Remanufactured-Single Use Device in Japan

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Introduction

- Since the launch of the remanufactured single-use medical device marketing system in 2017, 9 products from 2 companies have been approved in Japan.
- QMS is important for remanufactured single-use medical devices: Annual on-site inspection has been required for all the manufacturing sites engaged in remanufactured single-use medical devices for the time being after the launch of the system.
- This presentation outlines the Japanese regulatory requirements for remanufactured single-use medical devices.

Regulations for R-SUD

4. Materials

Main requirements of MHLW MO169 are stipulated in the second chapter of the ordinance. The requirements are aligned with ISO13485. The followings are comparison table between ISO13485 and MHLW MO169 Chapter 2.

- MHLW MO169, as revised in 2021 (Current version)
  Comparison table between ISO13485:2016 and MHLW MO169 Chapter 2, as revised in 2021
- MHLW MO169, as revised in 2014 (Previous version)
  Comparison table between ISO13485:2003 and MHLW MO169 Chapter 2, as revised in 2014

The addtional requirements of MHLW MO169 are stipulated in the third chapter of the ordinance. The followings are translation of the requirements.

- MHLW MO169, as revised in 2021 (Current version)
  Tentative translation of MHLW MO169 Chapter 3, as revised in 2021
- MHLW MO169, as revised in 2014 (Previous version)
  Tentative translation of MHLW MO169 Chapter 3, as revised in 2014

The product specific requirements of MHLW MO169 are stipulated in the chapter 4, 5,and 5-2 of the ordinance. The followings are translation of the requirements.

- Tentative translation of MHLW MO169 Chapter 4, as revised in 2021
- Tentative translation of MHLW MO169 Chapter 5, as revised in 2021
- Tentative translation of MHLW MO169 Chapter 5-2, as revised in 2021

The followings are translation of the requirements for R-SUDs other than MHLW MO169. Manufacturers shall comply with these requirements as well as MHLW MO169 Chapter 5-2, when they manufacture R-SUDs.

- Tentative translation of MHLW MO1 (Regulations for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices)
- Standards for Re-manufactured Single-use Medical Devices

https://www.pmda.go.jp/english/review-services/regulatory-info/0004.html

What's R-SUD?

Article 114-8 of the PMD Act Enforcement Regulations

The manufacturing processes specified in the MHLW Ordinance set forth in Article 23-2-3, Paragraph 1 of the PMD Act are listed in each of the following items according to the type of medical devices or *in vitro* diagnostics listed in each item.

4) **Single-use medical devices (medical devices that can be used only once; the same shall apply hereinafter) that are remanufactured (remanufacturing refers to the inspection, disassembly, cleaning, sterilization, and/or other necessary processing of used single-use medical devices for another marketing purpose; the same shall apply hereinafter) (hereinafter referred to as "remanufactured single-use medical devices")**The following manufacturing processes:

A. Design

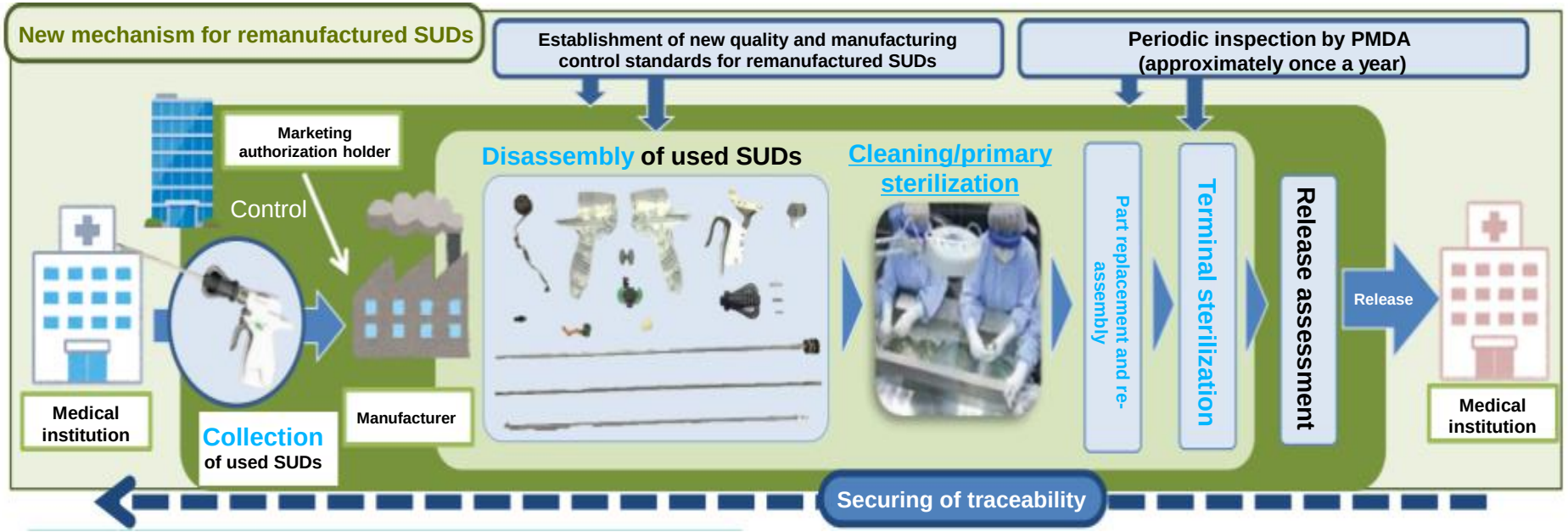
B. **Acceptance, disassembly, and cleaning, etc. of used single-use medical devices**

C. Main assembly and other main manufacturing processes (excluding design, and acceptance, disassembly & cleaning, etc., sterilization, and storage of single-use medical devices used)

D. Sterilization

E. Storage of finished products in Japan

Re-manufacturing/Re-processing?



- Remanufacturing refers to collecting used single-use medical devices from medical institutions, disassembling and cleaning them according to the predetermined procedures at the dedicated site (manufacturing site), and re-releasing them as medical devices.
- It does not refer to in-hospital cleaning and sterilization at medical institutions.

Japan Regulations (Basic Concept)

- “Remanufacturing” is defined as a process in which a used single-use medical device collected from a medical institution is disassembled, cleaned, part-replaced, re-assembled, and sterilized so that it can be used again as a single-use medical device intended for the same use as the original single-use medical device (original medical device).
- The marketing authorization holder license is required to market remanufactured single-use medical devices.
- Remanufactured single-use medical devices require approval as separate items from original medical devices.
- The responsibility for remanufactured single-use medical devices according to the PMD Act shall be borne by marketing authorization holders who remanufactured the devices (not necessarily the same as the marketing authorization holders of original medical devices).

Japan Regulations (Specific Measures)

1. The standards for the quality and manufacturing control of remanufactured single-use medical devices were newly established.
   - ✓ Article 42 on the standards for remanufactured single-use medical devices was added.
   - ✓ **Additional requirements of the QMS ministerial ordinance were specified.**
2. The traceability of remanufactured single-use medical devices was secured.
   - ✓ A serial number is assigned to each remanufactured single-use medical device to secure the traceability of the information from the medical institution in which the used single-use medical device was collected to the manufacturing process and distribution.
3. Periodic inspection of marketing authorization holders/manufacturers by PMDA
   - ✓ **PMDA periodically (approximately once a year) inspects each marketing authorization holder/manufacturer for whether the manufacturing process, etc. of remanufactured single-use medical devices meets the approved conditions and standards, etc.**
4. A face-to-face consultation system on the evaluation of safety, etc. of remanufactured single-use medical devices was newly established.
   - ✓ **A face-to-face consultation category in which PMDA made on-site inspection of the manufacturing process, etc. of each proposed remanufactured single-use medical device to give advice on the evaluation, etc. required for assuring safety** was newly established.
5. The scope of manufacturers requiring registration was enlarged.
   - ✓ Manufacturing sites conducting acceptance inspection and cleaning, which are the important manufacturing process steps for remanufactured single-use medical devices, were included in the scope of manufacturers to be registered.

Japan Regulations (Specific Measures)

Submission Requirements

> Shonin submission is required for ALL SUD reprocessed devices.

