Quality Control about APIs (Japan)

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7th India-Japan Medical Products Regulatory Symposium

Recent Topics about Japanese Pharmaceutical Quality Control System

Updates

- Stats of PMDA On-site Inspections in FY2023.
- All generic drug manufacturers inspect their factories from this April to October and submit reports of such inspections to the MHLW and Prefectural governments, as well as make them publicly accessible.
- Product Category-based Inspection System, including that the certificate will be issued to the manufacturer that meets the inspection, which started on 2021 based on the partial amendment of the act*.

*The Act on Securing Quality, Efficacy and Safete of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Law No. 145, 1960)

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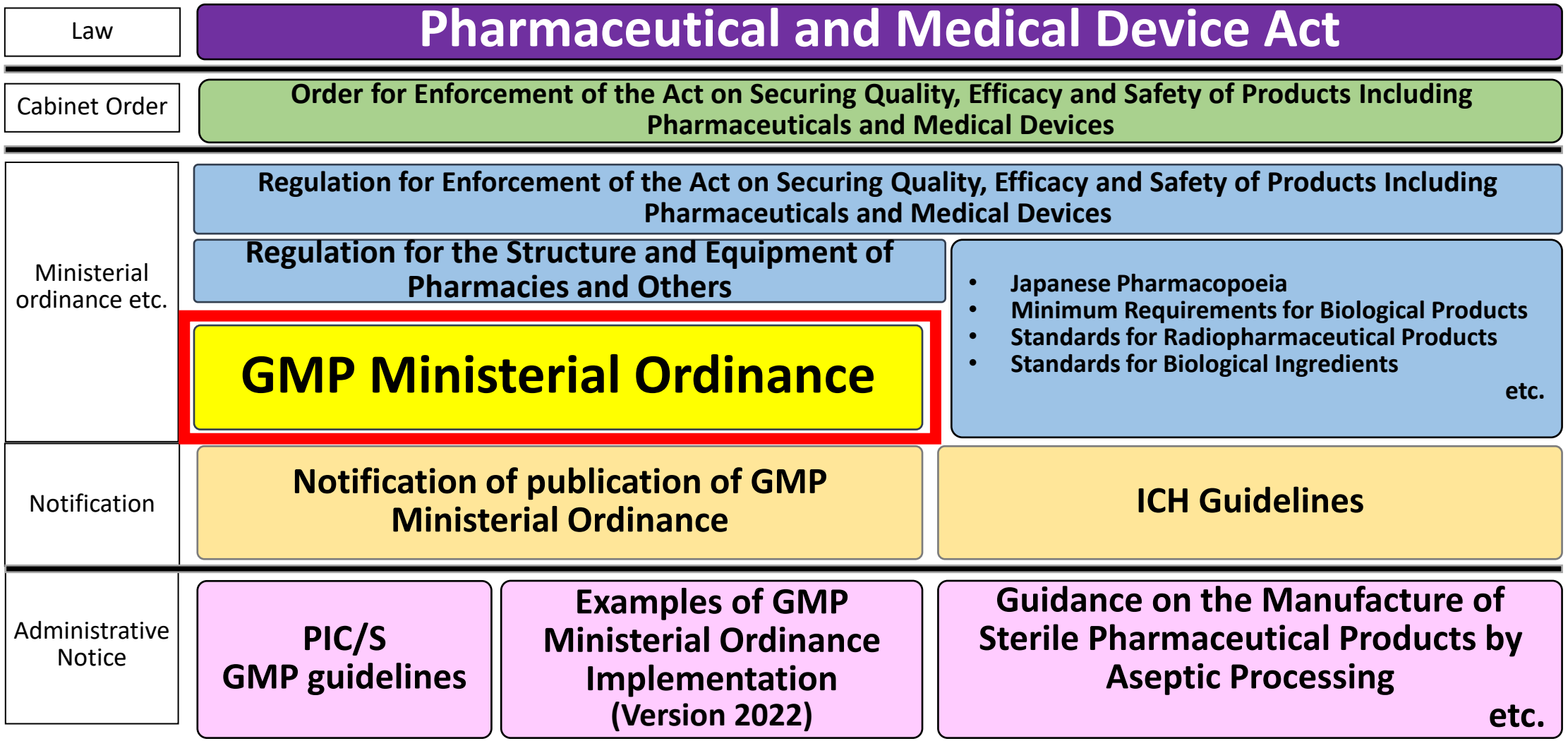
Regulatory System Related to GMP in Japan



Types of GMP Inspections

Purpose of inspection: Inspect the status of compliance with GMP Ministerial Ordinance.

