Updates of GMP and Quality Management (Japan)

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Recent Topics about Japanese GMP/GCTP* Inspection System

*GCTP :Good Gene, Cellular, and Tissue-based Products Manufacturing Practice

Updates

- PMDA has been conducting Remote Inspections with ICT tool on trial due to COVID-19 pandemic.
- New approach for GMP/GCTP compliance Inspection system was started on August 1st 2021 based on the partial amendment of the act*.
- GMP Ministerial Ordinance (ie. Japanese GMP regulation) which had been operated for 16 years since 2005 was partialy amended and enforced on August 1st 2021.

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Current GMP/GCTP Inspection method

On-site inspection: Takes place in manufacturing sites

Desktop inspection: Takes place in PMDA using pre-submitted documents

Type of Inspection	Advantages	Challenges
On-site	• Able to check the state of the manufacturing site on site, • Able to have immediate access to necessary facilities and materials, • Able to discuss directly with the personnel at the manufacturing site, etc.	• Inspectors and the personnel at the manufacturing site need to spend longer hours for the inspection, etc.
Desktop	• Able to spend as many hours as necessary for reviewing documents, etc.	• It is difficult for the inspectors to understand the actual status of the manufacturing site, etc.

Conduct Remote Inspections on trial due to COVID-19 pandemic

- **Traveling overseas has been strictly limited due to the COVID-19 pandemic.**
- On-site inspections at foreign manufacturing sites have not been conducted.
- It is difficult to predict the future international situation. There is a concern that on-site inspections at foreign manufacturing sites may not be conducted for an extended period of time.

⇒ PMDA mainly conducts (advanced) desktop inspections or postpones on-site inspections.
Since it is difficult to understand the actual situation of the manufacturing sites only by desktop inspections, a new method of inspection needs to be developed to thoroughly examine the manufacturing sites with higher risks.

As a more effective means of inspection compared to the conventional desktop inspections, **PMDA started the examination and operation of "Remote Inspection with ICT Tool."**

Status of PMDA's activities for Remote Inspection

Inspection methods		Details
Conventional methods		
On-site inspection		Visit the manufacturing site
Desktop inspection		Obtain documents from the manufacturing site and review them at the PMDA office
Methods that PMDA started the examination and operation to introduce in FY2021		
Desktop inspection	1. (Advanced) desktop inspection	● In addition to the requirements for the conventional desktop inspection, the submission of sufficient documents is required on the matters that need an intensive review. ● Teleconferences, etc. are held for specific matters if necessary. ● Operated in accordance with the paper-based inspection performed during an on-site inspection
	2. Remote inspection*	● Remotely check the manufacturing plant without visiting the manufacturing site ● Possible methods to be used to check the manufacturing plant: ・Real time check using a web camera ・Viewing a video, etc. recorded in advance ● Perform an online Q & A session about documents and records

*Presently, the remote inspection is classified as a method of desktop inspections.

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New approach for GMP/GCTP compliance Inspection system

Introduce a “Product Category-based Inspection System” as an option

Past system

○ Based on applications from marketing authorization holders, GMP/GCTP inspections were to be conducted for the manufacturing sites at the time of new approval of products, at the time of partial changes, and every 5 years after approval of the products.

○ In many manufacturing sites, products of multiple marketing authorization holders have been manufactured, and the date of approval differs for each product. Thus, during 5 years, frequent inspections were required for one manufacturing site.

Current system (enforced in August 2021)

○ While maintaining the inspections at the time of new approval of products and at the time of partial changes based on applications from marketing authorization holders, **a system** has been introduced **from the viewpoint of international consistency**, **which enables selection of GMP/GCTP inspections (Product Category-based Inspection) for each manufacturing site based on applications from manufacturers**, instead of the periodic inspections at every 5 years after approval of products by marketing authorization holders [Article 14-2, Paragraph 1 of the Act/Article 23-25, Paragraph 2 of the Act]

○ Specifically, **based on optional applications from manufacturers**, GMP inspections are conducted for each category of the manufacturing process classified taking into account the technical characteristics, etc. of the process, and **a “Certificate [*1]” effective for 3 years for each category of manufacturing process is issued to the manufacturer** [Article 14-2, Paragraph 3 of the Act/Article 23-25, Paragraph 2 of the Act]

○ During the effective period of the “Certificate,” for the manufacturing sites which manufacture the products belonging to such a category, **the periodic inspection for each product** based on the application from the marketing authorization holders **may be omitted** [Article 14, Paragraph 8 of the Act/Article 23-25, Paragraph 7 of the Act].

