

July 31, 2017

To: Directors of Health Departments (Bureaus) of Prefectural Governments

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

Amendment of the Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Medical Devices and *In Vitro* Diagnostics related to reprocessed single-use medical devices (R-SUDs)

The Ministry of Health, Labour and Welfare (MHLW) has decided to launch a new system to enable the reprocessing of single-use medical devices (operations on used single-use medical devices (medical devices designed to be used only once; the same shall apply hereinafter) including product inspection, disassembling, cleaning, sterilization or disinfection, and other appropriate processing of used single-use medical devices for the purpose of marketing them as new medical devices; the same shall apply hereinafter). In response to this decision, the “Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Medical Devices and *In Vitro* Diagnostics“ (MHLW Ministerial Ordinance No. 169 of 2004; hereinafter, the “QMS Ordinance”) has been partially amended as specified in “Amendment of the Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Medical Devices and *In Vitro* Diagnostics” (MHLW Ministerial Ordinance No. 84 of 2017, by MHLW; hereinafter, the “Amending Ministerial Ordinance”).

The standards for manufacturing control and quality control for products related to R-SUDs (single-use medical devices that have undergone reprocessing; the same shall apply hereinafter) are specified as additional requirements in Chapter 5-2 of the QMS Ministerial Ordinance (hereinafter, the “Amended QMS Ministerial Ordinance”) amended according to the Amending Ministerial Ordinance. The standards are to be handled in terms of their more specific applications as follows. We request your cooperation in circulating the information contained in this Notification to marketing authorization holders (MAHs) of medical devices, etc. under your supervision.

In addition, we remind you that MAHs of R-SUDs (MAHs of medical devices or *in vitro* diagnostics (except for designated foreign manufacturers with marketing approval for medical devices and designated foreign manufacturers with marketing approval for designated specially

controlled medical devices), designated foreign holders of special approval for medical devices, or foreign manufacturers of designated specially controlled medical devices; the same shall apply hereinafter) shall comply with the “Amendment of the Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Medical Devices and *In Vitro* Diagnostics in association with enforcement of the Law for Partial Amendment of the Pharmaceutical Affairs Law” (PFSB/CND Notification No. 0827-4, by the CND Director, PSFB, MHLW, dated August 27, 2014).

Please note that copies of this notification will be sent to the director-general of each regional Bureau of Health and Welfare; the Chief Executive of the Pharmaceuticals and Medical Devices Agency (PMDA); the Chairperson of the Japan Federation of Medical Devices Associations; the Chairperson of the Federation of Pharmaceutical Manufacturers’ Associations of JAPAN; the Chairperson of Japan Association of Clinical Reagents Industries; the Chairperson of Medical Devices and Diagnostics Subcommittee, the American Medical Devices and Diagnostics Manufacturers’ Association in Japan; the Chairperson of Medical Device and IVDs Committee, the European Business Council in Japan; and the Representative of the Japan Certification Council for Drugs and Medical Devices.

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## 1 Summary of amendment

- (1) MHLW has specified additional requirements for MAHs of R-SUDs in Chapter 5-2 of the Amended QMS Ordinance in conjunction with the establishment of the system for the reprocessing of single-use medical devices. These requirements include those meant to ensure traceability throughout processes from medical institutions which supply, as providers, recyclable components (components specified in Article 2, Paragraph 3 of the Amended QMS Ordinance; that constitute the whole or a part of a single-use medical device used at a medical institution and that are supplied for reprocessing; the same shall apply hereinafter) to after release of products related to the R-SUDs as well as those to prevent contamination of the finished products, such as requirements for buildings and facilities.
- (2) In Chapter 6 of the Amended QMS Ordinance, provisions of Chapter 2 to Chapter 5-2 (with certain exceptions) shall apply to manufacturing and quality controls in effect at the manufacturers of medical devices for export and registered manufacturers of medical devices to which MAHs outsource the process (manufacturers specified in Article 23-2-3, Paragraph 1 and Article 23-2-4, Paragraph 1 of the “Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics” (Act No. 145 of 1960); hereinafter, the “Act”), the same shall apply hereinafter).

