

Provisional Translation (as of January 2019) *

PSEHB/MDE Notification No. 0816-3
August 16, 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)

**Points to Consider for the Preparation of Applications for Marketing Approval of
Remanufactured Single-use Medical Devices**

The Ministry of Health, Labour and Welfare (MHLW) has decided to issue guidance concerning the preparation of applications for marketing approval of medical device products in a Ministerial Notification entitled, “Applications for Medical Device Marketing Approval” (PFSB Notification No. 1120-5, by the Director-General of the Pharmaceutical and Food Safety Bureau, MHLW, dated November 20, 2014; hereinafter, the “Director-General Notification”) and in “Points to Consider for Applications for Marketing Approval of Medical Devices” (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; hereinafter, the “Marketing Application Notification”).

We have prepared detailed instructions concerning the handling of applications for marketing approval of reprocessed single-use medical devices (R-SUDs) as provided below. We request your cooperation in circulating the information contained in this Notification to marketing authorization holders (MAHs) of medical devices, etc. under your supervision.

Please note that copies of this Ministerial Notification will be sent to 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 Medical Devices and Diagnostics Subcommittee of the American Medical Devices and Diagnostics Manufacturers’ Association in Japan, and the Chairperson of the Medical Devices and Diagnostics Committee of the European Business Council in Japan.

1 Scope

This Ministerial Notification applies to product recognized as R-SUDs as specified in Article 114-8, Item 4 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” (MHW (currently MHLW) Ministerial Ordinance No. 1 of 1961; hereinafter, the “Enforcement

* 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.

Regulations”).

2 Definitions

In this Ministerial Notification, definitions of terminology used in the “Standards for Reprocessed Single-use Medical Devices” (MHLW Ministerial Notification No. 261 of 2017), the Director-General Notification, and the Marketing Application Notification shall be used as defined therein, in addition to other terminology, defined as follows:

- (1) Reprocessing process
A process spanning from the receipt of recyclable components from medical institutions to the release of R-SUDs
- (2) Component recycling process
A process spanning from the receipt of recyclable components from medical institutions to the decontamination of recyclable components
- (3) Final production process
A manufacturing process in which R-SUDs are produced from recycled components released from the component recycling process and/or replacement components

3 Content to be included in marketing approval applications

Applicants shall compete each field/section of the application for approval to market R-SUDs as specified in the Marketing Application Notification and/or other notifications, or as follows: In the event that any information contained in this Notification is found to be inconsistent with the corresponding content in the Marketing Application Notification or other Ministerial Notification, this Notification shall take precedence, unless otherwise specified.

A “Category” field

The category of the R-SUD shall be the same as that of the original equipment manufacturer’s (OEM’s) single-use medical device (SUD).

B “Name” field

- (1) If no generic names based on Japanese Medical Device Nomenclature (JMDN) appropriate for the R-SUD can be identified while preparing the application, such applicant shall propose a generic name based on the generic name of OEM’s SUD that is preceded by the word “reprocessed” with a draft definition for this proposed name, a provisional device class, and a statement of rationale for the proposed class designation in an Appendix adhering to the formatting style specified in the “Handling of Generic Names of Medical Devices and *In Vitro* Diagnostics for Which Appropriate Generic Names Cannot Be Found” (Administrative Notice by the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated February 8, 2007) as directed by this Notice, and then submit the completed application to PMDA at the same time as submission of the application for review.
- (2) If multiple generic names are determined to be appropriate for a single product but a collectively appropriate generic name is not found, enter each generic

name while indicating the medical devices posing the greatest risk to patients with respect to the primary intended use or product action. The relevant generic name(s) must begin with the word “reprocessed”.

- (3) The brand name of the R-SUD must begin with the word “reprocessed” and end with the name of the relevant MAH in parentheses (abbreviated name may be acceptable (e.g.: Reprocessed XXXX (name of marketing authorization holder))).

C “Intended Use or Indication” section

The intended use(s) or indication(s) of the R-SUD shall not exceed the intended use(s) or indication(s) of the OEM’s SUD.