> Application of SUD reprocessed device has to be reviewed by PMDA.

Quality System Requirements

> Verification/ Validation of in-coming inspection and cleaning of used devices are required.

> Serial control of SUD reprocessed device is required.

> Cross-infection prevention measures and virus inactivation are required.

Regulations of SUD Reprocessing Starting since July 31, 2017

License Requirements

> Manufacturing site registration of responsible facility of acceptance, disassembly and cleaning of used devices is required.

> Person having bacteriological knowledge in MAH and Manufacturing site is required.

> Periodical on-site audit by PMDA

> Indication of device body for clearly identifying that it is reprocessed device.

> Traceability from collecting of used SUDs, cleaning, reprocessing, until shipment to the customers is required.

> Assessment and selection of hospitals are required.

> Agreement with hospitals is required.

Article 42 Standard of SUD Reprocessing

Design Control

The reprocessed SUDs must be designed to have the same effectiveness and safety as the original SUDs.

Collecting of used devices

Traceability from collecting of used SUDs, cleaning, reprocessing, until shipment to the customers is required.

Transportation

The parts to be reprocessed must be sorted according to the criteria prescribed in the approval file and stored separately from waste to prevent cross contamination.

Cleaning

It must be transported in a dedicated hermetic container in oder to prevent cross contamination.

In-coming Inspection

Make sure that the recycled parts used for reprocessing meet the requirements. Also, record the confirmation results.

Disassembly, cleaning, re-assembly

Sterilization

It must be cleaned and sterilized in validated methods.

Tenpu Bunsho

Direct pouch and Tenpu Bunsho (Package Insert) must be described as "reprocessed".

Release Judgement

Post-marketing Control

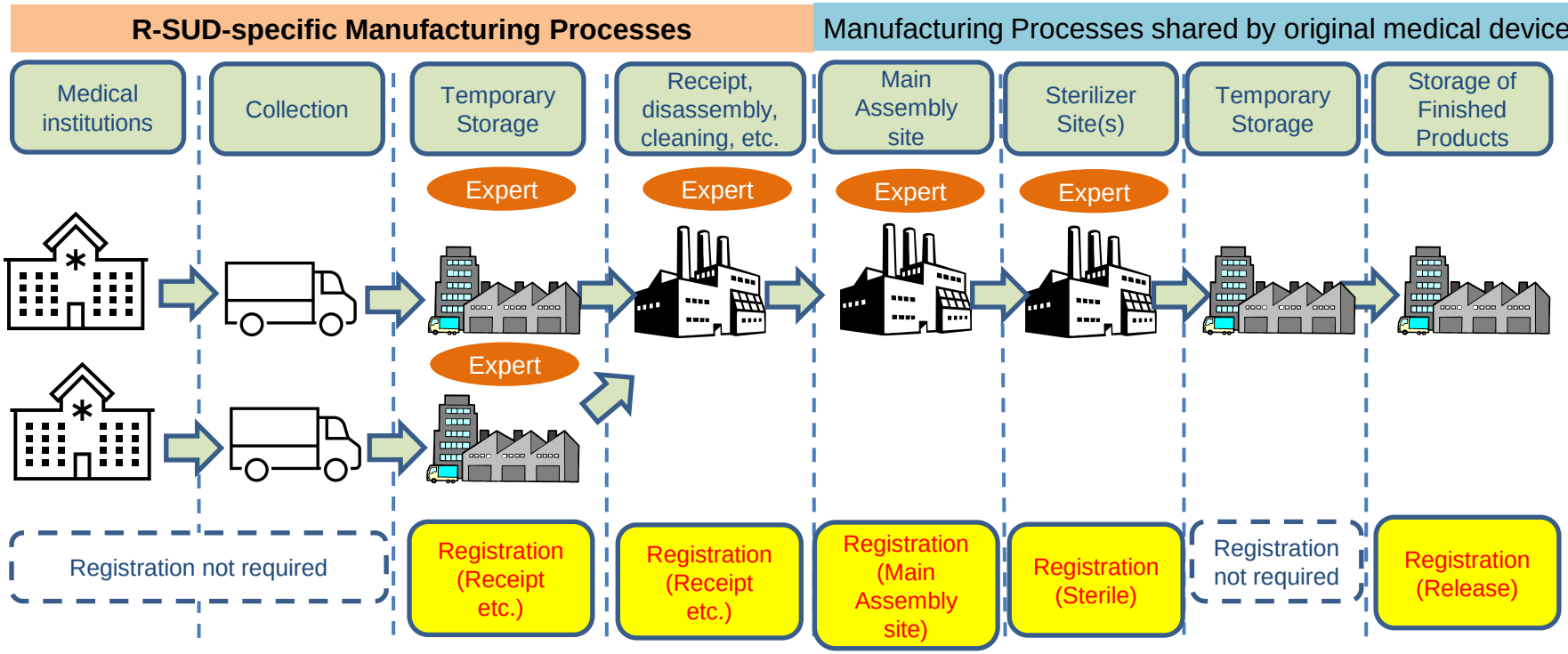
- ✓ Continuously monitor the presence or absence of changes in the original SUD and make any necessary changes to maintain the effectiveness of the reprocessed device in the event of a change.
- ✓ Information on safety of original SUD, collection information shall be monitored, and if company know this, please evaluate the effect on reprocessed device and take necessary measures.