## 2 Article-by-article explanations

- (1) Article 2 (Definitions)

- a. “R-SUDs” are single-use medical devices that have undergone reprocessing. R-SUDs shall be designed to have the quality, efficacy, and safety equivalent to those of the original medical device in consideration of potential decreases in characteristics and performance due to the reprocessing.
- b. “Recyclable components”: components among those specified in Article 2, Paragraph 3 that constitute the entirety or a part of a single-use medical device used at a medical institution, and are provided for reprocessing.
- c. “Original medical devices”: Single-use medical devices intended to be reprocessed and have not been previously reprocessed.

(2) Article 3 (Scope)

- a. Marketing authorization holders of R-SUDs shall implement manufacturing control and quality control on products related to R-SUDs in accordance with provisions in Chapters 2 and 3 as well as those described in Chapter 5-2. In addition, to R-SUDs that are classified as biological medical devices in accordance with provisions in Chapter 4 in addition to the above provisions.

(3) Article 6 (Documentation of quality management system)

- a. “Product Master File” in Paragraph 2 may include matters listed in Section 6. 6. (5) in “Amendment of the Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Medical Devices and *In Vitro* Diagnostics in association with enforcement of the Law for Partial Amendment of the Pharmaceutical Affairs Law” (PFSB/CND Notification No. 0827-4, by the CND Director, PSFB, MHLW, dated August 27, 2014; hereinafter, the “Explanatory Notification”), as well as each of the following.
  - (a) Generic name based on the JMDN (Japanese Medical Device Nomenclature) and the Japanese branded name of the original medical device (including the model if applicable)
  - (b) Date of premarketing approval (certification) of the original medical device and premarketing approval (certification) number (for products requiring neither premarketing approval nor premarketing certification, date of submission of premarketing notification)
  - (c) Drawing, specifications, and raw materials or ingredients and their quantities of the original medical device
  - (d) Agreement with a medical institution that provide recyclable components (name and location of the medical institution, generic name and branded name of recyclable components to be supplied (including the model if applicable), handling and storage method of recyclable components (including measures to prevent confusion with ones specified in Section 4. 1 (4) of the “Standards for Reprocessed Single-use Medical Devices” (MHLW Ministerial Notification No. 261 of 2017; hereinafter referred to as “Reprocessing Standards”)), selection criteria for recyclable components, periodic inspection method for control status of recyclable components at the medical

institution, training method for healthcare professionals, transportation form and method of recyclable components, and the other matters for handling of recyclable components as appropriate)

- (e) If transportation of recyclable components is commissioned to a third party, agreement with the consignee carrier

(4) Article 19 (Review input)

Item 3 “conformity to product requirements” may include information about the quality and safety of the original medical device. For instance, recall information or malfunction information related to the original medical device may be considered.

(5) Article 25 (Working environment)

a. Paragraph 5 “contaminated or potentially contaminated products” may include not only recyclable components but also used SUDs that have been rejected by acceptance inspection and thus are not selected as recyclable components and transportation containers contaminated with microbial pathogen and other pathogenic agents.

b. Paragraph 5 “guidance” may include requirements for prevention against contamination in operators; requirements for opening of transportation containers; disposal method of products contaminated or potentially contaminated with microbial pathogen and other pathogenic agents; disinfection method in the case of contamination in the operation environment; garment policies for operators such as gloves, mask, goggles, plastic apron, and cap (“Instructions for disinfection and sterilization under the Infectious Disease Act” (HSB/TIDCD Notification No. 0130001, by the TIDCD Director, HSB, MHLW, dated January 30, 2004; hereinafter, the “Infectious Disease Notification”)).

(6) Article 26 (Commercialization planning)

Paragraph 5 “all the process for product commercialization” may include storage of recyclable components at medical institutions and transportation from medical institutions to registered manufacturers.

(7) Article 27 (Determination of product requirements)

Product requirements for operations related to storage and transportation of recyclable component should be clearly determined so that the quality and safety of the R-SUDs would not be affected.

(8) Article 29 (Customer communication)

Communication with customers shall cover applicable information according to the provisions in this ordinance as well as the Reprocessing Standards.