D “Shape, Structure, and Principle” section

Applicants shall include the following information regarding the OEM’s SUD as well as any recyclable or replacement components.

- (1) Brand name(s), approval number (also including certification or notification numbers; the same shall apply hereinafter), and date of approval of the OEM’s SUD (or date of certification, date of notification). In addition, date of approval of partial changes to approved items (or the date of certification of partial changes to certified matters) or date of notification of minor changes in approved matters (also including dates of notification of minor changes in certified matters or dates of notification of changes in matters in marketing notification) necessary to identify raw materials, performance, and use method of the OEM’s SUD to be reprocessed.
- (2) Shape, structure, and dimensions of recyclable components
- (3) If a used SUD is supplied in its entirety for purposes of reprocessing as a recyclable component, applicants shall convey such in the application. If a part of such a device is supplied for reprocessing as a recyclable component, applicants shall enter the location of recyclable components in the R-SUD.
- (4) If recyclable components are disassembled due to a need for cleaning/sterilization or performance testing, applicants shall enter the shape, structure, and dimensions of the disassembled recyclable components (including all serial number(s) on the medical device body and information for identification of the product’s reprocessed status as specified in Section 6-1 of the Standards for Reprocessed Single-use Medical Devices as well as any other marks related to process control, where applicable).
- (5) If replacement components are used for remanufacturing, applicants shall enter the shape, structure, and dimensions of the replacement components and location of manufacture of the replacement components contained in the R-SUD (see Appendix 1).
- (6) If the shape or structure of the recyclable component used in the R-SUD partially differs from that of the OEM’s SUD (e.g., integrally molded, welded, or soldered components are used in the OEM’s SUD, but multiple components are used in the recyclable component), applicants shall describe in detail the difference(s) in shape and/or structure.
- (7) For recyclable components and replacement components with difficult to determine shape or structure (e.g., a microchip installed on the interior of a

device component at a position that does not come in contact with fluids), applicants shall indicate the presence or absence of such applicable components as well as the location of the applicable parts. In addition, applicants shall enter their handling procedure (e.g., the existence of the capacity for data rewriting on a microchip to be used as a recyclable component) where applicable.

E “Raw Materials” section

- (1) In accordance with Appendix 1, applicants shall describe raw materials of the recyclable components and replacement components in this section.
- (2) Descriptions about raw materials of recyclable components shall include information necessary for assessment of cleaning/sterilization, performance maintenance, and deterioration or durability; and must be comparable to descriptions related to identification of raw materials required for the OEM’s SUD. In accordance with Appendix 1, applicants shall describe the following matters at least.
 - [1] Information necessary for assessment of deterioration or durability (generic names of raw materials)
 - [2] Methods for the identification of raw materials
 - [3] Maximum number of reprocessing cycles on recyclable components
- (3) For product items on which the maximum number of reprocessing cycles is more than one, if replacement components used in a reprocessing run are used as recyclable components in the subsequent reprocessing cycles, applicants shall also describe the relevant replacement components as recyclable components.
- (4) Although R-SUDs from devices containing biological raw materials as recyclable components is believed to be technically impracticable from the viewpoint of maintenance of device performance, maintenance, and deterioration, remanufacturing may be possible if the materials in question are used as replacement components (materials). In such cases, applicants shall describe such circumstances as prescribed in the Marketing Application Notification.

F “Performance and Safety Specifications” section

The applicant shall describe the following matters in the “Performance and Safety Specifications” section from the viewpoint for ensuring the quality, safety, and efficacy of R-SUDs. It is not acceptable to omit the detailed description by stating “the same as those of the approved medical device”.

- (1) Of the design specifications required for R-SUDs, matters other than those described in the “Shape, Structure, and Principle” section shall be described. This section shall cover specifications necessary to ensure equivalence with the OEM’s SUD established primarily based on verification and validation of design development from the viewpoints of quality (including stability), safety (including physical, chemical, and biological safety), and efficacy (performance and function). This section shall also cover specifications related to the quality, safety, and efficacy of replacement components. In addition, R-SUDs subjected to multiple reprocessing cycles must demonstrate the

performance comparable to that of the OEM's SUD even after the maximum number of reprocessing cycles.

