

July 31, 2017

To: Prefectural Governors

Director-General of the Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)

Amendment of the Enforcement Regulations of the Act 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 (R-SUDs)

The Ministry of Health, Labour and Welfare (MHLW) has decided to establish a new system allowing for the reprocessing of single-use medical devices. Accordingly, the relevant laws and regulations are partially amended pursuant to the “Ministerial Ordinance for Partial Amendment of the Enforcement Regulations of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics” (MHLW Ministerial Ordinance No. 82 of 2017), the “Ministerial Ordinance for Partial Amendment of the Fee Regulations related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics” (MHLW Ministerial Ordinance No. 83 of 2017), and the “Ministerial Ordinance for Partial 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). In addition, the “Standards for Reprocessed Single-use Medical Devices” (MHLW Ministerial Notification No. 261 of 2017) are hereby established. We request your cooperation in circulating the information contained in this Notification to marketing authorization holders (MAHs) of medical devices, etc. under your supervision.

1 Definitions

The terminologies used in this Notification are defined as follows.

(1) The “Act”

“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)

(2) Amended Enforcement Regulations

“Enforcement Regulations of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics” (MHW Ministerial Ordinance No. 1 of 1961) amended according to “Ministerial Ordinance for Partial Amendment of the Enforcement Regulations of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics” (MHLW Ministerial Ordinance No. 82 of 2017)

(3) Amended Fee Regulations

“Fee Regulations related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics” (MHW Ministerial Ordinance No. 63 of 2000) amended according to the “Ministerial Ordinance for Partial Amendment of the Fee Regulations related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics” (MHLW Ministerial Ordinance No. 83 of 2017)

(4) Amended QMS Ministerial Ordinance

“Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Medical Devices and *In Vitro* Diagnostics” (MHLW Ministerial Ordinance No. 169 of 2004) amended according to “Ministerial Ordinance for Partial 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)

(5) Reprocessing Standards

“Standards for Reprocessed Single-use Medical Devices” (MHLW Ministerial Notification No. 261 of 2017)

(6) Single-use medical devices (SUDs)

Medical devices designed to be used only once

(7) Reprocessing

Operations related to product inspection, disassembling, cleaning, sterilization treatment, and other appropriate necessary processing in advance of the manufacturing and distribution of used SUDs

(8) R-SUDs

Single-use medical devices that were reprocessed

(9) Original medical devices

SUDs that are intended to be reprocessed and have not been previously reprocessed.

(10) Recyclable components

Components that constitute the entirety or a part of a SUD used at a medical institution, and are supplied for reprocessing

(11) Replacement components

Components designed to constitute a part of R-SUDs and are manufactured as new goods

2 Application for approval of R-SUDs

- (1) For marketing of R-SUDs, premarketing approval under Article 23-2-5, Paragraph 1 of the Act or premarketing approval of foreign manufactured medical devices under Article 23-2-17, Paragraph 1 of the Act (hereinafter, “approval”) is required as a different product item from the original medical device.
- (2) R-SUDs must conform to the Reprocessing Standards.
- (3) For submission of an application for approval of an R-SUD, the applicant must pay a prescribed fee as a medical device listed in Article 12, Paragraph 1, Item 1. A (2) or (4) of the “Order for Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics” (Cabinet Order No. 91 of 2000; hereinafter, “Fee Order”). (Article 3 of the Amended Fee Regulations)
- (4) The device class of the R-SUDs shall be the same as that of the original medical device in principle. If the original medical device is recognized as Class I, General Medical Device, the corresponding R-SUD shall be recognized as Class II, Control Medical Device irrespective of “Amendment of the Classification Rules for Specially Controlled Medical Devices, Controlled Medical Devices and General Medical Devices” (Notification No. 0510-8 by the PFSB Director-General, MHLW, dated May 10, 2013).

3 MAH authorization of R-SUDs

- (1) R-SUDs shall be marketed by medical device marketing authorization holders in accordance with Article 23-2, Paragraph 1 of the Act or marketing authorization holders designated according to the provisions in Article 23-2-17, Paragraph 1 of the Act (hereinafter referred to as “MAHs of R-SUD”).
- (2) In the reprocessing process of SUDs, it is critical to ensure implementation of cleaning and sterilization. To this end, MAHs of R-SUDs are required to comply with the following provisions as specified in Article 23-2-15, Paragraph 1 of the Act. Identically to the manner by which medical devices classified as biological products are handled, MAHs of R-SUDs shall appoint a person with appropriate knowledge of bacteriology to provide support to the general marketing supervisor responsible for medical devices products in cases where the general marketing supervisor, domestic quality assurance manager, and safety manager does not have such knowledge (Article 114-54, Item 4 of

the Amended Enforcement Regulations).

As required for biological product manufacturing manager, persons with bacteriological knowledge are required to be as follows.