(9) Article 31 (Design and development inputs)

a. For design and development, the original medical device shall be clearly

characterized. The characterization may cover the following items:

- (a) Requirements for the shape, structure, dimensions, raw materials, functions, performance, and safety of the original medical device
- (b) Lifecycle of used SUDs (control status on transportation from use by healthcare professionals to registered manufacturers)
- b. If used SUDs provided by medical institutions are stained with blood, the contamination status, transportation period from the use of the concerned medical devices at medical institutions to registered manufacturers, and period from the use to inactivation or removal of microbial pathogen and other pathogenic agents affect the cleaning effect. These periods shall be considered as input information.
- c. Input information shall be based on concepts such as points to consider for application for approval of R-SUDs, provided in a separate notification.

(10) Article 32 (Design and development outputs)

Output information for R-SUDs may include items listed in Section 6. 32. (2) of the Explanatory Notification as well as the following matters.

- (a) Requirements for receipt of recyclable components from medical institutions, transportation, and storage
- (b) Other matters necessary for ensuring the quality, efficacy, and safety of R-SUDs

(11) Article 33 (Design and development review)

Paragraph 2 “experts engaged in the concerned design and development” may include those in fields related to medicine, veterinary medicine, and/or microbiology.

(12) Article 35 (Design and development validation)

- a. “Design and Development Validation“ as defined in Paragraph 1 shall be implemented with respect to finished products manufactured from recyclable components in the worst-case scenario, or on prototype products under actual use conditions or comparable simulated use conditions.
- b. The worst-case condition for recyclable components shall be established in consideration of extent of contamination in recyclable components, storage condition, storage period, number of reprocessing cycles, lifecycle of used SUDs (control status on transportation from use by healthcare professionals to registered manufacturing sites), as well as materials degradation.

(13) Article 36 (Design and development change control)

Changes in design and development may include matters listed in Section 4. 2 (1) b, (2) b, and (3) c of the Reprocessing Standards.

(14) Article 45 (Process validation)

- a. Processes to be validated may include cleaning of recyclable components, products, or manufacturing equipment.

- b. Validation for processes for transportation, disassembling, cleaning, reassembly, inspection, and sterilization of recyclable components, products, or equipment shall be implemented in accordance with provisions in this article and Article 81-2-2, Paragraph 1, Item 1.

(15) Article 47 (Identification)

- a. Identification labeling shall be affixed to R-SUDs and recyclable components so that the number of reprocessing cycles can be made known. For example, the number of reprocessing cycles is included in the identification label.  
In addition, verification should be implemented on the identification label to ensure that the cleaning and sterilization processes are performed a number of times equal to that of the number of reprocessing cycles so as to avoid deterioration or malfunction of the label.
- b. Recyclable components and replacement components shall be appropriately identified to prevent confusion.

(16) Article 48 (Traceability)

According to the provisions in Section 6. 3 (1) a. of the Reprocessing Standards, the name and location of the medical institution that supplied the recyclable component can be traced.

(17) Article 52 (Product preservation)

Cleanliness of recyclable components shall be preserved as specified in the approval certificate by inactivation or removal of microbial pathogen and other pathogenic agents using validated methods utilized during reprocessing procedures (including identification, handling, storage, and protection).

(18) Article 60 (Control of non-conforming products)

If disassembly of recyclable components provided by medical institutions at registered manufacturers reveals that these components are not suitable for reprocessing, such components shall be handled as non-conforming products, and record on the relevant actions shall be prepared.

(19) Article 61 (Data analysis)

- a. Paragraph 2, Item 2 “conformity to product requirements” may include information about the quality and safety of the original medical device.
- b. Paragraph 2, Item 3 “characteristics and trends of processes and products (including opportunities for preventive actions)” may include disassembling, cleaning, reassembly, and sterilization processes.