Reprocessing Processes & Facilities Inspected

MAH

Expert

Marketing authorization holders, etc. need to manage a series of the following process steps including control of used single-use medical devices at medical institutions.
The site responsible for design control, which is not shown below, is also considered as a registered manufacturing site and an expert needs to be deployed.



MAH: Marketing Authorization Holder
Expert: Person having bacteriological knowledge

Inspection Method & Frequencies

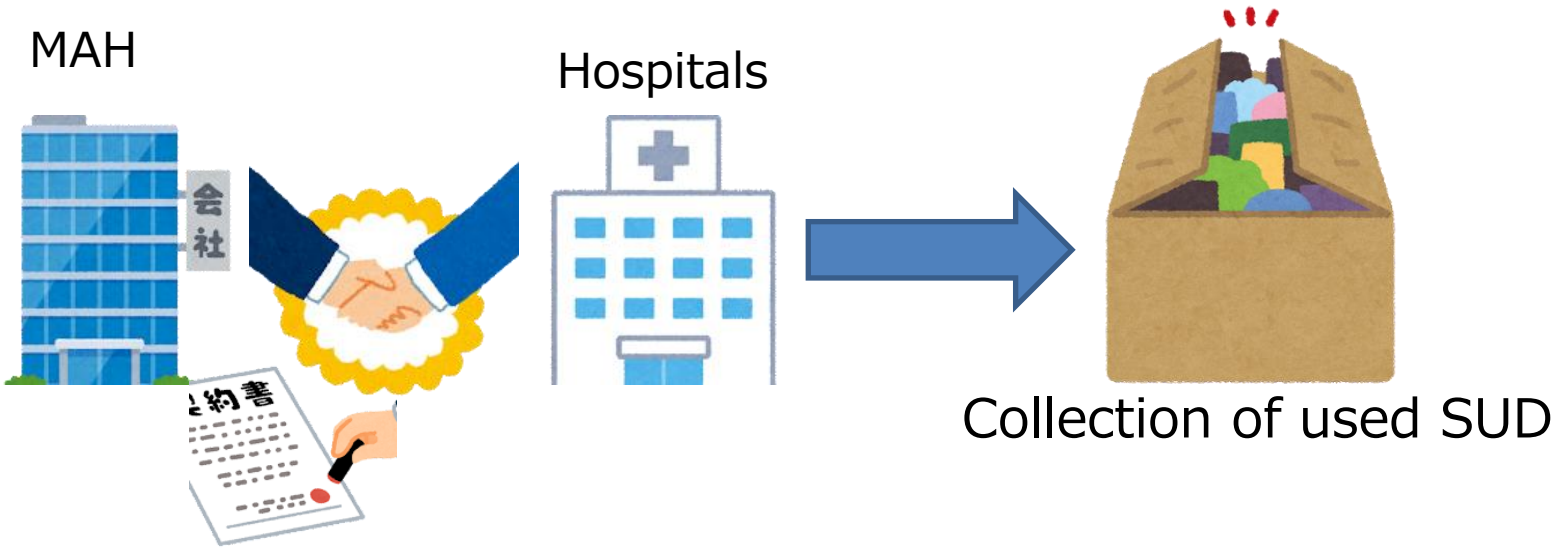
- Inspection Unit: each Approved Products (No Product Category)
- Inspection Method: Basically, On-Site Inspection
- Inspection Frequencies: Prior Approval, Annual Inspection after Approval, every 5 years Inspection

