Tentative translation of MHLW MO 169 revised in 2021, Chapter 4

(Note)
1) This English document is only for reference purpose. In case of any discrepancy, the Japanese text shall prevail.
2) The requirements of MHLW MO 169 are applied to both the Marketing Authorization Holder and the person operating the Registered Manufacturing Site. In this document the requirements are stipulated as the requirements for the Marketing Authorization Holder. Meanwhile, when they are applied to the Registered Manufacturing Site, the requirements must be paraphrased, as appropriate.

Chapter 4. Manufacturing control and quality control of biological medical devices, etc.

(Infrastructure for operation at a manufacturing site of a marketing authorization holder, etc. of specified biological medical devices, etc.)

Article 73 Marketing authorization holders, etc. (hereinafter referred to as "marketing authorization holders, etc. of specified biological medical devices, etc.") of products related to medical devices and cell/tissue-based medical devices (hereinafter referred to as "specified biological medical devices, etc." in this chapter), such as medical devices, etc. as specified biological products, designated by the Minister of Health, Labour and Welfare pursuant to the provisions of Paragraph 2, Article 43 of the Act shall satisfy the following requirements as an infrastructure for operation at manufacturing sites that manufacture the said products (excluding manufacturing sites that only perform packaging, labeling, storage, or design; the same shall apply in this chapter).

[1] Facilities supplying distilled water, etc. necessary for manufacturing products shall have a structure necessary for preventing contamination of distilled water, etc. by foreign matters or microorganisms (including viruses; the same shall apply hereinafter in this chapter and Chapter 6).

[2] Workplaces (places where manufacturing operations are performed; the same shall apply in this chapter and through Chapter 6) shall conform to the following requirements.

A. Work rooms or controlled work areas should have structures and facilities that can maintain and control appropriate temperature, humidity, and cleanliness according to the manufacturing process.

B. Work rooms for weighing of raw materials or materials or cleaning of containers should have a well-closed structure for dust prevention.

C. Work rooms for drying or sterilization of containers after cleaning should be dedicated.

This does not apply if there is no risk of contamination of cleaned containers.

D. Clean areas (work areas where weighing and preparation of parts, etc. are performed and where products, etc. are exposed to the air in the work areas after cleaning; the same shall apply hereinafter in this chapter and Chapter 6) and aseptic areas (work areas where sterilized products, parts, etc., or sterilized containers are exposed to the air in the work areas, areas where closure of containers is performed, and areas where aseptic operations, such as sterility testing, are performed; hereinafter the same in this chapter.) shall conform to the following requirements.

(1) The surfaces of ceilings, walls, and floors are smooth and free from cracks and do not cause dust.

(2) Drainage facilities have an appropriate structure to prevent contamination by harmful drainage.

E. Do not install drainage ports in clean areas. This shall not apply to the following cases.

(1) Drainage ports are equipped with traps that are easy to clean and devices to prevent backflow of drainage.

(2) Traps have a structure to allow disinfection.

(3) A ditch of the floor is shallow and easy to clean and connected to the outside of manufacturing areas (places where culture, extraction, and purification, weighing and preparation of parts, etc., cleaning and drying of containers, closure and packaging of containers, and gowning are performed) through drainage ports.

F. Aseptic areas shall conform to the following requirements.

(1) Do not install drainage ports.

(2) Do not install sinks.

G. Areas where tests using animals or microorganisms are performed and areas where animal tissues or microorganisms not necessary for manufacturing products related to specified biological medical devices, etc. are handled shall be clearly separated from the other areas where the said products are manufactured, and an air-handling system shall be separated.

H. Areas for aseptic operations shall be provided with clean air treated with filters and have a structure and facilities necessary for appropriate differential pressure control.

I. Areas, where pathogenic microorganisms, etc. are handled, shall have a structure and facilities necessary for appropriate negative pressure control.

J. Areas, where infectious microorganisms, etc. are handled, shall have facilities for cleaning, disinfection, and sterilization of apparatuses used in the areas and facilities for treatment of waste fluids, etc.

K. The following facilities shall be installed in rooms that are clearly separated from others,

excluding facilities that are considered unnecessary for manufacturing of the products depending on the type and manufacturing method, etc. of the products.