Type of Inspection	
Pre-approval inspections	• Inspection by new application
	• Inspection by partial change approval application
Post-approval inspections	• Periodic inspection
	• Product Category-based inspection
	• PACMP* GMP inspection
Unannounced inspections	• For-cause inspection
	• Surveillance inspection
Others	• GMP Inspection of Pharmaceuticals for Export
	• GMP Inspection of Investigational Products

Started in August 2021

* PACMP = Post-Approval Change Management Protocol

Scope of GMP Compliance Inspection by PMDA

- Overseas manufacturing site : PMDA
- Japanese manufacturing site : PMDA (limiting to the following) and prefectural government

Scope for GMP inspections		Japanese manufacturing site	Overseas manufacturing site
Drugs	Mainly new drugs	PMDA	PMDA
	Mainly generic drugs	Prefectural governments	PMDA
gene, cellular and tissue-based products		PMDA	PMDA

A) GMP inspection of manufacturing site where a new drug is manufactured pre-approval

B) GMP inspection of manufacturing sites where the following drugs are manufactured pre-approval

/ Drugs using genetical recombination technology including antibody products

/ Drugs designed by MHLW as requiring special attention among drugs manufactured using human or other living organism as raw materials such as a blood transfusion preparations

/ Radiopharmaceuticals including contrast media

C) Periodic GMP inspection performed every time of period (5 years) specified by a cabinet order, which is not than 3 years after approval of a drug, have elapsed (hereinafter referred to as “periodic inspection”)

/ The periodic inspection of drugs shown in B) is performed by the PMDA

/ For periodic inspection of drugs other than those shown in B), the first inspection is conducted by the PMDA, and the second and subsequent inspections are conducted by the prefectural government (the prefecture where the manufacturing site is located)

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.

Risk-based Decision-making Cycle

Risk assessment:

- Product characteristics
- Process characteristics
- Dosage form
- Inspection history by PMDA/other authorities
- Inspection report from PIC/S members
- Recall history
- Rating of manufacturing site: S, A, B, C and D

etc.

Update:

Internal database

Decision:

On-site inspection
or Desktop inspection

Inspection:

Rating based on assessment of 6 sub-systems : Rank S, A, B, C and D

1) Quality systems
2) Facilities & equipment
3) Materials control
4) Production control
5) Packaging & labelling
6) Quality control