  Additionally, Specific Inspection at prior approval and every 5 years inspection

Checkpoints as remanufactured single-use medical device

Remanufacturing process	Matters to be checked
Is there any disassembly process?	Traceability Has the impact of cleaning and re-assembly on cleanliness and product quality been considered?
Are there any replacement parts?	Traceability Replacement part quality, performance, and safety Are replacement parts equivalent to those used for the original medical device?
What is the maximum number of times of remanufacturing?	Traceability Is the product after the maximum number of times of remanufacturing subject to design and development?
Is the marketing authorization holder different from that of the original medical device?	Monitoring of post-marketing information on original medical device Provision of information to marketing authorization holder of original medical device

Relationship with Medical Institutions (MAH)



Points to be checked at an inspection of the marketing authorization holder:

- ✓ Does the marketing authorization holder have the predetermined procedures for deciding the frequency of collecting used single-use medical devices from medical institutions and assigning the responsibilities for collecting used single-use medical devices with medical institutions?
  (Article 4-1 (5), Certificate of approval, Remanufacturing standards)
- ✓ Lectures and training shall be periodically given to the personnel at medical institutions involved in selection and storage of used single-use medical devices so that they can perform their duties according to the procedure predetermined by marketing authorization holders (approval conditions).

Relationship with Medical Institutions (MAH)

Points to be checked at an inspection of the marketing authorization holder:

- ✓ Recycled parts must have been used in Japan.
  (Article 4-1 (1), Remanufacturing standards)
- ✓ Recycled parts must meet the following conditions. Recycled parts must be appropriately selected at medical institutions so that they will not be mixed up with single-use medical devices that do not meet the conditions.
  (Article 4-1 (2)(3)(4)(6), Remanufacturing standards)
  - A) Recycled parts must not have a history of contacting the brain, spinal cord, dura mater, ganglia, spinal ganglia, retina, or optic nerve because it is difficult to clean off and remove prions.
  - B) Recycled parts must not have a history of being implanted in the human body.
  - C) Recycled parts must not have a history of being used for the treatment or examination of patients with the infections in the first, second, third, or fourth category, infections such as novel influenza, designated infections, or new infections as stipulated in Article 6 of the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (the Act No. 114 of 1998) or of patients stipulated in Article 8, Paragraphs 1 to 3 of the Act.
  - D) Recycled parts must be stored separately in medical institutions to prevent damage, deterioration, or contamination with pathogenic microorganisms or other disease-causing agents that cannot be inactivated or removed in the manufacturing process.

Collection and Transportation

(Matters to be observed by marketing authorization holders of medical devices or *in vitro* diagnostics)
Article 114-54 of the PMD Act Enforcement Regulations
12) Marketing authorization holders of remanufactured single-use medical devices who transport single-use medical devices that were used at medical institutions and have not been cleaned and sterilized (excluding transportation by a vessel or airplane; the same shall apply hereinafter in this item) shall meet the matters listed in the following items.

A. The devices must be transported in sealed containers.

B. The containers specified in the preceding item shall meet the following criteria.

(1) They can be handled easily and safely.

(2) They pose no risk of cracking or damage, etc. by the vibration or change in temperature and/or internal pressure, etc. expected to occur during transportation.

(3) Measures, such as attaching a seal that does not break easily, are taken to prevent the containers from being opened without reason.

(4) They shall have sufficient strength and water resistance to prevent leakage of the contents.

(5) When they are used repeatedly, it shall be easy to remove contamination by potentially pathogenic microorganisms, etc.

