

Provisional Translation (as of December 2018) *

PSEHB/MDE Notification No. 0731-8

PSEHB/PSD Notification No. 0731-5

PSEHB/CND Notification No. 0731-1

July 31, 2017

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

Director of the Medical Device Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
(official seal omitted)

Director of the Pharmaceutical Safety Division,
Pharmaceutical Safety and Environmental Health Bureau,
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Points to Consider for Reprocessed Single-use Medical Devices

The Ministry of Health, Labour and Welfare (MHLW) has decided to launch a new system to enable the reprocessing of single-use medical devices. In response to this decision, the relevant laws and regulations have been amended in part as specified in 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), “Ministerial Ordinance for Partial Amendment of the Regulations 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” (MHLW Ministerial Ordinance No. 83 of 2017), and “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, MHLW has issued “Standards for Reprocessed Single-use Medical Devices” (MHLW Ministerial Notification No. 261 of 2017). The handling of reprocessed single-use medical device (R-SUDs) are specified as the “Amendment of Enforcement Regulations of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and

* This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

Cellular Therapy Products, Gene Therapy Products, and Cosmetics related to Remanufactured Single-use Medical Devices” (PSEHB Notification No. 0731-7, by the Director-General of the Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated July 31, 2017). Points to consider regarding each of the above items are provided 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.

1 Definitions

The following terminology used in this Ministerial Notification shall be defined as follows.

- (1) The “Act”: The “Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics” (Law No. 145 of 1960)
- (2) “Amended Enforcement Regulations”: 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” (MHW (currently MHLW) Ministerial Ordinance No. 1 of 1961), amended as specified in 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)
- (3) “Amended QMS Ordinance”: 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), amended as specified in 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)

2 Application for approval

- (1) Various topics related to applications for approval of R-SUDs are discussed in the “Points to Consider during the Preparation of Application Forms for Medical Device Marketing Approval” (PFSB/MDRMPE Notification No. 1120-1, by the Director of the Medical Device and Regenerative Medicine Product Evaluation, Pharmaceutical and Food Safety Bureau, MHLW, dated November 20, 2014) and the “Points to Consider regarding the Preparation of Attachments to an Application for Medical Device Marketing Approval” (PFSB/MDRMPE Notification No. 0120-9, by the Director of the Medical Device and Regenerative Medicine Product Evaluation, Pharmaceutical and Food Safety Bureau, MHLW, dated January 20, 2015). Additional matters related to R-SUDs will be discussed in a separate notification.
- (2) When a prospective applicant plans to submit an application for approval of R-SUDs,

such applicant shall use “Consultation for assessment of R-SUDs (QMS conformity assessment)” service offered by the Pharmaceuticals and Medical Devices Agency (PMDA) and be subject to an on-site inspection for an assessment for ensuring quality and safety concerning the manufacturing process, as part of the consultation , in advance where necessary. Especially, it is particularly advisable to use QMS conformity assessment whenever possible in conjunction with initial application submissions or when a manufacturing site will initiate reprocessing operations of SUDs products for the first time.

- (3) The generic name of R-SUDs shall be created by adding “reprocessed” to the beginning of generic name of the original medical device (“reprocessed + generic name of the original medical device”).
- (4) The brand name of R-SUDs shall clearly indicate the reprocessed status of the medical device and also include the name of the relevant MAH(s). An abbreviated name of the MAH of the R-SUDs may be used in the brand name.
- (5) If the original medical device is designated as a subject to use-results survey under Article 23-2-9, Paragraph 1 of the Act, and the surveillance period has not expired, such R-SUDs will also be subject to comparable use-results survey as the original medical device.

(2) Cleaning and sterilization

- [1] For details concerning the cleaning of R-SUDs, see the fundamental concept in the Appendix.
- [2] Methods for validating sterilization processes used for R-SUDs are provided in the “Amendment of Sterilization Validation Standards” (PSEHB/CND Notification No. 0215-13, by the Director of Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated February 15, 2017). This Notification should be consulted for more details concerning these methods.