Types of GMP Compliance Inspections - Timing of Implementation

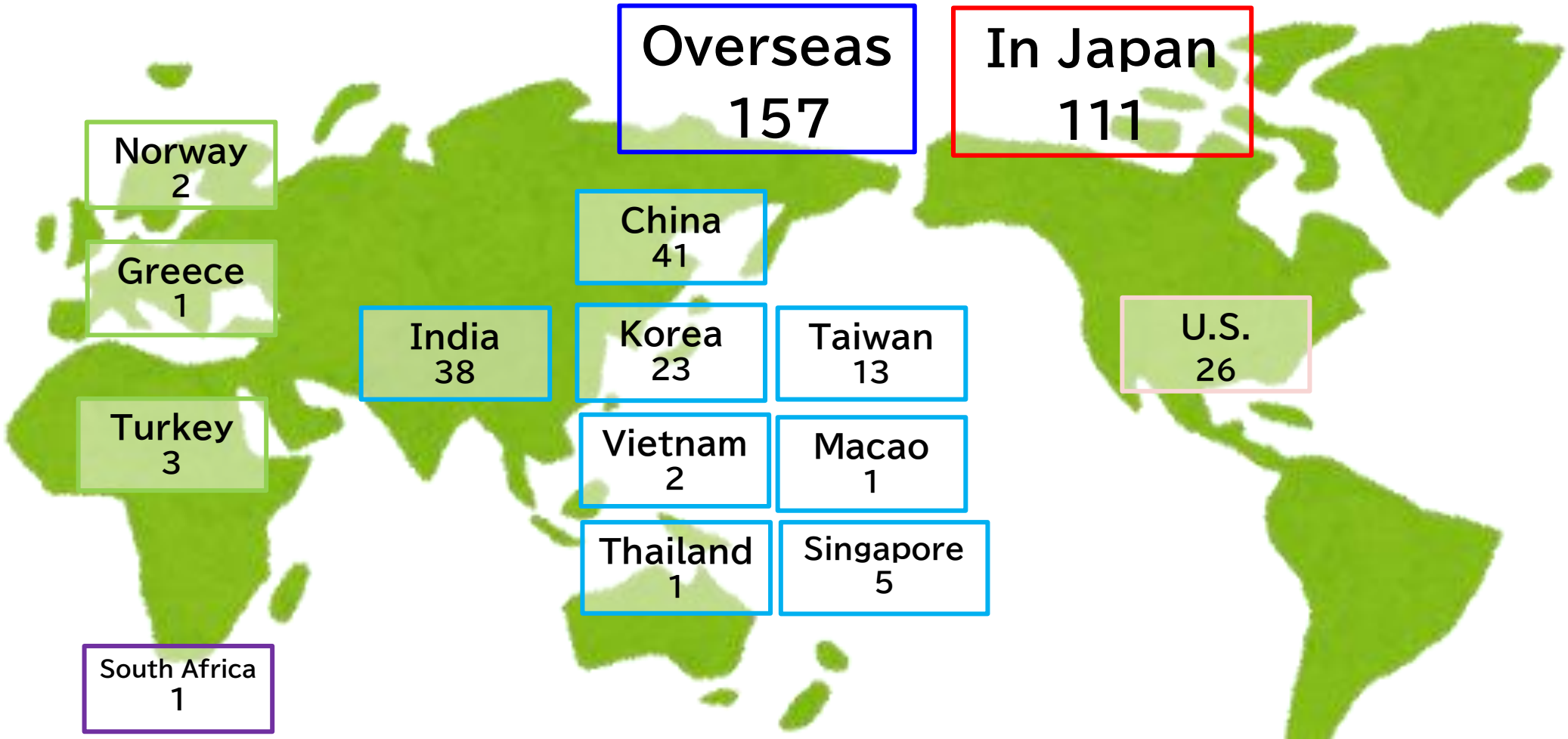
Development phase	Clinical study	Marketing approval review	Marketing approval	Product distribution
Manufacturing of investigational product		Manufacturing of pharmaceutical product		

GMP Inspection of Investigational Products

Pre-approval inspections (new / partial change)

- Periodic inspection
- Product Category-based inspection
- PACMP GMP inspection
- GMP Inspection of Pharmaceuticals for Export
- For-cause inspection
- Surveillance inspection