- a. Physicians or other persons with a degree in medicine
- b. Dentists specializing in bacteriology
- c. Persons specializing in bacteriology with a minimum of a Master's degree
- d. Persons who completed coursework and training of microbiology at the university level, acquired relevant skills, and was subsequently engaged for a minimum of 3 years in manufacture of biological products or medical devices requiring special attention from the viewpoint of public health and safety as with biological products (including manufacture of investigational devices)

4. Registration of manufacturer of R-SUDs

- (1) During the reprocessing process of SUDs, it is critical to ensure implementation of cleaning and sterilization. Implementation of the following steps in the manufacturing process of R-SUDs shall be registered pursuant to Article 23-2-3, Paragraph 1 of the Act or Article 23-2-4, Paragraph 1 of the Act (Article 114-8, Item 4 of the Amended Enforcement Regulations).

[1] Design

[2] Receipt, disassembling, and cleaning etc. of used SUDs

The relevant steps cover a place for temporarily storage of SUDs that were used but have not been cleaned and a step for inspecting used SUDs received from medical institutions in terms of whether they can be supplied with respect to the subsequent reprocessing processes.

[3] Primary assembly and other principal manufacturing steps (other than design, receipt of used SUDs, disassembling, cleaning, sterilization and storage).

[4] Sterilization

[5] Storage of finished products in Japan

- (2) During the reprocessing process of SUDs, it is critical to ensure implementation of cleaning and sterilization. In light of this, the following compliance rule for manufacturers of medical devices specified in Article 23-2-15, Paragraph 2 of the Act is stipulated: Such manufacturers shall appoint a physician, or a person with appropriate knowledge of bacteriology or expertise in sterilization of medical devices as an assistant to the technical supervisor of medical devices at the manufacturing site for reprocessing of SUDs (except for storage of the finished product in Japan) in cases where the relevant technical supervisor of medical devices is not a physician or does not have the knowledge and experience described previously (Article 114-54-2 of the Amended Enforcement Regulations).

Persons with appropriate knowledge of bacteriology are as described in 3 (2). Persons with expertise in sterilization of medical devices shall be ones certified as Type 1, Sterilization Technologist by the Japanese Society of Medical Instrumentation or shall be ones who have skills comparable to the above.

5. Manufacturing process of R-SUDs

(1) Receipt of recyclable components from medical institutions

- [1] Recyclable components must be those currently used in Japan. (Section 4-1 (1) of the Remanufacturing Standards)
- [2] Recyclable components must meet the following conditions. Appropriate selection shall be conducted at medical institutions to ensure that used SUDs not meeting these conditions are not included in recyclable components. (Section 4-1 (2) (3) (4) (6) of the Reprocessing Standards)
 - a Because it is difficult to neutralize or remove prions, components to be recycled must be ones that have not come in contact with the brain, spinal cord, dura mater, cerebral ganglion, spinal ganglion, retina or optic nerve.
 - b. Components to be recycled must not have been previously implanted in a human body.
 - c Components to be recycled must have not been previously used to treat or examine patients presenting with any Class I Infectious Disease, Class II Infectious Disease, Class III Infectious Disease, Class IV Infectious Disease, novel influenza infection, Designated Infectious Disease, or Novel Infectious Disease as specified in Article 6 of the “Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases” (Act No. 114 of 1998), or those specified in Article 8, Paragraphs 1 through 3 of the aforementioned law.
 - d Recyclable components must be ones that have been separately stored to avoid damage, deterioration, or contamination with microbial pathogen and other pathogenic agents that cannot be inactivated or removed in the manufacturing process.
- [3] MAHs of R-SUDs must specify procedures for receiving used SUDs from medical institutions to ensure that the above conditions are appropriately observed. The concerned procedures shall specify shape of transportation containers, frequency of receipt of recyclable components from medical institutions, and agreement with medical institutions in terms of responsibilities related to their receipt. The relevant procedures must each be reviewed individually and specifically during the review process and then specified in the approval certificate (Section 4-1 (5) of the Reprocessing Standards).
- [4] MAHs of R-SUDs must inspect whether recyclable components are selected by an appropriate method in accordance with the procedures previously specified at each medical institution (Section 4-1 (7) of the Reprocessing Standards).

In addition, as a condition for approval of R-SUDs under Article 79 of the Act, MAHs of R-SUDs will be requested to implement seminars and training for selection and storage in each medical institution. In addition, the inspection for appropriate selection and storage at a medical institution must be implemented not only at the start of receipt of recyclable components from the concerned medical institution but also periodically. The following inspection method is considered: The MAH periodically visits the medical institution to inspect the selection and storage methods and to provide a seminar about selection and storage to healthcare professionals involved.

- [5] Due care must be given under the following circumstances due to the potential for violation of the “Act for Disposal and Cleaning of Waste” (Act No. 137 of 1970): Medical waste that should have been disposed of at a medical institution was delivered to a MAHs of R-SUDs due to insufficient selection. If medical waste requiring disposal at a medical institution is discovered among the delivered contents, it should be returned to the medical institution.
- [6] The following circumstance is not considered to constitute the sale of a medical device: Delivery by a medical institution of recyclable components to be used as recyclable components to MAHs of R-SUDs.