3 Labeling

(1) Medical device product labeling

- [1] R-SUDs shall indicate the serial number or similar code on their body to ensure traceability of records on recyclable components, inspection, manufacturing, work environment conditions, and distribution.

Considering that serial number is provided to ensure traceability of records from receipt of recyclable components from medical institutions to the manufacturing process including inspection, manufacturing, work environment conditions, and distribution, the number should be provided in a form of a GS1 barcode.

- [2] R-SUDs must indicate its status in an appropriate method, such as by indicating the word “reprocessed” on the body of the device in order to prevent confusion for the original medical device. Where labeling to the body of the reprocessed product is difficult due to reasons such as product material or size, use of an attached tag indicating the status of a reprocessed product may also be acceptable, but care should be taken so that the tag does not come off during use.

(2) Items to be indicated on external containers

The word “reprocessed” must be indicated on external containers or wrappings of R-SUDs.

(3) MAHs of R-SUDs must maintain a record of the following information with respect to recyclable components.

- a. Name and location of the medical institution at which the SUD is supplied for remanufacturing
- b. Date of receipt of recyclable components from medical institutions
- c. If the recyclable component has been reprocessed in the past, product/component serial number
- d. Number of reprocessed cycles the recyclable component has been undergone
- e. Assessment results for conformity to matters listed in Section 4-1 (1) to (12) of the “Standards for R-SUDs” (MHLW Ministerial Notification No. 261 of 2017)
- f. Matters necessary to ensure the quality, performance, and safety of recyclable components, other than ones listed in items a-e.

4. Maintenance of records of the sales of R-SUDs

- (1) Sellers or lessors (hereinafter, “Sellers, etc.”) of specially controlled medical devices or specially designated maintenance and management required medical devices (hereinafter, “specially controlled medical devices, etc.”) shall maintain records concerning their sales of specially controlled medical devices, etc. for 3 years after completion of such sales, pursuant to Article 173, Paragraph 1 of the Amended Enforcement Regulations. The aforementioned records shall include information concerning the receipt and delivery of R-SUDs designated as specially controlled medical devices, etc. to medical institutions.
- (2) Sellers, etc. of specially controlled medical devices, etc. shall maintain records concerning the sales of controlled medical devices or general medical devices (excluding specially designated medical devices requiring specified maintenance and management procedures) in accordance with Article 173, Paragraph 4 of the Amended Enforcement Regulations. The above records shall include information concerning the receipt and delivery of R-SUDs designated as controlled medical devices (excluding specially designated medical devices requiring specified maintenance and management procedures) to medical institutions.
- (3) Sellers, etc. of specified controlled medical devices shall maintain records concerning product sales as specified under Article 175, Paragraph 3 of the Amended Enforcement Regulations. The above records include those concerning thereceipt and delivery of R-SUDs designated as specified controlled medical devices to medical institutions.

5. Package inserts of R-SUDs products

Items to be indicated on the package inserts of R-SUDs according to the provisions of Article 63-2 of the Act shall be stated as with the other medical devices, by referring to “Revision of

Guidance for Statements in Medical Device Package Inserts” (PFSB Notification No. 1002-8, by the Director-General of Pharmaceutical and Food Safety Bureau, MHLW, dated October 2, 2014) and “Guidance for Statements in Medical Device Package Inserts (detailed regulations)” (PFSB/SD Notification No. 1002-5, by the Director of Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, dated October 2, 2014). In addition, MAHs shall also comply with each of the following.

- [1] The package insert shall be prepared to ensure that the content is consistent with that for the original medical device wherever possible.
- [2] A section of approval number, etc. in the package insert shall include not only the approval number of R-SUDs but also a statement of “Single-use only. Reprocessed (name of the original medical device).”
- [3] A section for the name(s) or corporate name(s) of the MAH and manufacturer shall include name or corporate name(s) of the MAH (including the designated marketing authorization holder). In addition, the following items related to the original medical device must also be included. MAHs must exercise due care in such statements to prevent confusion between the relevant R-SUDs and original medical device product.
 - a. The name of the original medical device product;
 - b. The approval number and date of approval of the original medical device; certification number and date of certification of the original medical device; or notification number and date of notification of the original medical device
 - c. The name(s) or corporate name(s) of the MAH of the original medical device; name(s) or corporate name(s) of the designated foreign holder of special approval for medical devices, designated foreign manufacturers of medical devices, and the designated foreign MAH of the designated specially controlled medical devices.