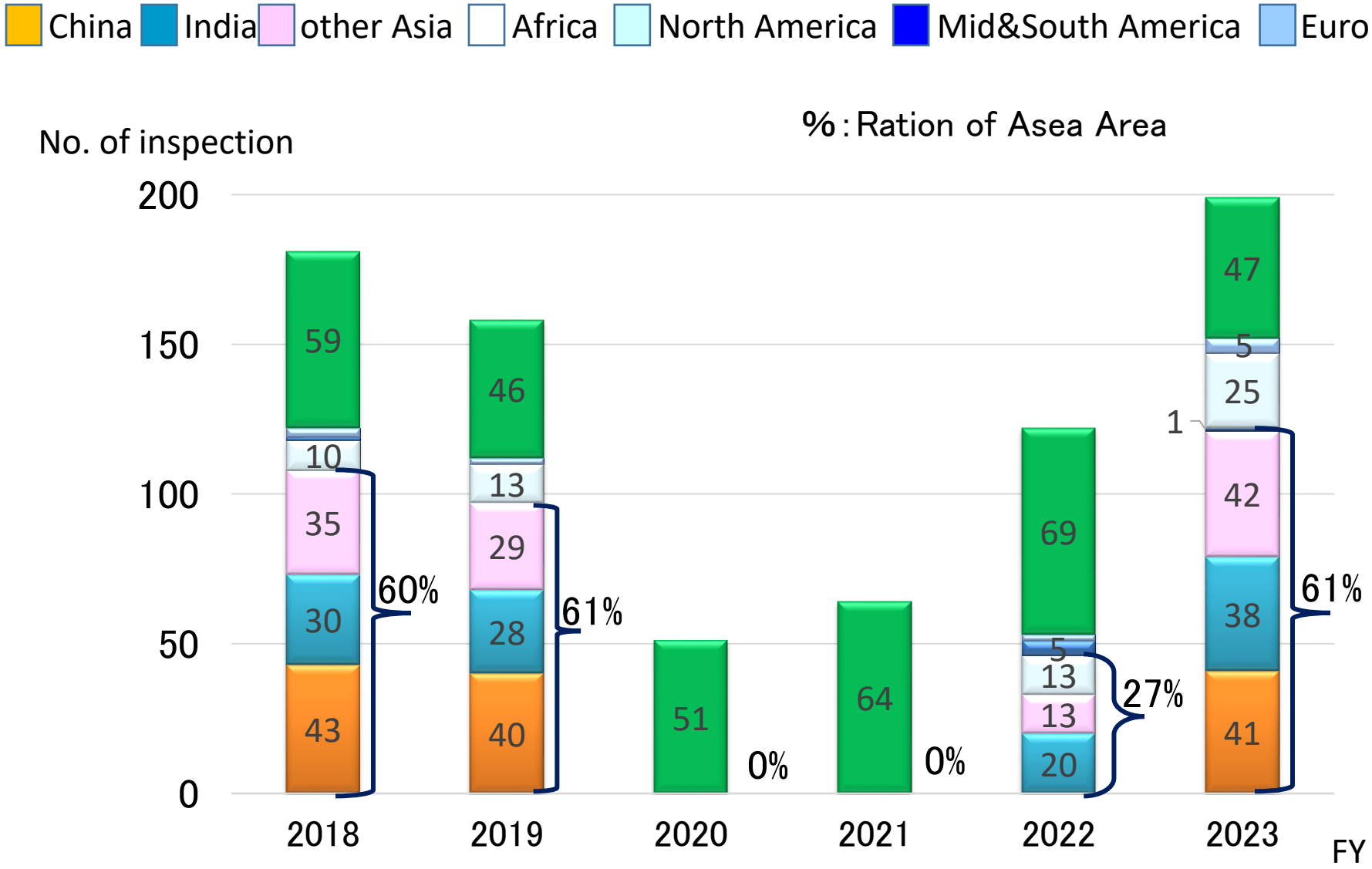
GMP/GCTP on-site inspections by PMDA 《FY2023》



- FY2023: from April 2023 to March 2024
- Inspections of India resumed in May 2022.
- Desktop inspections ca. 2,000 in FY2023

- Including facility investigations and investigational new drug GMP inspections
- GCTP : Good Gene, Cellular, and Tissue-based Products Manufacturing Practice

GMP Compliance on-site inspections by PMDA



GMP/GCTP Annual Report

PMDA summarizes the Business accomplishment related to GMP inspection, regulatory system, international activities, current issues, future vision, etc., to issue a GMP/GCTP Annual Report.