(2) Transportation of recyclable components

- [1] To prevent spread of contamination caused by recyclable components received from medical institutions, MAHs of R-SUDs must comply with the provisions set forth in Article 114-54, Item 12 of the Amended Enforcement Regulations.
- [2] Recyclable components must be placed in dedicated well-closed containers, which are designed to avoid damage, deterioration, or contamination with microbial pathogens and/or other pathogenic agents that cannot be inactivated or removed in the manufacturing process, and the containers are completely and firmly shut, and then received from medical institutions for transport (Section 4-1 (10) of the Reprocessing Standards). Compliance with this provision shall be assessed even during the approval review process.

6 Change control procedures for R-SUDs with respect to changes to the original medical devices

- (1) Because R-SUDs must exhibit the same degree of quality, efficacy, and safety as the original medical device product, MAHs of R-SUDs are required to comply with the following procedures: MAHs of R-SUDs shall continuously check the original medical devices for any change on the raw materials or the other change that may potentially affects the quality, efficacy, and safety of the R-SUDs. If the concerned change occurs, the authorization holders shall make appropriate design changes and other actions to ensure the quality, efficacy, and safety of the R-SUDs (Article 114-54, Item 9 of the

Amended Enforcement Regulations).

- (2) If an additional indication is approved for the original medical device, it would not be automatically approved for the R-SUDs. To avoid confusion at medical institutions, the MAHs of R-SUDs shall consider application for approval of the additional indication immediately.

7 Post-marketing safety measures

- (1) MAHs of R-SUDs shall bear primary responsibility for post-marketing safety measures on the R-SUDs.

- (2) Recall and malfunction reporting

[1] Post-marketing safety measures of R-SUDs shall include not only collection of malfunction information originated from the reprocessing process, but also collection of post-marketing safety information such as malfunction reporting and recall information about the original medical devices, which shall be then properly reflected in post-marketing safety measures of the R-SUDs. To this end, MAHs of R-SUDs are stipulated to comply with the following actions: MAHs of R-SUDs shall continuously collect information about malfunctions and recalls of the original medical devices and the other information about the quality, efficacy, and safety; assess the collected information for an impact on the quality, efficacy, and safety of the R-SUDs; and take appropriate actions to prevent occurrence or expansion of any hazard or risk to public health and hygiene (Article 114-54, Item 10 of the Amended Enforcement Regulations).

[2] MAHs of R-SUDs are stipulated to comply with the following actions: They shall immediately inform MAHs of the original medical devices of the matters that affect appropriate control of the original medical devices, such as obtainment of approval of the concerned products, recall information, and safety control information (Article 114-54, Item 11 of the Amended Enforcement Regulations).

8 Inspection under Article 23-2-5, Paragraph 2, Item 4 of the Act (QMS inspection)

- (1) To the QMS Ministerial Ordinance, standards for manufacturing control and quality control for R-SUDs are hereby added as Chapter 5-2. In this new part, MAHs of R-SUDs must comply with the following: Ensure traceability throughout a process from medical institutions, suppliers of recyclable components, to customers of the R-SUDs and have facilities to prevent contamination of the final products (Article 3, Paragraph 4 of the Amended QMS Ministerial Ordinance).
- (2) R-SUDs shall be subjected to additional inspection (Article 114-33, Paragraph 1, Item 2, G of the Amended Enforcement Regulations).
- (3) MAHs of R-SUDs shall periodically undergo document inspection or on-site inspection

as specified in Article 23-2-5, Paragraph 8 of the Act, which is assigned as a condition for marketing approval, according to the provisions in Article 79, Paragraph 1 of the Act (hereinafter referred to as “periodic inspection for R-SUDs”) (Article 114-33, Paragraph 1, Item 1 of the Amended Enforcement Regulations).

It is stipulated as follows: When the relevant inspection is implemented, the Minister of Health, Labour and Welfare shall issue an inspection result certification to certify the result (Article 114-33, Paragraph 2 of the Amended Enforcement Regulations).

In principle, the head office of the MAHs of R-SUDs shall be the target of such inspections. All registered manufacturing sites listed in the approval application documentation shall be subject to inspections occurring approximately once per year, starting with the date of approval of the relevant product. (excluding the year of an inspections implemented every 5 years following the date of approval, in accordance with Article 23-2-5, Paragraph 6 of the Act)

In addition, the fee for the periodic inspection for R-SUDs is planned to be set by amending the Fee Order in the future.

- (4) Each R-SUD product shall be subject to QMS inspection.
- (5) Fees are stipulated for QMS inspection and additional inspection on manufacturing sites engaged in “receipt, disassembly, and cleaning of used SUDs in conjunction with the production of R-SUDs”. (Articles 7 and 8 of the Amended Fee Regulations)
- (6) Others

Further details concerning the treatment of QMS inspections including the matters described in the preceding items (1) through (5) shall be provided in a subsequent Ministerial Notification.

9 Others

Before applying for approval of an R-SUD, prospective applicants shall confirm that the proposed content does not infringe any patents or trademark rights of the original medical device. In addition, whether relevant patent(s) are present shall be determined on the planned date of application approval.