6 Post-marketing safety measures for R-SUDs

(1) Recalls

Recalls of R-SUDs shall be handled in accordance with the provisions specified in the Ministerial Notification “Recall of Drugs and Medical Devices” (PFSB Notification No. 1121-10, by the Director-General, Pharmaceutical and Food Safety Bureau, MHLW, dated November 21, 2014; hereinafter referred to as the “Recall Notification”), and as follows:

- [1] If recall of an original medical device is implemented, the corresponding R-SUDs shall be also recalled, excluding cases where the cause(s) of the recall clearly do not affect the quality, etc. of the R-SUDs in question.
- [2] If review of the causes of the recall of the original medical device reveals that the corresponding R-SUDs were in violation or otherwise noncompliant with relevant requirements, the concerned R-SUDs shall be also recalled.

(2) Communication with the MAH of the original medical device product

In principle, all communication with the MAH of the original medical device product should be conducted in writing (e-mail is permissible) pursuant to Article 114-54, Item 11 of the Amended Enforcement Regulations. MAHs of R-SUDs shall retain records on such communication for a minimum of 5 years. In case of emergency, a telephone may

be used prior to the communication in writing where necessary.

In addition, as set forth under Article 114-54, Item 11 C of the Amended Enforcement Regulations, when the safety control manager of the MAH associated with the relevant R-SUDs plans and implements measures to ensure product safety in accordance with the requirements specified in the “Ministerial Ordinance on Good Vigilance Practice for Drugs, Quasi-drugs, Cosmetics, Medical Devices, and Regenerative and Cellular Therapy Products” (MHLW Ministerial Ordinance No. 135 of 2004), such manager shall inform the MAH of the original medical device of these plans or measures as well as any applicable safety information on which these plans or measures based. If the relevant safety measures are implemented immediately, repetitious communications at each stage of planning and implementation may be omitted as appropriate. Communications related to recalls ordered pursuant to Article 114-54, Item 11 B of the Amended Enforcement Regulations may be omitted if they are redundant in consideration of prior communications concerning safety measures implemented pursuant to the proceeding Item 11 C.

Basic concept for the assessment of cleaning/sterilization procedures for R-SUDs

1. Basic concept

R-SUDs are manufactured and distributed through a process in which SUDs used at medical institutions are collected under the supervision of the relevant MAH(s) of such device(s), subsequently disassembled and cleaned/sterilized applying appropriate methods to remove sources of contamination that stained during the use at medical institutions, and then reassembled. Such reprocessed devices are redistributed as SUDs that have the same quality, efficacy, and safety of the original medical device.

Applicants are required to establish cleaning/sterilization standards and test methods as needed to distribute R-SUDs, based on cleaning/sterilization methods conventionally applied to reusable medical devices at the medical institutions, and verifying whether such methods can be used in the manufacturing process of R-SUDs; and to what impact cleaning/sterilization effects the performance of the recyclable components in question. . Furthermore, the levels of sanitation/sterilization required for R-SUDs shall be identical to those of the corresponding original medical device.

2. Appropriateness of cleaning assessment for R-SUDs

Reusable medical devices are designed and developed so that they can be appropriately cleaned at medical institutions by methods provided in the existing cleaning guidelines. Therefore, such devices are characterized by structure ensuring appropriate cleaning; such as configuration allowing easy cleaning, configuration allowing removal of parts and post-cleaning reassembly to address the complicated structure and thereby improve the cleaning effect, and statement indicating the maximum acceptable number of reuse sessions established in light of deterioration effects of the cleaning solutions.

On the other hand, medical devices designed and developed for single use are not designed or manufactured to ensure appropriate cleaning at the medical institutions, unlike reusable medical devices.