Topics

- PMDA's philosophy and Overviews of the organization and operations
- Achievements (No. of Applications, Inspection results)
- Analysis of Deficiencies (Ranking, Trends, Case Studies)
- Outline of new projects (GMP roundtable meeting, ORANGE Letter, GMP education support)
- Other activities (Consultation services, International activities)

- English version

  Website：https://www.pmda.go.jp/english/review-services/gmp-qms-gctp/0007.html
- Japanese version

  Website：https://www.pmda.go.jp/review-services/gmp-qms-gctp/gmp/0011.html

ORANGE Letter (Observed Regulatory Attention/Notification of GMP Elements)

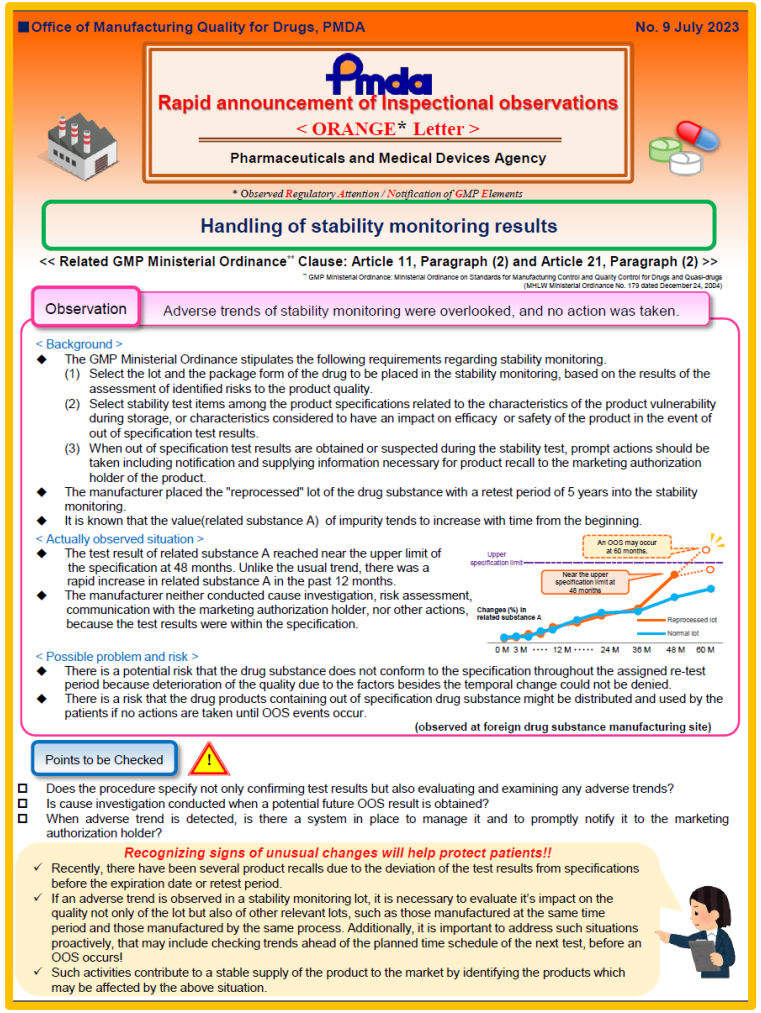
As of June 2024

Observed Regulatory Attention / Notification of GMP Elements (Orange Letters)

- No.1 Failure to confirm adequacy of raw materials[118.71KB] (April, 2022)
- No.2 Risks associated with handling substances with unknown pharmacological activities and toxicities[185.26KB] (May, 2022)
- No.3 Overlooked risks to the quality of products due to insufficient CAPA[114.76KB] (July, 2022)
- No.4 Importance of thorough management of outsourced activities[170.49KB] (September, 2022)
- No.5 Improper recording[230.78KB] (December, 2022)
- No.6 Improper modification of records to align with instructions[262.68KB] (December, 2022)
- No.7 Mislabeling of the products caused by the violation of procedures[159.01KB] (March, 2023)
- No.8 Environmental monitoring in aseptic processing areas[127.64KB] (June, 2023)
- No.9 Handling of stability monitoring results[112.73KB] (July, 2023)
- No.10 English version is under preparation. (October, 2023)
- No.11 English version is under preparation. (October, 2023)
- No.12 English version is under preparation. (January, 2024)
- No.13 English version is under preparation. (March, 2024)

https://www.pmda.go.jp/review-services/gmp-qms-gctp/gmp/0011.html

Rapid announcement of Inspectional observations



■Office of Manufacturing Quality for Drugs, PMDA No. 9 July 2023

Rapid announcement of Inspectional observations

< ORANGE* Letter >

Pharmaceuticals and Medical Devices Agency

* Observed Regulatory Attention / Notification of GMP Elements

Handling of stability monitoring results

<< Related GMP Ministerial Ordinance** Clause: Article 11, Paragraph (2) and Article 21, Paragraph (2) >>