(6) They shall be labeled to indicate that they contain single-use medical devices used in medical institutions.

Requirements for Transport Containers (Inspection Approach)

The specifications of the transport containers are determined by the design manufacturing site.

YES

Inspect at the time of designing

NO

Transport containers are accepted at the registered manufacturing sites.

YES

Inspect when the registered manufacturing site purchases

NO

Inspect at the purchase by the marketing authorization holder

The design manufacturing site should design transport containers. If not, marketing authorization holders take the final responsibility for the design of transport containers because they must comply with the specifications of transport containers.

Requirements for Transportation

(Matters to be observed by marketing authorization holders of medical devices or *in vitro* diagnostics)
Article 114-54 of the PMD Act Enforcement Regulations
12) Marketing authorization holders of remanufactured single-use medical devices who transport single-use medical devices that were used at medical institutions and have not been cleaned and sterilized (excluding transportation by a vessel or airplane; the same shall apply hereinafter in this item) shall meet the matters listed in the following items.

C. Loading of cargoes onto vehicles, etc. shall be done so that safety will not be compromised by movement, turnover, and falling, etc. during transportation.
D. They shall be separated from the other cargoes during transportation to prevent them from being mixed up with the other cargoes.
E. A document that describes the method for handling cargoes, measures to be taken in the event of an accident, and other matters to be considered for transportation shall be carried.
F. If any contamination by potentially pathogenic microorganisms, etc. is caused by cargoes, the spread of the contamination should be promptly prevented, and decontamination should be performed.
G. The date and method of transportation, consignee or consignor and person, who carries out the transportation, shall be recorded. The records shall be retained for 5 years.
H. When transportation is contracted out to a third party, the third party must carry out the transportation by the method conforming to the following matters.
 (1) The contractor must not subcontract transportation.
 (2) The contractor shall be instructed to follow the transportation method conforming to the matters described in A to G. Necessary conditions for the transportation contract shall be set and documented.

Requirements for Transportation (Inspection Approach)

- The marketing authorization holder needs to control transportation contractors as suppliers, if applicable.
- Subcontracting transportation is prohibited.
- Contractors must be instructed to retain transportation records (marketing authorization holders are not necessarily required to retain the records by themselves).

Remanufacturing Processes (Receiving)

Points to be checked at an inspection of the acceptance process:

- ✓ Is the used single-use medical device equivalent to the original medical device?
  → Are the accepted devices free from other types of devices?
  → Does the original medical device remain unchanged?
- ✓ Is the remanufacturing frequency not more than the maximum number of times of remanufacturing?
  → (For devices remanufactured twice or more) Is the specified identification method used?
  Is there any device remanufactured more than the maximum number of times of remanufacturing?
- ✓ Any device different from the original medical device or remanufactured more than the maximum number of times of remanufacturing shall be handled as a nonconforming device (article-by-article description).
- ✓ Any incorrect used single-use medical device collected due to the inadequate selection by the medical institution shall be returned to the medical institution (enforcement notification).
- ✓ Used single-use medical devices must pass the acceptance inspection to be considered as recycled parts.
- ✓ Additionally, it is also important to identify single-use medical devices used in Japan.

Remanufacturing Process (Cleaning)

(Process control)
Article 81-2-2. Marketing authorization holders, etc. of remanufactured single-use medical devices must, when handling products related to remanufactured single-use medical devices, appropriately control the following process control operations of products related to remanufactured single-use medical devices based on the product master formula and establish and document the operation procedures.
1) Instruct the persons designated beforehand depending on the following duties to conduct the duties.
F. In the following cases, perform validation of cleaning process and other necessary validation, and prepare and retain the records.
(1) When manufacturing of products related to remanufactured single-use medical devices is newly started at the manufacturing site
(2) When there is a change in manufacturing procedures, etc., which has a significant impact on the quality of products related to remanufactured single-use medical devices
(3) When there is any change in the quality, performance, or specifications of the original medical device
(4) Other cases where it is deemed necessary to appropriately conduct manufacturing control and quality control for products related to remanufactured single-use medical devices

Remanufacturing Process (Cleaning)