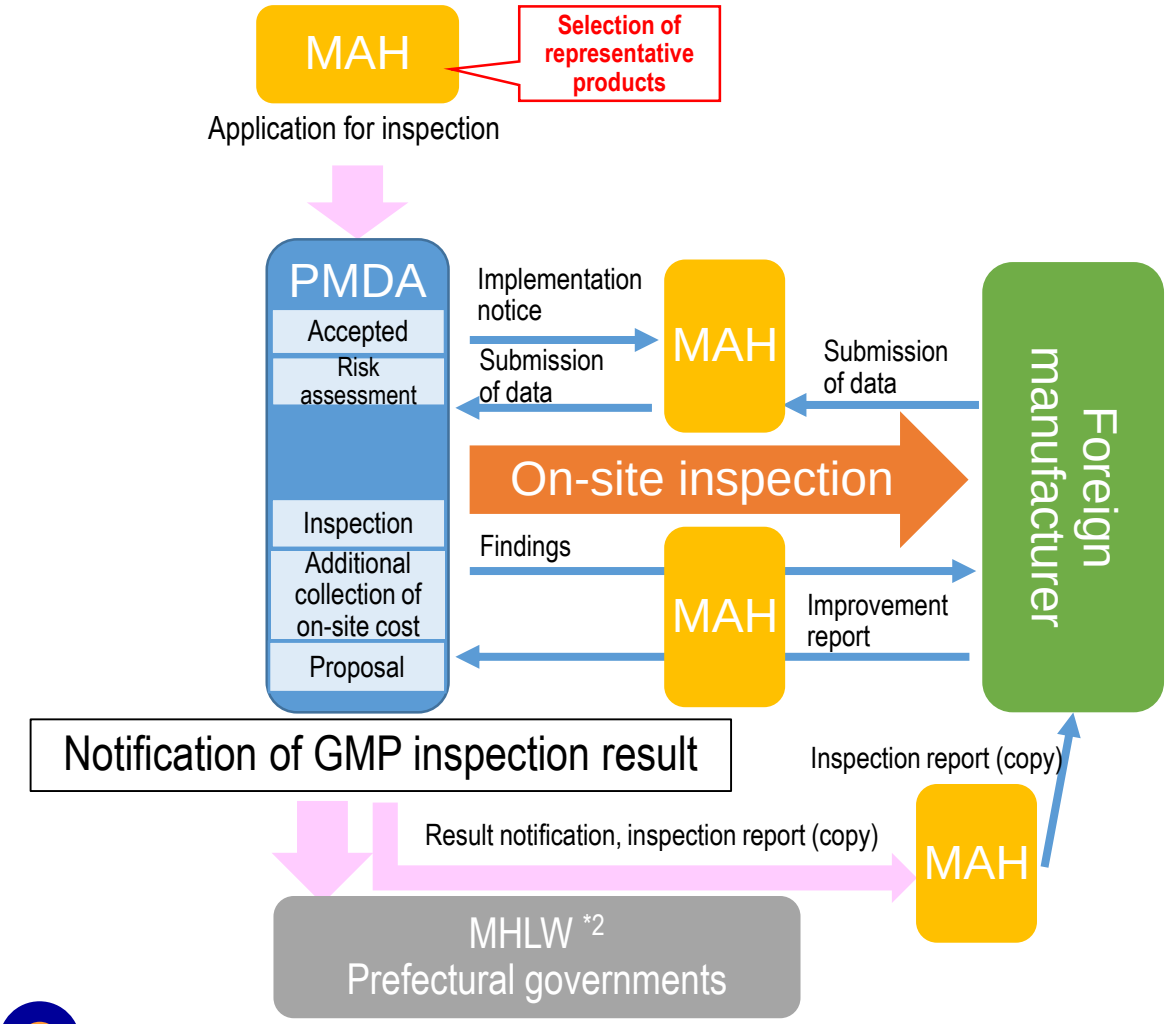
[*1] Certificate: GMP certificate for product category-based inspection