(20) Article 62 (Improvements)

In consideration of provisions set forth in Paragraph 6, if a recall is implemented due to quality reasons, pursuant to Article 114-54, Item 11, B. of the “Enforcement

Regulations of the Law on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics” (MHLW Ministerial Ordinance No. 1 of 1961; hereinafter, the “Enforcement Regulations”), information related to the applicable issue(s) shall be immediately provided to the MAH of the original medical device following recognition of such issue(s) (excluding cases where the reason for the recall is clearly attributable to reprocessing of the relevant R-SUD(s)).

(21) Article 66 (Additional QMS requirements)

Marketing authorization holders of R-SUDs shall implement manufacturing control and quality control of the products according to the provisions of Chapters 2 and 3 as well as Chapter 5-2.

(22) Article 72 (Domestic QA managers)

- a. Section 2, Items 4 and 5 “products distributed in Japan” indicates R-SUDs and original medical devices.
- b. Paragraph 2, Item 4 “information about changes on manufacturing methods and testing and inspection methods that potentially affect the quality of the concerned product, if any” may include information listed in Section 4. 2. (3) c of the Reprocessing Standards and notifications from the MAH of the original medical device which may have a potential impact on the quality of the product.
- c. Paragraph 2, Item 5 “quality information” may include information of recalls implemented by the MAH of the original medical device.

(23) Article 81-2 (Infrastructure at registered manufacturers such as MAHs of R-SUDs)

- a. This article defines infrastructure requirements at the registered manufacturers where products related to R-SUDs are processed, which MAHs of R-SUDs must meet.
- b. The registered manufacturers subject to the provisions of this article are sites where products related to R-SUDs as stipulated in Article 2, Paragraph 27 are manufactured.
- c. The provisions of this article do not apply to the registered manufacturing sites where products related to R-SUDs are manufactured but the relevant manufacturing process includes only design or storage of the finished products in Japan.
- d. Item 1, A. “microbial pathogens and other pathogenic agents” may include blood, body fluids, microbial pathogens, and/or other pathogenic agents.
- e. Item 1, A. “inactivation or removal” means an operation in which microbial pathogen and other pathogenic agents are inactivated or removed to the level specified in the approval certificate by the approved cleaning, sterilization, and other methods.
- f. Item 1, A (1) “hazardous waste water” may include waste water that contains

substances with an impact on human body or environment, such as blood, and microbial pathogen and other pathogenic agents.

- g. Item 1, B (1) “handle” indicates actions including testing and inspection, not limited to manufacturing (the same shall apply hereinafter).
- h. Item 1, B (1) “area(s) where recyclable components contaminated with microbial pathogens and/or other pathogenic agents are handled” may include areas where handling of recyclable components potentially stained with blood or body fluids, or that have become contaminated with microbial pathogens and/or other pathogenic agents occurs. Examples include, areas where used SUDs to be cleaned are handled or where transportation containers are cleaned.
- i. Item 1, B (1) “microbial pathogens and other pathogenic agents” shall be handled according to the latest versions of the “Biosafety Control Code of the National Institute of Infectious Diseases”, the Infectious Disease Notification, and related guidelines.
- j. Item 1, B (2) “transportation containers” to be used shall be those specified in the approval certificate.
- k. Item 1, C may include instruments for measurement of the status of cleanliness of recyclable components and for analysis of ingredients in raw materials, for instance.
- l. Item 2 “clearly separated” means that a given area is wholly separated from the area(s) involved in the manufacture of products other than R-SUDs (e.g. recyclable components contaminated with microbial pathogen and other pathogenic agents must be handled separately from recyclable components following sterilization/decontamination). Specifically, the concerned item requires measures to prevent contamination of post-cleaning recyclable components and R-SUDs with stained recyclable components (i.e. pre-cleaning components).  
In addition, for separation of recyclable components contaminated with microbial pathogen and other pathogenic agents from post-cleaning recyclable components, they are required to be controlled at separate places. Separation of the area(s) involved in manufacture of products other than R-SUDs means that the relevant operations are carried out in a separate room.
- m. Item 2 aims to eliminate hazards caused by microbial pathogens and/or other pathogenic agents and to prevent occurrence of quality/safety issues resulting from inappropriate manufacturing or handling practices in the course of the manufacture of products related to R-SUDs.