For application for approval or certification of a R-SUD using the OEM's SUD conforming to the approval or certification standard as a raw material, this section shall cover items that are listed in the approval or certification standards and related to performance and safety. If the acceptance limit or test method has not been specified for each item, applicants shall explain clearly that the proposed acceptance limit and test method ensure the performance and safety comparable to those of the OEM's SUD. For others, applicants shall list reference specifications and standards such as Japanese Industrial Standard (JIS) and international standards, where applicable. If no reference specifications or standards are available, applicants shall include summary of test methods additionally.

- (2) Of the specifications required for recyclable components, matters other than those described in the "Shape, Structure, and Principle" section shall be described. This section shall cover assessment for reprocessing feasibility with appropriate specimens (the OEM's SUD in simulated clinical-use and post-clinical-use conditions) ("reverse engineering" in Appendix 1) and specifications (including the following matters) required for recyclable components to ensure the quality, efficacy, and safety of the finished R-SUDs as mentioned in (1), which are based on available information about design specifications of the OEM's SUD.

If recyclable components are disassembled due to necessity of cleaning and sterilization, or performance test, applicants shall enter appropriate information for each of the disassembled recyclable components. In addition, R-SUDs subjected to multiple remanufacturing cycles must demonstrate the performance comparable to that of the OEM's SUD even after the maximum number of reprocessing cycles.

- [1] Specifications related to cleaning and sterilization of recyclable components (storage method and period of recyclable components prior to cleaning, test methods and acceptance limits for residual proteins, pyrogens, and viruses, and test methods and acceptance limits for residual cleaning agents)
 - [2] Specifications related to the performance of recyclable components established to ensure the efficacy and safety of R-SUDs (including physical, mechanical, and electrical requirements for recyclable components)
 - [3] Identification methods for raw materials of recyclable components (test method) and specification for identified raw materials of recyclable components
- (3) Applicants shall describe matters related to specifications and test methods applied to testing and inspection in the manufacturing process for recyclable components (including the following matters). The specifications and test methods in this section shall be linked to steps in the "Manufacturing Method" section.
 - [1] Specifications applied during qualification inspections for recyclable components (including tests to verify conformity with items specified in

Section 4-1 of the Standards for Reprocessed Single-use Medical Devices and discrimination method to identify recyclable components not eligible for reprocessing due to damage.)

- [2] Methods and acceptance limits on recyclable components for testing and inspection (post-cleaning cleanliness) related to cleaning and sterilization process, function tests for physical, mechanical, and electrical characteristics, and visual inspection
 - [3] Methods for identifying changes to on the OEM's SUD, if any, and actions taken in response to detection of a change
- (4) Applicants shall specify procedures for the receipt of used SUDs from medical institutions and feasible method and criteria for selection of recyclable components at medical institutions, and describe such in this section. This section shall address each of the following (the above items should be linked to the steps described in the "Manufacturing Method" section).
- [1] Control methods related to the receipt of recyclable components from medical institutions such as separation from medical waste at medical institutions and quarantine against contamination capable of rendering reprocessing operations impossible (storage methods for used SUDs as well as specifications for containers dedicated to recyclable components used for receipt and transportation containers and methods to ensure the safety using these containers, and method for pre-treatment of recyclable components at medical institutions, such as primary cleaning, where applicable.)
 - [2] Identification methods specified in Section 4-1 (7) of the Standards for Reprocessed Single-use Medical Devices
 - [3] The content of any agreements between MAH(s) and medical institutions specifying terms of responsibilities related to the receipt of used SUDs
- (5) Applicants shall describe methods to ensure traceability in the reprocessing process as specified in Section 6-3 of the Standards for Reprocessed Single-use Medical Devices. The concerned methods in this section shall be linked to the "Manufacturing Method" section to ensure the traceability in the manufacturing process. If an approved R-SUD is used in the proposed medical device as a component, applicants must describe methods to ensure traceability starting with the reprocessing process of the concerned component, irrespective of whether it is supplied internally or externally.