** GMP Ministerial Ordinance: Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs (MHLW Ministerial Ordinance No. 179 dated December 24, 2004)

Observation: Adverse trends of stability monitoring were overlooked, and no action was taken.

< Background >

- The GMP Ministerial Ordinance stipulates the following requirements regarding stability monitoring.
  (1) Select the lot and the package form of the drug to be placed in the stability monitoring, based on the results of the assessment of identified risks to the product quality.
  (2) Select stability test items among the product specifications related to the characteristics of the product vulnerability during storage, or characteristics considered to have an impact on efficacy or safety of the product in the event of out of specification test results.
  (3) When out of specification test results are obtained or suspected during the stability test, prompt actions should be taken including notification and supplying information necessary for product recall to the marketing authorization holder of the product.
- The manufacturer placed the "reprocessed" lot of the drug substance with a retest period of 5 years into the stability monitoring.
- It is known that the value(related substance A) of impurity tends to increase with time from the beginning.

< Actually observed situation >

- The test result of related substance A reached near the upper limit of the specification at 48 months. Unlike the usual trend, there was a rapid increase in related substance A in the past 12 months.
- The manufacturer neither conducted cause investigation, risk assessment, communication with the marketing authorization holder, nor other actions, because the test results were within the specification.

< Possible problem and risk >

- There is a potential risk that the drug substance does not conform to the specification throughout the assigned re-test period because deterioration of the quality due to the factors besides the temporal change could not be denied.
- There is a risk that the drug products containing out of specification drug substance might be distributed and used by the patients if no actions are taken until OOS events occur.

(observed at foreign drug substance manufacturing site)

Points to be Checked

- ☐ Does the procedure specify not only confirming test results but also evaluating and examining any adverse trends?
- ☐ Is cause investigation conducted when a potential future OOS result is obtained?
- ☐ When adverse trend is detected, is there a system in place to manage it and to promptly notify it to the marketing authorization holder?

Recognizing signs of unusual changes will help protect patients!!

- ✓ Recently, there have been several product recalls due to the deviation of the test results from specifications before the expiration date or retest period.
- ✓ If an adverse trend is observed in a stability monitoring lot, it is necessary to evaluate it's impact on the quality not only of the lot but also of other relevant lots, such as those manufactured at the same time period and those manufactured by the same process. Additionally, it is important to address such situations proactively, that may include checking trends ahead of the planned time schedule of the next test, before an OOS occurs!
- ✓ Such activities contribute to a stable supply of the product to the market by identifying the products which may be affected by the above situation.

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The MHLW Panel's final report

May 22 2024

The MHLW Panel on Industrial Structure for Realization of Stable Supply of Generic Drugs

●What the Generic Drug Industry Should be

- To ensure a stable supply of quality-assured pharmaceutical products, we aim to (1) secure manufacturing and quality control systems, (2) ensure stable supply capacity, and (3) achieve a sustainable industrial structure.
- Establish an intensive reform period of about five years, starting promptly with those items that can be realized, while steadily implementing measures to quickly eliminate supply instability and prevent its recurrence.

●Direction of measures

(1) secure manufacturing and quality control systems

○ Conducting thorough self-inspections
- Simultaneous self-inspection of all companies, including non-JGA members(April to October 2024)
- Recommend the use of outside agencies. Conduct written inspections and hearings with employees, publish inspection results, and report to the government.

○ Strengthening Governance
- Foster a quality culture in each company and develop human resources based on this culture.
- Provide external training and sharing of best practices, particularly with industry associations. Promote the transfer of knowledge and skills during business-to-business collaboration.

○ Improved pharmaceutical inspection

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Product Category-based Inspection System

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].