(24) Article 81-2-2 (process control)

- a. Paragraph 1, Item 1, A. “evaluate medical institutions for selection” means that appropriate control is required under “Amendment of Enforcement Regulations of the Law on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical



Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics related to Reprocessed Single-use Medical Devices” (PSEHB Notification No. 0731-7, by the PSEHB Director-General, MHLW, dated July 31, 2017).

- b. Paragraph 1, Item 1, A (1) “standards specified by the Minister of Health, Labour and Welfare” indicate a part of matters specified in the Reprocessing Standards that are applicable.
- c. Paragraph 1, Item 1, B “cleaning and disinfection of transportation containers” require validation to demonstrate that transportation containers are not contaminated with microbial pathogen or other pathogenic agents where necessary.
- d. Paragraph 1, Item 1, C “appropriate actions” mean that pre-cleaning recyclable components contaminated with microbial pathogen and other pathogenic agents and post-cleaning recyclable components are required to be controlled in separate places to ensure discrimination.
- e. Paragraph 1, Item 1, D “prevention of cross contamination with microbial pathogen and other pathogenic agents” may include appropriate preventive measures against cross-contamination to ensure that recyclable components received from medical institutions outside of Japan are not confused and do not come into contact with recyclable components received from products marketed in Japan. For example, appropriate measures may be as follows; considerations are given to operation schedule so that both components are not handled at the same time; and manufacturing equipment and testing instruments in common use are cleaned to ensure their cleanliness where applicable.
- f. Paragraph 1, Item 1, E “take appropriate actions to remove contamination” means that appropriate inactivation or cleaning, or other actions based on scientific knowledge should be taken to remove the concerned contamination. In addition, appropriate actions should be taken on products involved in the concerned contamination.
- g. Paragraph 1, Item 1, F (1) indicates that cleaning validation should be performed in a worst-case scenario, using recyclable components, as described in 2 (12) or comparably simulated samples.
- h. Paragraph 1, Item 1, F (2) may include changes on transportation containers and carrier in the transportation process and changes on cleaning method, cleaning agents, and cleaning equipment in the cleaning process.
- i. Paragraph 1, Item 1, F (3) means that in the event of a change in raw materials used in the original medical device or in the course of its intended use, its impact on the R-SUDs should be evaluated, and appropriate actions should be taken.
- j. Paragraph 1, Item 1, G “reprocessing clean area” means places designated for manufacturing and storage activities where recyclable components containing inactivated and/or removed microbial and/or other pathogenic agents are handled,

and may also include spaces set aside for tasks such as packaging prior to sterilization.

- k. Paragraph 1, Item 1, J “Records” corresponds to matters specified in Section 6-3 of the Reprocessing Standards.
- l. Paragraph 1, Item 2 “names of establishments of shipping address” include those of medical institutions to which the products are delivered.
- m. The provisions in Paragraph 2 aim to control traceability in manufacture of products related to R-SUDs: For example, even in the event that a problem occurs in the product or an infectious disease is contracted due to use of the product, records from all stages of the use of recyclable components in the manufacture to release of the products manufactured from the concerned recyclable components can be traced in order to enable to identify concerned products and investigation of the cause immediately.

(25) Article 81-2-4 (Training)

- a. “Training” consists of conceptual education and practical, on-the-job training.
- b. “Training for microbiology, medicine, and veterinary concerns” covers the various fields necessary for reprocessing such as methods for handling microbial and/or other pathogenic agents, and the content corresponds to the manufacturing of R-SUDs and the duties assigned to trainees.

(26) Article 81-2-5 (Document control)

“Shelf life” shall mean shelf life of R-SUDs described in the approval certificate.

(27) Article 81-2-6 (Traceability of products related to R-SUDs)

MAHs of R-SUDs shall ensure post-release traceability of the concerned products so that these products will not be delivered to medical institutions that do not intend to use R-SUDs by mistake. Such MAHs, therefore, are required to request that retailers of the relevant products prepare records on their distribution and retain the records. In addition, these MAHs must establish and implement a control system for the concerned records in cooperation with retailers so that these records can be submitted without delay in response to a request in inspections and audits on the MAHs of R-SUDs