G "Method of Use" section

The use method shall not be beyond that of the OEM's SUD and shall be described in the same manner as that for the original one.

H "Storage Method and Shelf Life" section

The applicant shall establish the shelf life based on the quality evaluation (including stability) in 6 (1) and enter the established period in this section. If the shelf life differs depending on the number of reprocessing cycles, the shelf life corresponding to each number of times shall be entered.

I "Method of Manufacture" section

- (1) The applicant shall describe the reprocessing process using a process flow chart according to Appendix 2 to clarify steps covered by each manufacturing site. In-process inspection specifications required for each step in the component recycling process and the manufacturing conditions as well as process flow charts shall be described in detail including relationships to contents in 6 (3) to 6 (5). For the commercialization process, descriptions for each step and process flow charts may be omitted in principle as done for manufacturing process of conventional medical devices not classified as R-SUDs. In addition, the remanufacturing method shall be described in terms of the following matters:
 - [1] If one R-SUD is manufactured from one used single-use medical device, using replacement components, this effect
 - [2] If a R-SUD is manufactured from parts obtained by disassembling multiple used SUDs, using replacement components, the relevant details as well as the following:
 - a) Summary of the method to ensure traceability of recyclable components
 - b) If reprocessing is repeated twice or more, summary of the method to control the number of reprocessing cycles.
- (2) If an approved R-SUD is used in the proposed medical device as a component, name of the marketing authorization holder of the concerned medical device, approval number, and brand name shall be entered, but the manufacturing method of the concerned component may not have to be described.
- (3) If manufacturing conditions affect the intended use and performance of a R-SUD, applicants shall describe such manufacturing conditions even with respect to operations performed at facilities other than the registered manufacturing site(s). However, in such cases, inclusion of conditions present during any final production processes in this section may not be necessary, if the purpose of the processing and post-processing specifications are entered in the “Raw Materials” section.
- (4) Applicants shall describe cleaning/sterilization procedures implemented during the component recycling process as well as any and all acceptance criteria, including relationships to contents in sections 6(1)-6(3). Descriptions about the sterilization shall include the sterilization methods and reference standards, and those about cleaning shall include the cleaning methods (cleaning conditions and cleaning agents used) as well as standards and guidelines for cleaning validation. If the cleaning or sterilization method differs depending on parts of the recyclable components, each method shall be clearly described.
- (5) Applicants shall describe the sterilization method of R-SUDs. If the sterilization method differs from component to component, sterilization methods shall be clearly described for each component.

J “Manufacturing Site(s) of the Marketed Product” section

The applicant shall enter the name, manufacturing business registration number, and manufacturing process for each of the manufacturing sites involved in marketing of the proposed product item according to Appendix 2.

In accordance with Article 114-8, Item 4 of the Enforcement Regulations, the

manufacturing process shall be described for each manufacturing site in terms of “Design”, “Receipt, disassembling, and cleaning”, “Principal assembly and other principal manufacturing steps”, “Sterilization”, and “Storage of final products in Japan”.

For cleaning and sterilization methods used in the reprocessing process, purpose of each method, either cleaning or sterilization, shall be identified by manufacturing site.

If the manufacturing site is currently applying for registration, applicants must indicate such.

4 Points to consider for handling and preparation of the data to be submitted in support of the application for marketing approval

Points to consider for handling in detail and preparation of the data to be submitted in support of the application for marketing approval (hereinafter referred to as “attached data”) provided in Article 114-19, Paragraph 1, Item 1 of the Enforcement Regulations shall be referred to instructions for preparation of attached data in support of the application for marketing approval of R-SUDs, provided in a separate notification.

5 Others

Application for approval of partial changes and notification of minor changes in approved matters for R-SUDs shall be in accordance with the Marketing Application Notification and other notifications for change procedures and as follows.

