketing approval. Item 19 does not require an exclusive room if nothing impedes testings at the manufacturing site.

2. Article 15 (Buildings and facilities at manufacturing sites of manufacturers of cellular and tissue-based products in the category of packaging, etc.)

(1) This Article shall be the standards for buildings and facilities at manufacturing sites of manufacturers of cellular and tissue-based products in the category of packaging, etc. category prescribed in Article 137-9, Item 2 and Article 137-19, Item 2 of the Ordinance for Enforcement.

(2) Manufacturing sites applicable to this Article shall be those that conduct only the packaging, labeling, or storing. The manufacturing sites that conduct only the packaging, labeling, or storing stated here shall mean manufacturing sites that put what has completed the process of filling into immediate containers or packages (including inner packages) into outer containers or packages, or that conduct other operations that do not directly influence the quality of the product that has been filled, such as those in a sterilized condition, etc.

(3) Group packaging of products pertaining to cellular and tissue-based products shall not be regarded as a manufacturing operation that manufacturers of cellular and tissue-based products in the category of packaging, etc. may conduct, since this handles products that have not completed the process of filling into immediate containers or packages (including inner packages). Therefore, manufacturing sites that conduct such operations shall not be applicable to this Article, but shall be applicable to Article 14.

(4) "Facilities and equipment for testings" indicated in Item 3 shall mean facilities and equipment necessary for conducting testings pertaining to marketing approval. If a testing that is not included in the marketing approval is independently specified, facilities and equipment necessary for only this testing shall not fall under the "facilities and equipment necessary" indicated in Item 3, but shall be managed based on GCTP.

Item 3 does not require an exclusive room if nothing impedes testings at the manufacturing site.

Section 3 Qualification Criteria

1. Conformity status to the Articles prescribed in the Regulations for Buildings and Facilities (related to cellular and tissue-based products) shall be evaluated for each manufacturing site based on the "Qualification Criteria for Each Article of the Regulations for Buildings and Facilities (Related to Cellular and Tissue-based Products)" (hereinafter referred to as the "Conformity Criteria of the Regulations for Buildings and Facilities") in Attachment 1.

2. Conformity Criteria of the Regulations for Buildings and Facilities shall have the evaluation items indicated in the form of questions according to each Article. The final evaluation results of conformity status according to each Article shall be determined after explaining the reasons for the evaluation to the persons subject to this conformity inspection, and after thoroughly hearing opinions from the persons subject to this conformity inspection.

3. Basic principles for operating the Conformity Criteria of the Regulations for Buildings and Facilities shall be to evaluate as Rank A (conforming) if matters indicated in the question are appropriately conducted (including cases where immediate improvement is made on-site); as Rank D (serious defect) if there is apparent conflict with the criteria; and as Rank B and C from the following perspective.

   (1) Rank B (mild defect) shall be for cases where although there is not much of a problem regarding influence on product quality, improvement is necessary for completeness in terms of operation regarding the criteria.

   (2) Rank C (moderate defect) shall be for cases where influence on product quality cannot be denied and improvement is necessary in terms of operation regarding the criteria.

4. Conformity status shall be evaluated via the following criteria using the evaluation results for each Article obtained according to the procedure indicated in the above section "3."

   (1) Conforming : Only As.

   (2) Generally conforming : As and Bs, or only Bs.

   (3) Require improvement : The number of Cs is half of all items or less and there are no Ds.