(1) Storage facilities for microorganisms

(2) Facilities to control animals inoculated with microorganisms for use in manufacturing or testing

(3) Facilities for treating animals for use in manufacturing or testing

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

(5) Facilities for culturing microorganisms

(6) Facilities for collecting, inactivating, and sterilizing cultured microorganisms

(7) Facilities to disinfect apparatuses and instruments, etc. used for manufacturing or testing

L. The surfaces of the ceilings, walls, and floors of the rooms with facilities listed in (2) to (4) and (6) of K shall be structured so that they can be cleaned and disinfected.

M. Rooms having facilities listed in (4) and (6) of K and rooms having facilities for sterility testing among those necessary for testing of products, etc. shall meet the following requirements.

(1) They shall be aseptic rooms. This does not apply to cases where work rooms are equipped with facilities that can perform aseptic operation without hindrance according to the type of product and manufacturing method, etc.

(2) The aseptic rooms in (1) shall have a dedicated anteroom and structure so that a work room can normally be entered only through the anteroom, and a doorway of the anteroom does not face the outside.

N. In addition to the facilities listed in K, facilities listed below shall be provided.

(1) Facilities necessary for breeding control of animals for use in manufacturing or testing

(2) Facilities for preparation of culture media and diluent

(3) Facilities necessary for cleaning, drying, sterilization, and storage of apparatuses, instruments, and containers, etc. for use in manufacturing or testing

(4) Facilities for container closure

(5) Facilities to properly dispose of animal carcasses and other dirt and to purify polluted water

O. Storage facilities shall be equipped with a thermostat, self-recording thermometer, and other necessary instruments.

P. An air-handling system shall conform to the following requirements.

(1) The structure should be appropriate to prevent contamination of products, etc. by microorganisms, etc.

(2) When pathogenic microorganisms, etc. are handled, the structure should be appropriate to prevent air diffusion of the microorganisms, etc.

(3) The structure should be such that the air emitted from areas, where pathogenic microorganisms, etc. are handled, is emitted after removal of the microorganisms, etc. by high performance air filters.
(4) The structure should be such that the air emitted from work rooms, where pathogenic microorganisms, etc. may leak, is not re-circulated. This does not apply if the microorganisms, etc. have been sufficiently removed by the structure specified in (3) and if re-circulation is considered inevitable.
(5) A separate line should be used for each work room where necessary.
Q. Pipes, valves, and vent filters shall have a structure that can be easily cleaned or sterilized according to the intended use.
R. The following testing facilities and apparatuses are provided. This does not apply to cases where testing is performed by using other testing institutions of a marketing authorization holder, etc. of specified biological medical devices, etc. on their own responsibility without any problem.
(1) Facilities and apparatuses for sealing inspection if it is necessary to perform the sealing inspection
(2) Facilities and apparatuses for foreign substance inspection
(3) Facilities and apparatuses for physicochemical tests of products, process agents, and materials
(4) Facilities and apparatuses for sterility testing
(5) Facilities and apparatuses for pyrogen tests if it is necessary to perform the pyrogen tests
(6) Facilities and apparatuses for biological tests if it is necessary to perform the biological tests
[3] Work areas for products related to cell/tissue-based medical devices shall conform to the following requirements.
A. Areas for receiving and processing raw materials or materials and storage of products, etc. shall be separated from the other areas for manufacturing products related to cell/tissue-based medical devices.
B. Areas for receiving and processing raw materials or materials and storage of products, etc. shall have a structure and facilities necessary for these operations.
[4] Areas for manufacturing products using human blood or plasma as raw materials or materials should be clearly separated from the other areas, and there should be facilities and apparatuses exclusively for use in manufacturing. This shall not apply to manufacturing processes after a process to inactivate or remove viruses.
[5] Facilities used to control animals for use in manufacturing or testing (donor animals [including animals providing cells or tissues that become raw materials or materials of

cell/tissue-based medical devices; the same shall apply in this chapter]; hereinafter referred to as “animals used”) shall meet the following requirements.