- (1) If changes are made in approved matters for a R-SUD in response to changes in approved matters for the OEM’s SUD, the necessary change procedure shall be determined based on which application for approval of partial changes and notification of minor changes is used as the procedure for changes in approved matters of the R-SUD.
- (2) Because the reprocessing process differs among individual R-SUDs, and thus it is difficult to determine uniformly which of the application for approval of partial changes or the notification of minor changes is appropriate for the change in approved matters for the reprocessing process, applicants is recommended to utilize consultation services for reprocessing offered by the PMDA in advance.

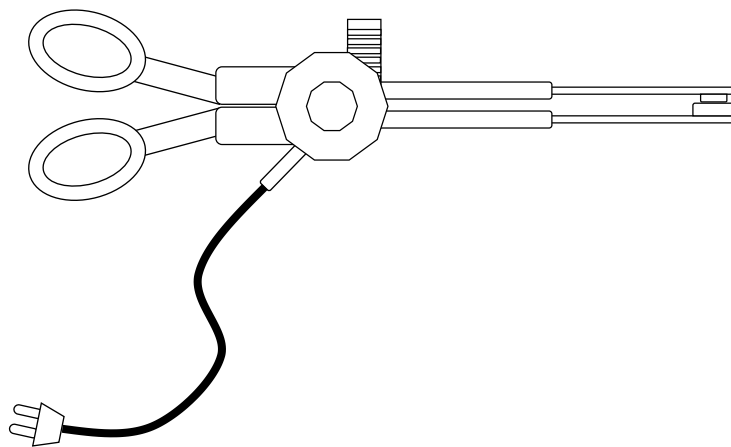
Appendix 1

Example of entries in the “Raw Materials” section

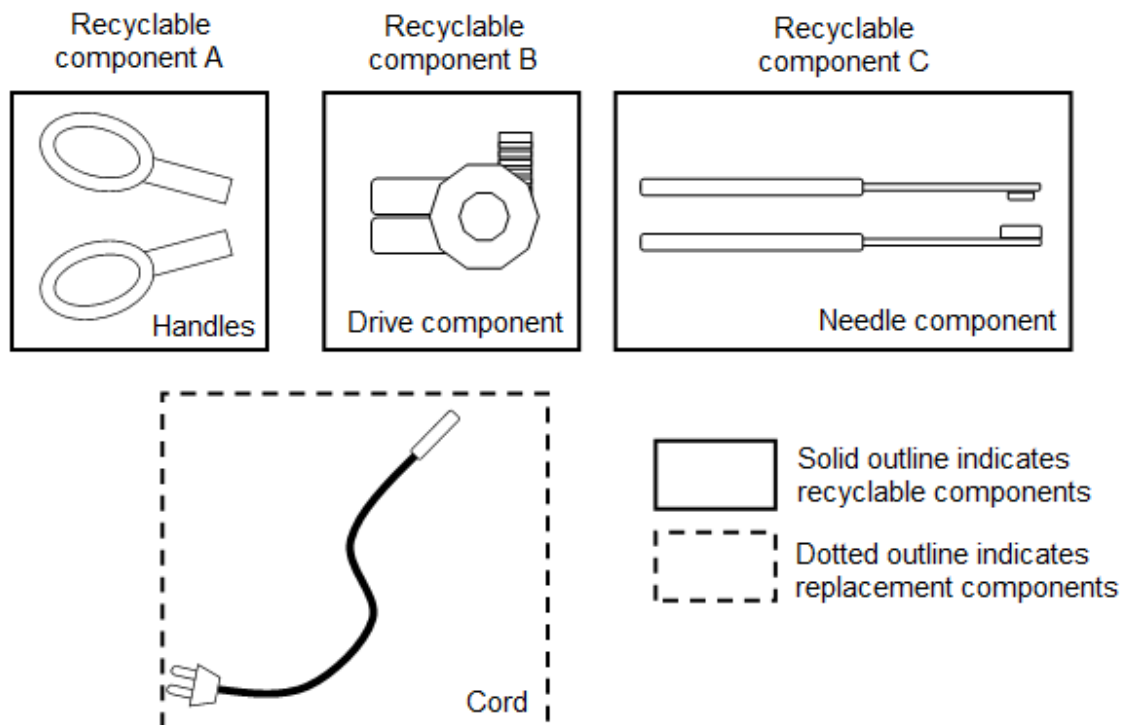
The following example of a “Raw Materials” section entry presents general drawings of a medical device product and its replacement and recyclable components as they would be described in the “Shape, Structure, and Principle” section of the application document. The drawings below, however, illustrate the shape, structure, and names of the components of a hypothetical medical device product as well as replaced and recyclable components, while product/component dimensions and other information are omitted.