Points to be checked at an inspection for cleaning validation:
Since the cleaning conditions for remanufactured single-use medical devices are specified in the certificate of analysis, it should be checked in the validation whether the approved cleaning conditions are met.
(Article 5 (1) Certificate of approval, Remanufacturing standards)

Since the certificate of analysis of a remanufactured single-use medical device specifies the cleanliness and cleaning method of the device, the validity of the cleaning conditions (conditions of the worst-case sample) needs to be checked at the verification of the design development. At the same time, it is necessary to check whether the cleanliness results were obtained under the equivalent cleaning conditions to those of the certificate of approval.
Furthermore, it is necessary to check whether the cleaning conditions of the manufacturing process do not deviate from the certificate of approval.

Remanufacturing Process (Infrastructure for Operation)

(Infrastructure for operations at registered manufacturing sites of marketing authorization holders, etc. of remanufactured single-use medical devices)
Article 81-2. Marketing authorization holders, etc. of products related to remanufactured single-use medical devices (hereinafter referred to as "marketing authorization holders, etc. of remanufactured single-use medical devices") must meet the following requirements as the infrastructure for operations at registered manufacturing sites that manufacture the products (excluding registered manufacturing sites that only design in the manufacturing process or store finished products in Japan; the same shall apply hereinafter in this chapter).
1) Work areas shall conform to the following requirements.
A. Remanufacturing clean areas (work areas where recycled parts are exposed to air in the work areas after pathogenic microorganisms and other substances that cause diseases are inactivated or removed; the same shall apply in this chapter) **shall have a drainage facility conforming to the following requirements**.
(1) **The facility shall have an appropriate structure to prevent contamination by harmful drainage.**
(2) The facility shall have a structure that can be easily cleaned or disinfected.

The drainage facility is always checked during the site tour. The following points must be considered.
- ✓ The point after which the cleaning process steps inactivate pathogenic microorganisms on recycled parts (the process steps before the point are considered to have a possibility of generating harmful drainage)
- ✓ Different definitions of contamination by countries/regions (for example, invisible foreign matters are not considered as a source of contamination in the US)

Remanufacturing Process (Traceability)

(Process control)
Article 81-2-2. Marketing authorization holders, etc. of remanufactured single-use medical devices must, when handling products related to remanufactured single-use medical devices, appropriately control the following process control operations of products related to remanufactured single-use medical devices based on the product master formula and establish and document the operation procedures.
1) Instruct the persons designated beforehand depending on the following duties to conduct the duties.
I. For components, etc. used for manufacturing remanufactured single-use medical devices, confirm that they are appropriate based on the product master formula, and prepare/retain records of the results by a serial number, etc. of remanufactured single-use medical devices (a serial number, etc. refers to the unique number, symbol, or other code to identify individual re-manufactured single-use medical devices; the same shall apply hereinafter).
J. **For recycled parts, prepare and retain records of matters to be recorded pursuant to the provisions specified by the Minister of Health, Labour and Welfare.**
2) Control the name of the business establishment to which products are released and date of release for each serial number, etc. of remanufactured single-use medical devices, and prepare/retain the records.
2. Marketing authorization holders, etc. of remanufactured single-use medical devices must store records described in the preceding paragraph for each serial number, etc. so that a series of records from recycled parts used in manufacturing to products manufactured using the recycled parts can be checked appropriately.

Remanufacturing Process (Traceability)

- The "Records" referred to in Article 81-2-2, Paragraph 1, Item 1-J of the QMS Ministerial Ordinance correspond to Article 6-3 of the Remanufacturing Standard.

Article 6. Labeling, etc.
3. Recording and Storage
(1) The following items related to recycled parts must be recorded and stored.
A. Name and address of the medical institution where single-use medical devices for remanufacturing were used
B. Date when the marketing authorization holder of remanufactured single-use medical devices collected recycled parts
C. Serial No., etc. of recycled parts that have already been remanufactured, if applicable
D. The number of times of remanufacturing recycled parts
E. Compliance review results with the matters listed in Article 4-1 (1) to (12)
F. Matters required for securing quality, performance, and safety of recycled parts in addition to the above A to E
(2) Remanufactured single-use medical devices must be traceable by appropriately preparing and retaining records related to the conditions of recycled components, inspection, manufacturing, and work environment as well as distribution.