A. An area for inspection of animals used shall be separated from the other areas.

B. There should be a storage facility for feed with no risk of intrusion of pests.

C. There should be a housing room for animals for use in manufacturing and housing room for animals for use in testing.

D. The housing rooms for animals used have a different line of the air-handling system from those of the other areas. This does not apply to animals that are considered appropriate to be kept outside.

E. When animals used are inoculated with antigens, etc., there should be an inoculation room separated from a necropsy room for animals.

(Documents related to manufacturing control and quality control)

Article 74 Marketing authorization holders, etc. of products related to biological medical devices, etc. (hereinafter referred to as "marketing authorization holders, etc. of biological medical devices, etc.") shall, when handling products related to biological medical devices, etc., describe the following matters in a product master formula in addition to those specified in Article 7-2.

[1] Names, nature, properties, ingredients and their contents, and other specifications of materials obtained from humans, animals, plants, or microorganisms, which are used as parts, etc.

[2] Specifications of animals used (including a method of breeding control)

[3] Other necessary matters

(Process control)

Article 75 Marketing authorization holders, etc. of biological medical devices, etc. shall, when handling products related to biological medical devices, etc., appropriately control operations related to process control of products related to biological medical devices, etc. listed below and document the procedures based on a product master formula in addition to the operations described in the preceding article.

[1] Instruct a person designated beforehand to conduct the following operations according to the details of the operations.

A. When biological raw materials (raw materials or materials which are derived from organisms [excluding plants] and used for manufacturing biological medical devices, etc.; the same shall apply hereinafter) and microorganisms, etc. contained in products, etc. are inactivated or removed in the manufacturing process, take measures necessary to prevent

contamination by raw materials, materials, or products, etc. that have not undergone inactivation or removal.

B. When biochemical technologies, such as fermentation, are used in the manufacturing process, items, such as temperature and hydrogen ion index, necessary for controlling the manufacturing process shall be continuously measured.

C. If a column chromatography device, etc. is used in the manufacturing process, take necessary measures to prevent contamination of the device by microorganisms, etc., and measure endotoxin where necessary.

D. If a culture system is used in the manufacturing process to continuously supply culture media to a culture vessel and continuously discharge culture fluid, take necessary measures to maintain culture conditions in the culture vessel during the culture period.

E. In the following cases, perform validation, and prepare and retain the records.

(1) When manufacturing of products related to biological medical devices, etc. is newly started at the manufacturing site

(2) When there is a change in manufacturing procedures, etc., which has a significant impact on the quality of products related to biological medical devices, etc.

(3) Other cases where it is deemed necessary for proper conduct of manufacturing control and quality control of products related to biological medical devices, etc.

F. Access to work areas by persons other than those engaged in manufacturing operations should be restricted as much as possible.

G. Implement hygiene control of members in accordance with the following provisions.

(1) Restrict entry of members to clean areas or aseptic areas where operations are being conducted as much as possible.

(2) Members engaged in manufacturing operations shall not be engaged in operations related to control of animals used (excluding those currently used in the manufacturing process).

H. Implement hygiene control of members engaged in operations in clean areas or aseptic areas in accordance with the following requirements.

(1) Persons engaged in manufacturing operations shall wear disinfected work clothes, shoes, caps, and masks.

(2) Medical check-ups shall be given periodically members to confirm that they do not suffer from diseases that may contaminate products, etc. with microorganisms, etc.

(3) If members are in a health condition that may cause contamination of products, etc. by microorganisms, etc. (including skin or hair infection, cold, injury, or symptoms, such as diarrhea or fever of unknown cause; the same shall apply hereinafter), they shall report it.

I. Animals used (limited to those used for manufacturing; the same shall apply hereinafter in

this item) should be bred under proper control at all times, and their health should be monitored so that animals with infectious disease and other animals unsuitable for use would not be used.

J. All goods contaminated by microorganisms (limited to those contaminated in the manufacturing process) and carcasses of animals used should be treated so as not to cause hazards to the public health and hygiene.

K. Prepare and retain records on the following matters concerning the handling of strains of microorganisms used for manufacturing.

(1) Name of microorganism and number assigned to each container

(2) Date of receipt and name and address of the other party (name and address in the case of a corporation)

(3) Biological properties and date of inspection

(4) Status of subculture

L. Verify that biological raw materials are appropriate based on a product master formula of the products concerned, and prepare and retain records on the results of the verification.