The cord in the drawing below is a replacement component, but is described as a component to be incorporated as a recyclable component under Section 3-5 (3) of this notification.

[Device body]



[Recyclable and replacement components]



1. Body prior to disassembling (recyclable component)

Information about the original medical device	Brand name	Electron ABC Plus
	Marketing authorization holder	XX Science Medical Device Co., Ltd.
	Approval number	25000BZX00XXX000
	Date of approval	XXXX, 2013
	Others	Of approved matters for the concerned original medical device, Type A remanufacturing is carried out. (*1)
Maximum number of reprocessing cycles	3	

(*1) Enter special information such as remanufacturing of a part of the original medical device

2. Recyclable components

(1) Handles (*1)

Generic name or common name	XXXX			
General scientific information	-			
Chemical name	XX styrene/YY methyl copolymer (*2)			
CAS Number, USAN, CSCL Notification Number	CAS Number: 123XXXX-XX-3			
Structural formula	See Appendix X-1 Chemical Structures of Raw Materials (*2)			
Specifications (*2)	Item	Acceptance limit	Unit	Test method
	Flexural strength	XX	N	ISO XXX
	Purity	95	%	-
	XX	YY	g/cm ³	-
	• •			
Product name	ABC-500 (*3)			
Manufacturer	XX Chemical Industry Co., Ltd. (*3)			
Maximum number of reprocessing cycles	2			

(*1) Describe for each recyclable component.

(*2) Describe the specifications and identification methods of raw materials identified through reverse engineering. This entry may refer to descriptions about the identification methods and specifications in the “Performance and Safety Specifications” section if the content is the same.

(*3) Where available, enter the name of supplier(s) of the components used in the OEM’s SUD.

(2) Drive component

Generic name or common name	Titanium			
General scientific information	Ti			
Specifications	ASTM XXXX-X Grade 2			
	Item	Acceptance limit	Unit	Test method
	Flexural strength	XX	N	ISO XXX
	Purity	95	%	-
	XX	YY	g/cm ³	-
		•	•	
Maximum number of reprocessing cycles	3			

(3) Needle component

(omitted) *In the actual application form, complete this section as done in (1).

(4) Cord

As described in (1) Cord part in 3. Replacement components. *In the case where the replacement component is used as a recyclable component.

3. Replacement components

(1) Cord (*1)

Generic name or common name	XXXX			
Specifications (*2)	Item	Acceptance limit	Unit	Test method
	Maximum rating	X	A	ISO XXX
	Resistance	X	Ω	-
	XX	YY	g/cm ³	-
			•	•
Product name	C-200			
Manufacturer	XX Electric Industry Co., Ltd.			
Maximum number of reprocessing cycles	2 (*2)			

(*1) Descriptions of replacement components shall correspond to the information required for newly manufactured components.

(*2) If the replacement component is to be used as a recyclable component, enter the maximum number of reprocessing cycles.