Remanufacturing Process (Traceability)

(Securing of traceability of products related to remanufactured single-use medical devices)
Article 81-2-6 Marketing authorization holders, etc. of remanufactured single-use medical devices must secure the traceability of all the records related to components, etc. and work environment conditions if there is a risk that products related to remanufactured single-use medical devices may not conform to product requirements depending on the components, etc. or work environment conditions.
2) To ensure the traceability of products related to remanufactured single-use medical devices after release, **marketing authorization holders, etc. of remanufactured single-use medical devices must instruct distributors, etc. handling such products (distributors or loaners of specially-controlled medical devices or controlled medical devices; the same shall apply in the following paragraph.) to prepare and retain records of distribution of the products concerned.**
3) If marketing authorization holders, etc. of remanufactured single-use medical devices **have received an inspection pursuant to the provisions of Article 23-2-5, Paragraph 6 or Paragraph 8 of the Act or on-spot inspection, etc. pursuant to the provisions of Article 69, Paragraph 1 or Paragraph 4 of the Act for the said products and if it is requested by the Minister of Health, Labour and Welfare, prefectural governor, or implementer of compliance inspection of medical devices, etc. stipulated in Article 37-23 of the PMD Act Enforcement Ordinance, distributors, etc. must be instructed to retain the records of the preceding paragraph so that the records can be presented.**

Remanufacturing Process (Education and Training)

(Education and training)
Article 81-2-4: Marketing authorization holders, etc. of remanufactured single-use medical devices must, when handling products related to remanufactured single-use medical devices, establish and implement procedures for education and training related to microbiology, medicine, and veterinary medicine, etc. **for members engaged in manufacturing or testing/inspection of the products** in addition to the operations specified in Article 23, and document the procedures.
2. Marketing authorization holders, etc. of remanufactured single-use medical devices, etc. must prepare and retain records on the education and training mentioned in the preceding paragraph.

Note that this applies to all the registered manufacturing sites including exceptional manufacturing sites (although the degree of application varies).

Remanufacturing Process (Design)

- Unlike the design development of ordinary medical devices, the design development of remanufactured single-use medical devices is intended to verify that remanufactured single-use medical devices are equivalent to their original medical devices, and validate the entire remanufacturing process including collecting and cleaning of used single-use medical devices to inactivate pathogenic microorganisms.
- Since the certificate of analysis of these used single-use medical devices specifies the pathogenic microorganism inactivation method and standard related to the storage to cleaning at medical institutions and method to verify the equivalence to original medical devices, the validity of the design development process is basically inspected for a deviation from the certificate of analysis.

Remanufacturing Process (Design)

Remanufacturing standards
Article 3. Shape and Structure
3. Remanufactured single-use medical devices
(1) **Remanufactured single-use medical devices must be equivalent to their original medical devices in shape and structure.**
Article 4. Performance and Safety
2. Performance and safety (recycled parts, replacement parts, and regenerated single-use medical devices)
(3) Remanufactured single-use medical devices
A. Remanufactured single-use medical devices **must have the equivalent quality, effectiveness, and safety to their original medical devices**, considering the loss in characteristics and/or performance potentially caused by remanufacturing.

Considerations on Inspection Strategy

- It is unknown whether it is possible to appropriately include the following relevant process steps into the subsystem of the regular inspection: Selection of medical institutions, arrangements with medical institutions, education and training, selection of collection/transportation service providers, documentation of the transportation procedure, and establishment of specifications of transportation containers. Therefore, it is necessary to assign responsibility and make an inspection schedule before starting inspection.
- Since all the registered manufacturing sites are subject to on-site inspection, the compliance with the requirements by the QMS Ministerial Ordinance, Standards for Remanufacturing, and Enforcement Regulations of the Act is comprehensively checked through the entire inspection.
- Since the points to be inspected depend on the characteristics of the remanufactured single-use medical device to be inspected (e.g., the presence/absence of replacement parts), it is necessary to understand the remanufacturing process beforehand to some degree.

Any questions?