M. For biological raw materials for use in manufacturing of biological medical devices, etc., records shall be prepared and retained as specified by the Minister of Health, Labour and Welfare. An agreement shall be concluded with the relevant collector, etc. of raw materials or materials falling under the category of the biological raw materials concerned (hereinafter referred to as "raw material collector, etc.") to store them appropriately at the raw material collector.

[2] Prepare and retain records of E, L, and M of the preceding item for each lot.

2. Marketing authorization holders, etc. of biological medical devices, etc. shall, when handling products related to cell/tissue-based medical devices, appropriately control operations related to process control of products related to cell/tissue-based medical devices listed below at a manufacturing site of the products in question and document the procedures based on a product master formula in addition to the operations described in the preceding paragraph.

[1] Instruct a person designated beforehand to conduct the following operations according to the details of the operations.

A. When handling cells or tissues collected from different donors (persons providing cells or tissues as raw materials or materials of cell/tissue-based medical devices [excluding those related to bodies of brain-dead persons specified in Paragraph 2, Article 6 of the Act on Organ Transplantation <Act No. 104 of 1997>]; the same shall apply in this chapter) or donor animals, take necessary measures to prevent mix-up and cross-contamination of the cells or tissues.

B. At the time of receipt of cells or tissues as raw materials or materials, verify that they are appropriate based on a product master formula of the products and records of the following matters, and prepare records on the results.
(1) Site where the cells or tissues were collected
(2) Date of collection of the cells or tissues
(3) Status of donor screening (a diagnosis of a donor is made through history taking or tests, etc., and whether the donor is fully eligible to provide cells or tissues that become raw materials or materials of products related to cell/tissue-based medical devices is judged by history taking and tests, etc.) if the cells or tissues are derived from humans
(4) Acceptance status of donor animals and status of donor screening (testing and rearing management are performed for donor animals, and whether the donors are fully eligible as providers of cells or tissues that become raw materials or materials of products related to cell/tissue-based medical devices is judged by the testing and breeding control) if the cells or tissues are derived from animals
(5) Process of operations to collect the cells or tissues
(6) In addition to those listed in (1) to (5), matters necessary for ensuring the quality of products related to cell/tissue-based medical devices
C. When collecting cells or tissues as raw materials or materials from donor animals, take necessary measures to prevent contamination by microorganisms, etc. in the process of collection, and prepare records of such measures.
D. When any of the following is applicable to a member, do not allow the member to engage in operations in a clean area or aseptic area.
(1) He/she is in a health condition that may cause contamination of products by microorganisms, etc.
(2) Microorganisms, etc. that may contaminate cells or tissues are handled immediately before collection or processing of cells or tissues.
E. Know the name of a business office to which products are released, date of release, and lot for each product, and prepare records thereof.
F. Take measures necessary to ensure the quality of products for distribution, and prepare records of such measures.
G. Prepare records on breeding control after receipt of donor animals.
[2] Prepare and retain records of B, C, F, and G in the preceding item for each lot and records of E in the same item for each product.
3. Marketing authorization holders, etc. of biological medical devices, etc. shall store records of the preceding two paragraphs so that a series of records from biological raw materials used in manufacturing to products manufactured by using the biological raw materials can

be checked appropriately.