Comparison between a Basic approach and the Optional approach

Basic approach	Optional approach (Product category-based Inspection)
Applicant	
Marketing authorization holder	Manufacturer* *Manufacturing sites licensed/certified/registered under the provisions of Article 13, etc. of the Act Manufacturing sites of drug substance intermediates without license, etc., external testing institutions, etc. are excluded.
Application unit	
For each product (Applications may be made collectively for each marketing authorization holder/manufacturing site.)	For each pruduct category
Timing of application	
Every 5 years after obtaining approval (Applications may be moved forward according to the timing of renewal of manufacturing license, etc.)	Optionally, (applications should be made in a planned manner so that the Certificate, which is effective at the time of every 5 years after approval of the product for which the periodic inspection is intended to be omitted, is issued).
Action due to failure of application	
A legal obligation is imposed, and the failure falls under a violation of Article 14, Paragraph 7 of the Act (cancellation of approval, order for improvement, etc.)	This is an optional system and excluded from a violation of laws and regulations. (However, the periodic inspection may not be omitted, and accordingly, the failure may fall under a violation described in the left column.)
Notification of inspection results	
Issuance of compliance inspection result notification (no concept of expiry date)	Issuance of the Certificate (expiry date: 3 years)

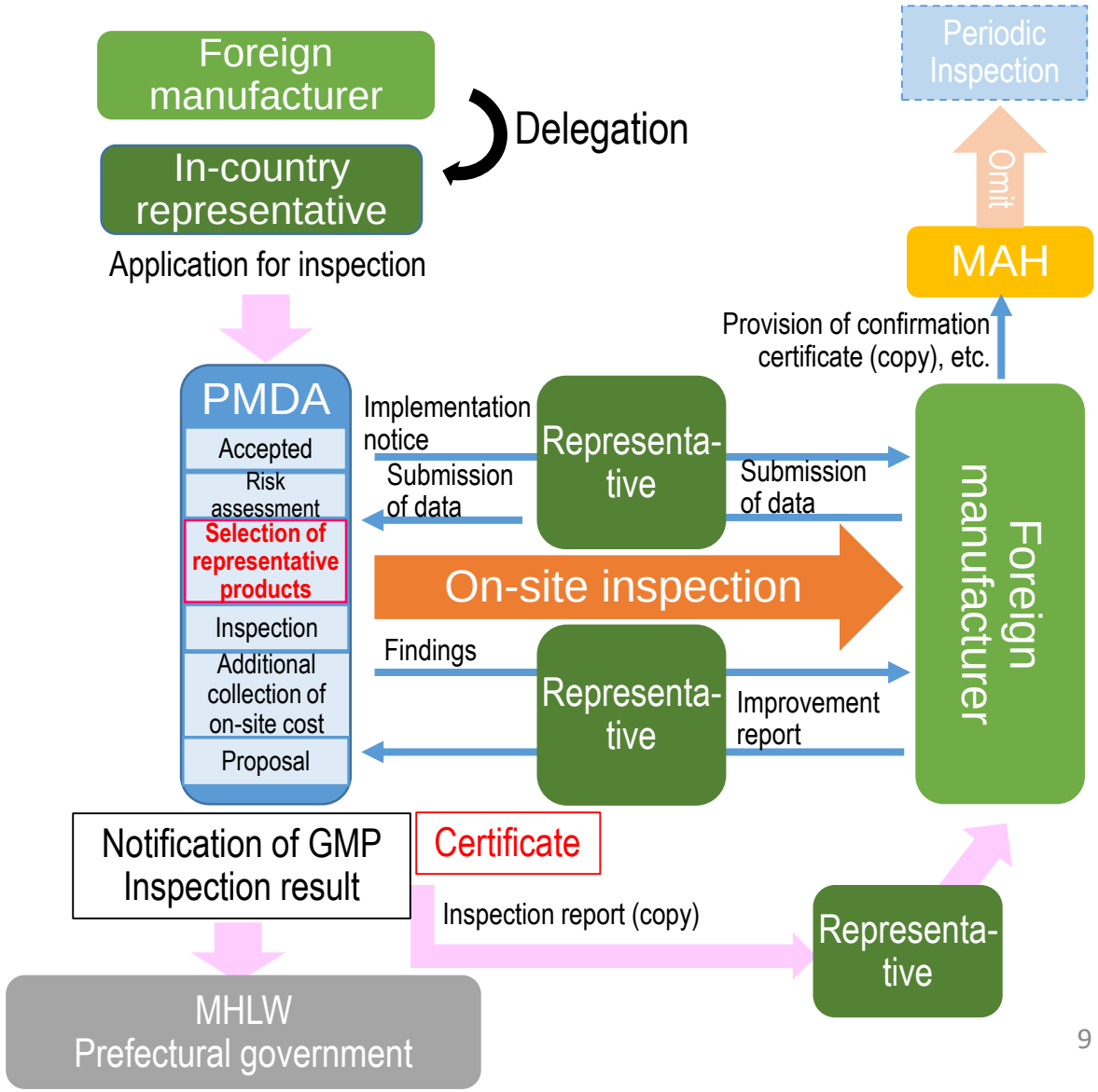
Comparison between a Basic approach and the Optional approach