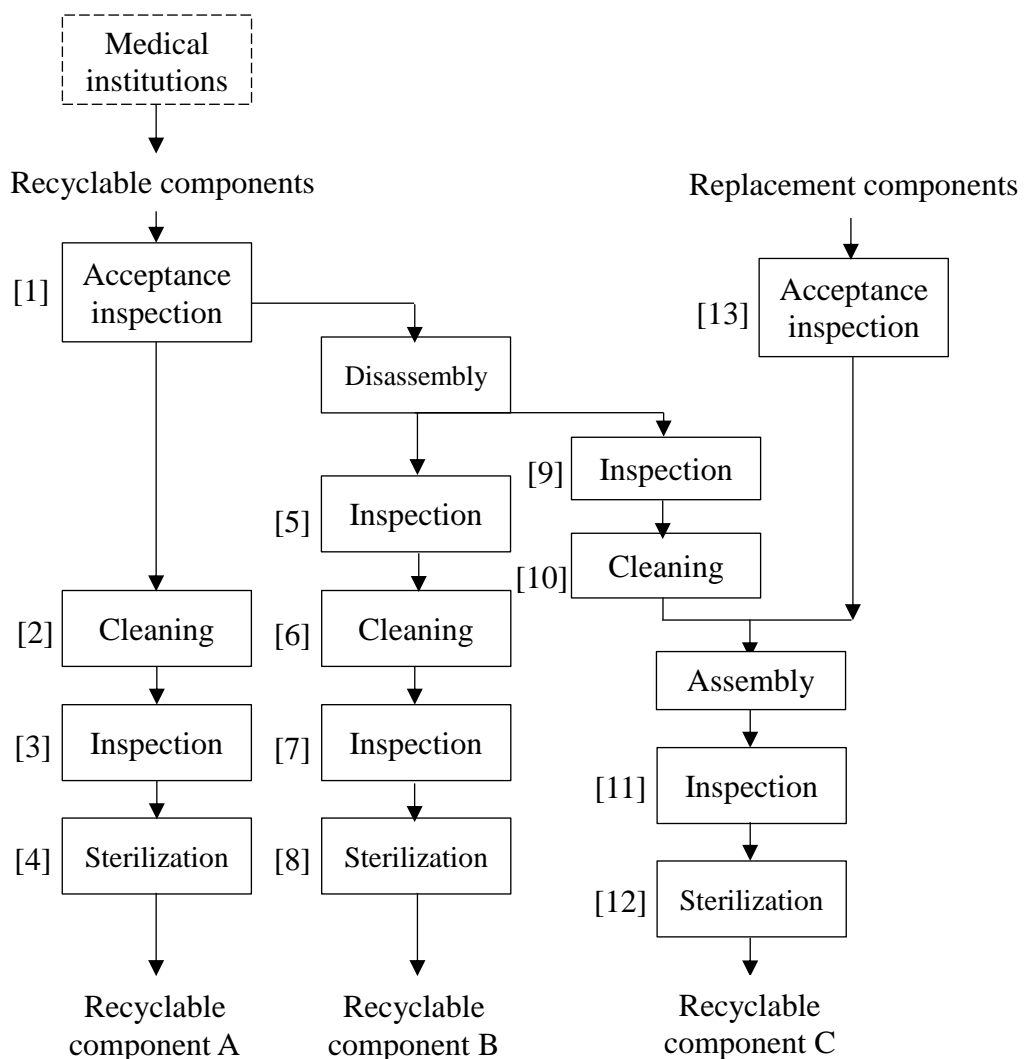
Appendix 2

Examples of entries in the “Method of Manufacturing” section

The reprocessing process shall be described such that each step is identified as either a component recycling operation or a commercialization operation. The following example of entries is for the product which is reprocessed using replacement components, as provided in the example of the medical device in Appendix 1. Enter according to the example of manufacturing sites in 1. Commercialization process to clarify the manufacturing sites in charge for each step. Descriptions about components not involved in reprocessing shall be according to the previous example.