(Testing)
Article 76 Marketing authorization holders, etc. of biological medical devices, etc. shall, when handling products related to biological medical devices, etc., appropriately control operations related to testing of products related to biological medical devices, etc. listed below at a manufacturing site of the products and document the procedures based on a product master formula in addition to the operations described in the preceding article.
[1] In order to prevent mix-up and cross-contamination of samples, samples should be separated by appropriate identification labeling.
[2] Testing that is important for quality control and cannot be performed with finished products should be conducted at an appropriate stage in the manufacturing process.
[3] Animals used (limited to those used for testing; the same shall apply hereinafter in this item) should be bred under proper control at all times, and their health should be monitored so that animals with infectious disease and other animals unsuitable for use would not be used.
[4] All goods contaminated by microorganisms (limited to those contaminated in the testing process) and carcasses of animals used should be treated so as not to cause hazards to the public health and hygiene.
[5] Prepare and retain records on the following matters concerning the handling of strains of microorganisms used for testing.
A. Name of microorganism and number assigned to each container
B. Date of receipt and name and address of the other party (name and address in the case of a corporation)
C. Biological properties and date of inspection
D. Status of subculture
[6] For each lot (biological raw materials used for manufacturing of products related to medical devices, etc. as specified biological products not constituting a lot: For each manufacturing number of the products or for each lot of the biological raw materials) of products related to specified biological medical devices, etc., reference samples in an amount of at least twice the quantity necessary for specified tests shall be stored under appropriate storage conditions for an appropriate period from the date of manufacturing (shelf life plus 10 years if medical devices related to the products are medical devices, etc. as specified biological products). This does not apply to products related to medical devices, etc. as specified biological products, not constituting a lot, for which reference samples are stored by a raw material collector, etc. for the relevant period as specified by operating

procedures agreed by the raw material collector, etc., and to products related to medical devices or cell/tissue-based medical devices designated by the Minister of Health, Labour and Welfare pursuant to the provisions of Paragraph 2, Article 43 of the Act, which do not constitute a lot. For products related to medical devices, etc. as specified biological products that constitute a lot, storage of biological raw materials used for manufacturing of the products may be substituted for storage of products after a period of the shelf life of the products plus one year.

2. Marketing authorization holders, etc. of biological medical devices, etc. shall, when handling products related to cell/tissue-based medical devices, appropriately control operations related to testing of products related to cell/tissue-based medical devices listed in each of the following items at a manufacturing site of the products in question and establish/document the procedures based on a product master formula in addition to the operations described in the preceding paragraph.

[1] Instruct a person designated according to the details of operations beforehand to conduct testing at the time of receipt and after receipt of donor animals and other necessary operations.

[2] Prepare and retain records of the operations specified in the preceding item.

3. Marketing authorization holders, etc. of biological medical devices, etc. shall store records of the preceding two paragraphs so that a series of records from biological raw materials used in manufacturing to products manufactured by using the biological raw materials can be checked appropriately.

(Education and training)

Article 77 Marketing authorization holders, etc. of biological medical devices, etc. shall, when handling products related to biological medical devices, etc., document procedures for the following operations in addition to those specified in Article 23.

[1] Provide education and training related to microbiology, medicine, and veterinary medicine, etc. to members engaged in manufacturing or testing of products related to biological medical devices, etc.

[2] Provide education and training on measures necessary for prevention of microbial contamination to members engaged in operations in aseptic areas, areas handling pathogenic microorganisms, and so forth.

2. Marketing authorization holders, etc. of biological medical devices, etc. shall prepare and retain records on the education and training in the preceding paragraph.

(Management of documents and records)

Article 78 Marketing authorization holders, etc. of biological medical devices, etc. shall retain documents specified in this chapter or at least one copy of the documents for the periods listed in the following items (5 years for those related to education and training) from the date of abolition of the documents. However, for documents used for manufacturing or testing of products, it is enough to store those documents so that they can be used during storage of records related to the products specified in the following paragraph.

[1] Shelf life plus 30 years for products related to medical devices, etc. as specified biological products, etc. or biological medical devices, etc. manufactured using human blood as raw materials (origin of raw materials or materials used in manufacturing [including those used in the manufacturing process; the same shall apply hereinafter]; the same shall apply hereinafter)

[2] Shelf life plus 10 years for products related to biological medical devices, etc. (excluding those listed in the preceding item)

2. Marketing authorization holders, etc. of biological medical devices, etc. shall retain records specified in this chapter for the period specified in Item 1 or Item 2 of the preceding paragraph from the date of preparation (5 years for those related to education and training).

(Exceptions for retention of records)

Article 79 Marketing authorization holders, etc. of biological medical devices, etc. shall, notwithstanding the provisions of this chapter, retain records specified in this chapter for products related to biological medical devices, etc. designated by the Minister of Health, Labour and Welfare for the period designated by the Minister. This does not apply to cases where an agreement is concluded with a raw material collector, etc. and the raw material collector, etc. stores them appropriately for the said period.