◆ Basic approach

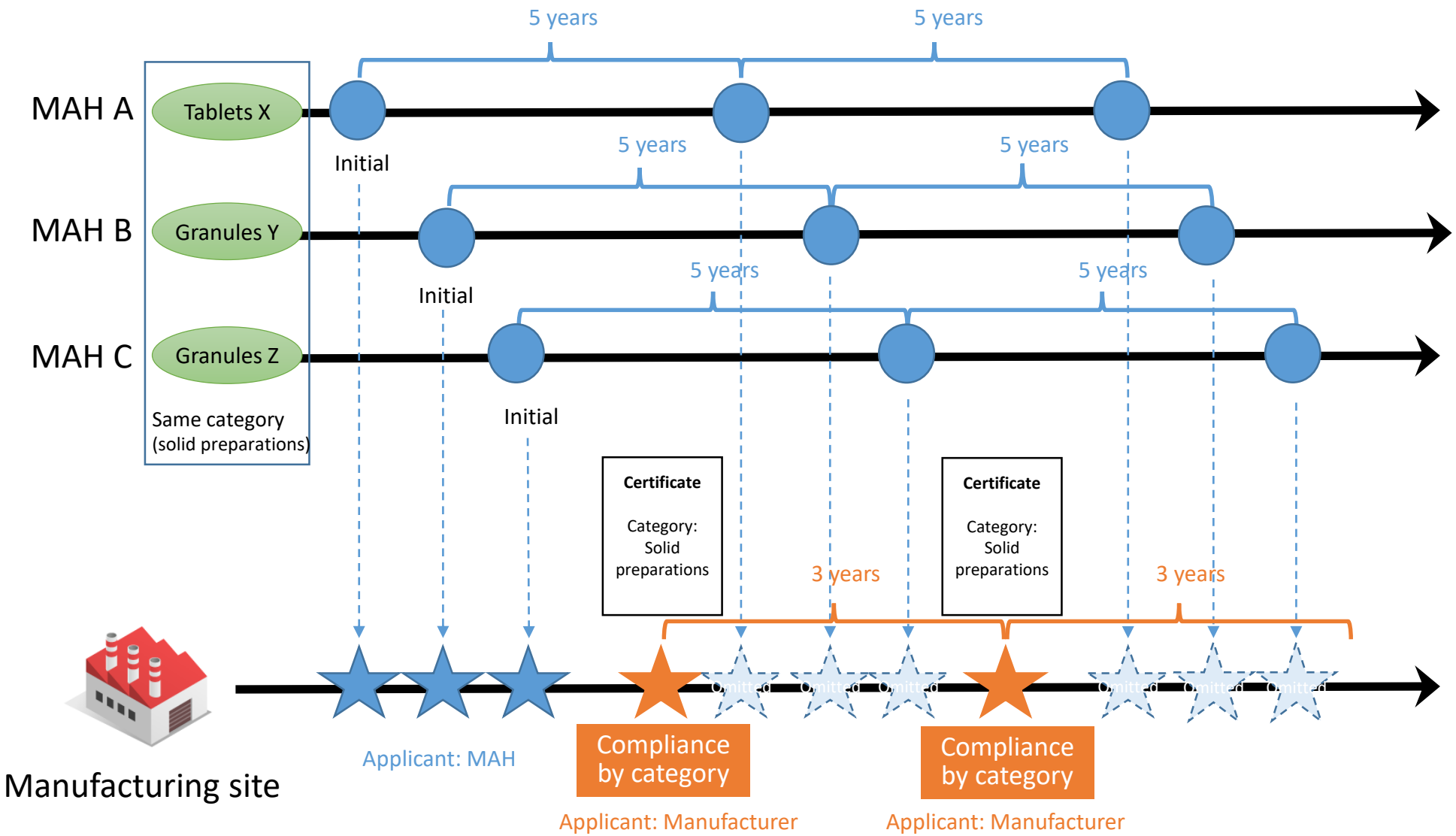


*2 MHLW: Ministry of Health, Labour and Welfare

◆ Optional approach (Product