[Remanufacturing processes]

1. Component recycling operations

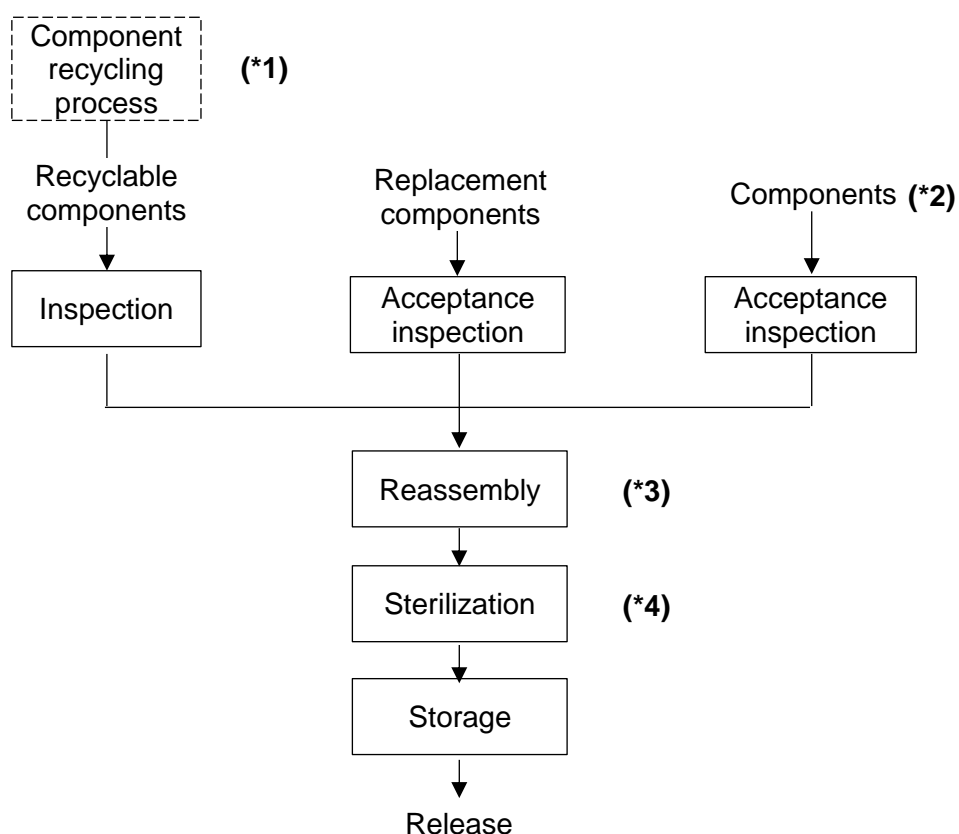


Each step shall be linked to entries in the “Performance and Safety Specifications” section by numbering the steps to organize the information into a table as shown below.

(Example entries)

Process	Content	In-process control test	Remarks
[1]	Inspect recyclable components received from medical institutions for XX, dispose of XX, and do not use in remanufacturing.	Acceptance criteria and test methods are as described in the internal specifications in the “Performance and Safety Specifications” section.	(*) If applicable, include any special notes here.
-	-	-	-
-	-	-	-
[13]	Confirm whether the component is comparable to the corresponding part XX of the original medical device, and check if the specifications of XX and the relevant parts have not been changed.	Acceptance specifications and test methods are as described in the internal specifications in the “Performance and Safety Specifications” section.	

2. Final production process



(*1) Component recycling process may be described separately.

(*2) If an approved medical device is used as a component, enter information about the concerned medical device using a table below as a reference.

Name of marketing authorization holder	-----
Address of major business establishment	-----

Marketing business license number	-----
Approval number	-----
Brand name	-----
Product item name	-----

- (*3) Describe the reprocessing method required under Section 3-9 (1) of this Notification using the example of entries below as a reference. Because information concerning methods to ensure traceability and to control the number of reprocessing cycles may vary by product due to complexity of the manufacturing process, more detailed information than the example of entries may be necessary.

(Example entries)

Recyclable components A, B, and C are reassembled into the same configuration as was applied before disassembly during the commercialization process. If any of the components is found to be defective, the other used components may be used as supplements for reassembling.

[Traceability]

Make a link to the manufacturing record related to the supplementing used SUD by recording the serial number of the supplementing SUD on the manufacturing record of the reprocessed product.

[Control of reprocessing cycles]

Control the number of reprocessing cycles on each component by giving unique serial numbers to recyclable components A, B, and C.

- (*4) Describe the sterilization methods and conditions in accordance with Section 3-9c of this Notification.