Therefore, if the manufacturer applied the existing cleaning guidelines for reusable medical devices to cleaning of a R-SUDs, the MAH shall investigate the original medical device of the R-SUD (reverse engineering), and thereby assess whether contamination potentially occurring in clinical settings can be completely removed to achieve appropriate cleaning in light of materials and structures in use, potential contamination status in clinical settings, and storage status until their receipt from medical institutions. If it is difficult to achieve appropriate cleaning due to the complex structure, cleaning on disassembled recyclable components must be considered where necessary. Medical devices in which appropriate cleaning cannot be achieved by the existing cleaning methods even for the disassembled parts shall be handled as ones which are impossible to be reprocessed as R-SUDs.

If a method more appropriate than those mentioned in existing guidelines is identified, such method must be demonstrated to be capable of achieving cleaning/sterilizing results comparable or superior to those obtained through existing methods. Use of consultation

services related to medical devices offered by PMDA is recommended when determining whether assessment etc. of cleaning/sterilization method is suitable for a specific R-SUD product. The existing guidelines for cleaning of reusable medical devices are available as listed in section 3. Currently, guidelines similar to the above should be used to justify assessments of cleaning/sterilization procedures concerning R-SUDs.

These guidelines are continuously reconsidered based on the most current scientific knowledge, potentially leading to changes in cleaning/sterilization standards. MAHs of R-SUDs therefore must continuously verify the suitability of the cleaning assessment based on current knowledge even after approval of the R-SUDs, and if it requires changes in approved items such as cleaning/sterilization methods, must immediately proceed with a procedure for changes to approved items. In addition, review of the guidelines may reveal that the existing cleaning/sterilization methods cannot sufficiently mitigate the public health hazard. It should be noted that such cases may result in suspension of the distribution of R-SUDs if no alternative method is established.

Use of consultation services offered by PMDA concerning change procedure related to approved products is strongly recommended in consideration of the anticipated timing of revision of the guidelines.

3. Existing guidelines related to the cleaning etc. of reusable medical device products

Please refer to the following guidelines when considering cleaning and sterilization methods for recyclable components of R-SUDs. When related reusable medical devices do not currently use cleaning/sterilization methods that are listed in these guidelines for reuse, potential MAH should be investigated for whether these methods are appropriate for R-SUDs.

- Guideline for Disinfection and Sterilization in Healthcare Facilities by the US Center for Disease Control and Prevention (CDC)
CDC. Guideline for Disinfection and Sterilization in Healthcare Facilities, 2008.
- Hygiene Requirements for the Reprocessing of Medical Devices, a guideline by the Germany Robert Koch Institut (RKI) and Committee of the Germany Federal Institute for Drugs and Medical Devices (BfArM) (KRINKO: Kommission für Krankenhaushygiene und Infektionsprävention beim Robert Koch-Institut)
- Japanese Society of Medical Instrumentation: Guideline for Cleaning of Steel Utensils 2004. Hospital Supply, Vol.9, No.1, 2004.
- Study Working Group for Survey and Preparation of Cleaning Assessment and Judgment, Sterilization Technologist Certification Committee, Japanese Society of Medical Instrumentation: Guideline for Cleaning Assessment and Judgment. August 2012.
- Japanese Society of Medical Instrumentation: Guideline for Sterilization Assurance in Clinical Settings 2015. May 2015.
- Japan Gastroenterological Endoscopy Technicians Society: Guideline for Cleaning and Disinfection of Endoscopes (Version 2). 2004.
- Japanese Society for Infection Prevention and Control, Japan Gastroenterological Endoscopy Society, and Japan Gastroenterological Endoscopy Technicians Society.

Multidisciplinary Practical Guidance for Control of Gastrointestinal Endoscopy-associated Infection, Revised edition. 2013.

- Society of Gastroenterology Nurses and Associates: Guideline for Use of High Level Disinfectants & Sterilants for Reprocessing Flexible Gastrointestinal Endoscopes
SGNA Practice Committee. Guideline for Use of High Level Disinfectants & Sterilants for Reprocessing Flexible Gastrointestinal Endoscopes. SGNA 2013.

(References related to the guidelines)

- Hiroyoshi Kobayashi: [Supplement to the new edition] Guideline for Sterilization and Disinfection. Herusu Shuppan, Co. Inc., 2015.