category-based Inspection)



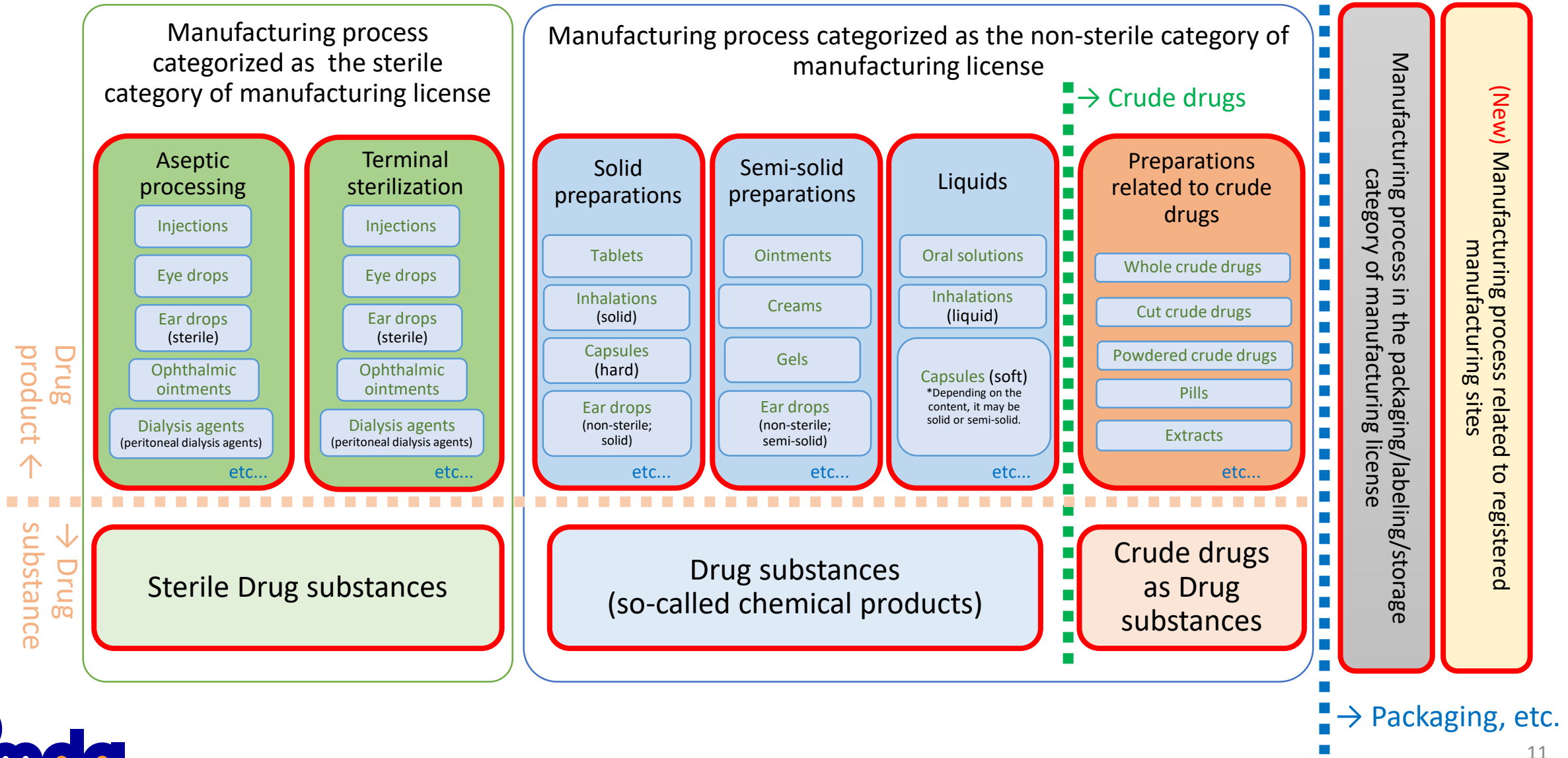
Example of omission of periodic Inspection based on the Certificate



Product Categories

Domestic Inspection: Prefectural governments are in charge
Overseas Inspection: PMDA is in charge

Categories to be described in the Certificate



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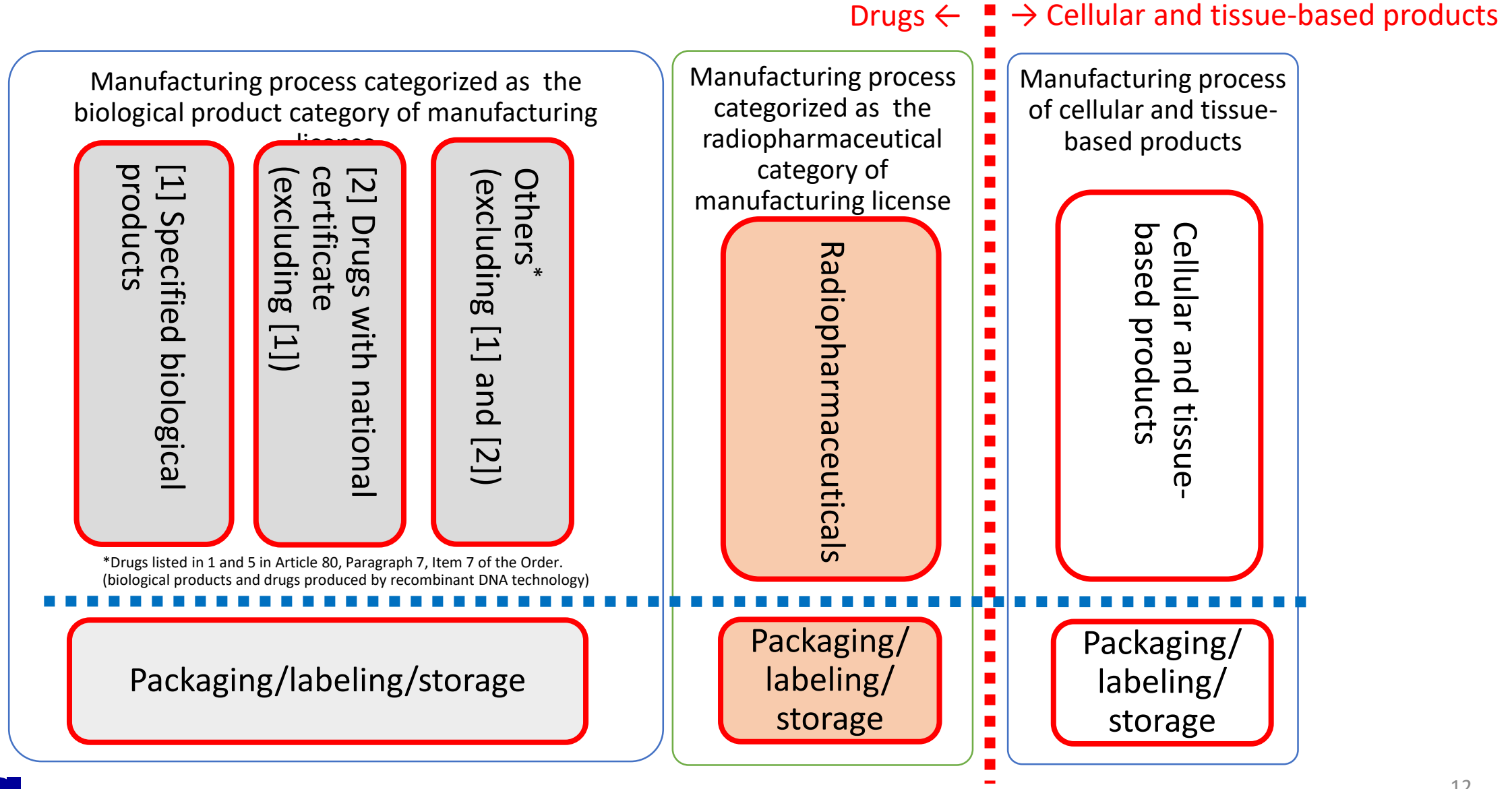
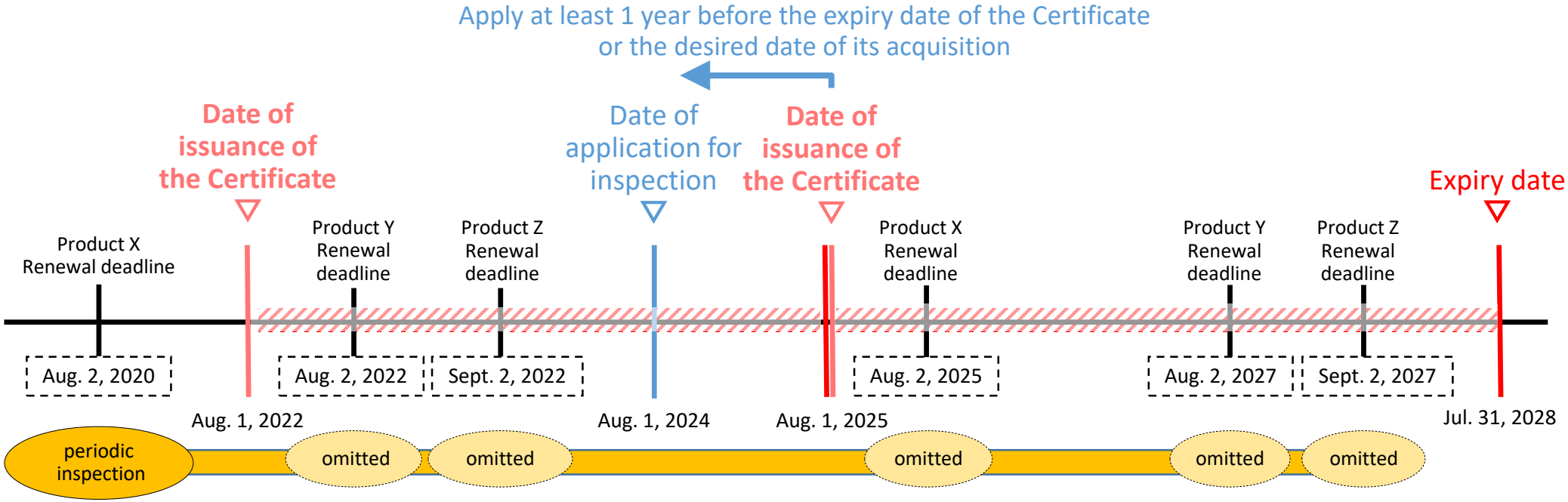


Standard paperwork period, etc. for Product Category-based Inspection

- The period (standard paperwork period) required for PMDA's inspection related to Product Category-based Inspeciton is 1 year (6 months for new, periodic, and partial changes).
- The applicant needs to apply for the inspection to the PMDA by the day 1 year before the expiry date of the Certificate or the desired date of its acquisition.



- The application for periodic inspection may be omitted only if the Certificate effective at the renewal deadline for each product has been issued.
- If the Certificate is not issued by the renewal deadline for the product, the periodic inspection may not be omitted, and it is necessary to undergo the periodic inspection. Thus, if the periodic inspection is omitted based on the Certificate, an application at an appropriate timing will be appreciated so that the Certificate can be acquired in a planned manner.

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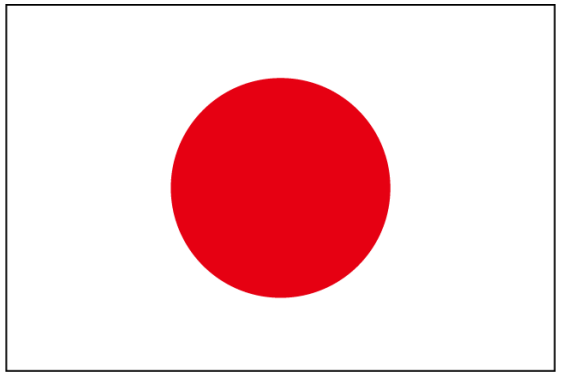

Thank you