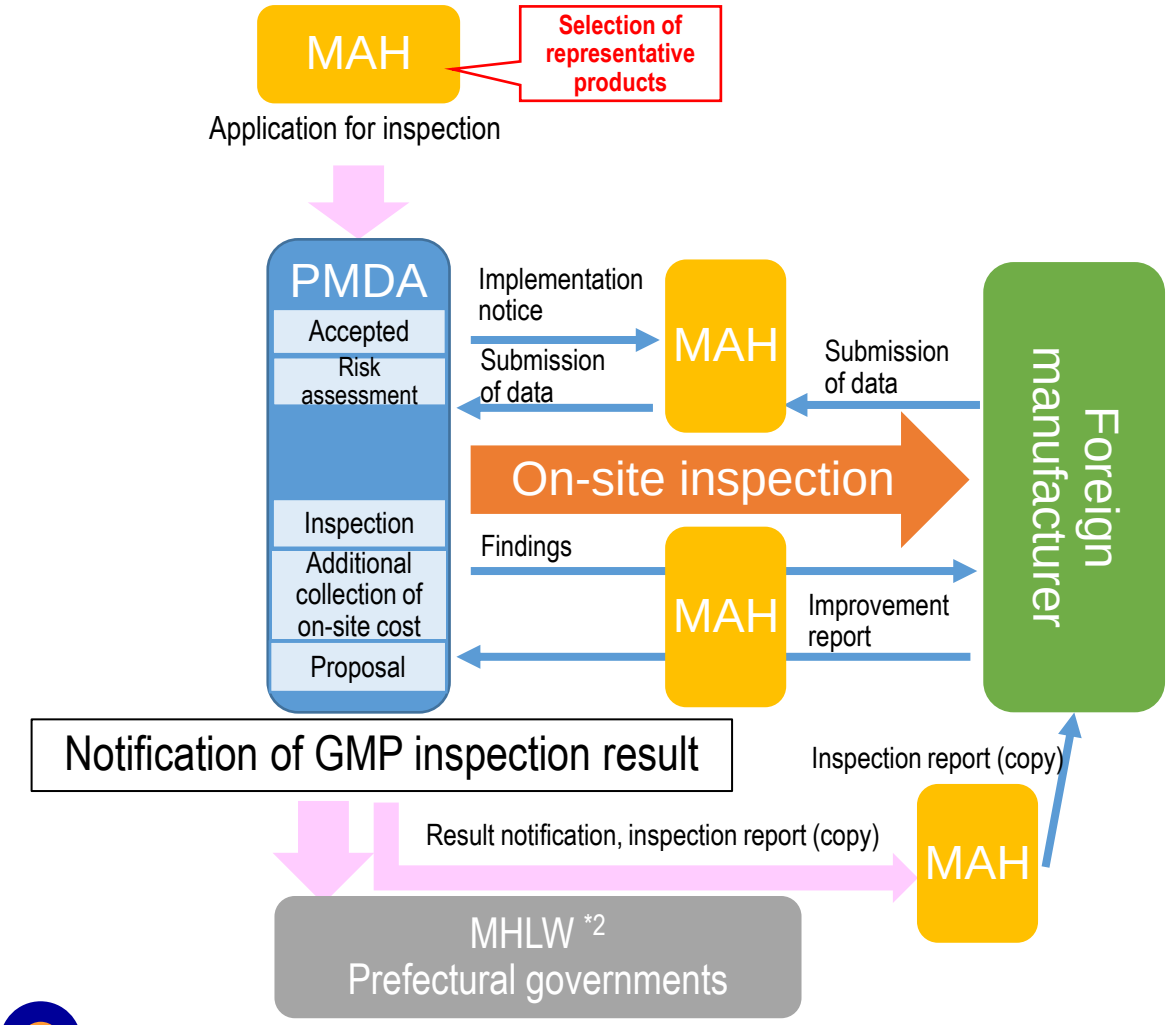
[*1] Certificate: GMP certificate for product category-based inspection

Comparison between a Basic approach and the Optional approach

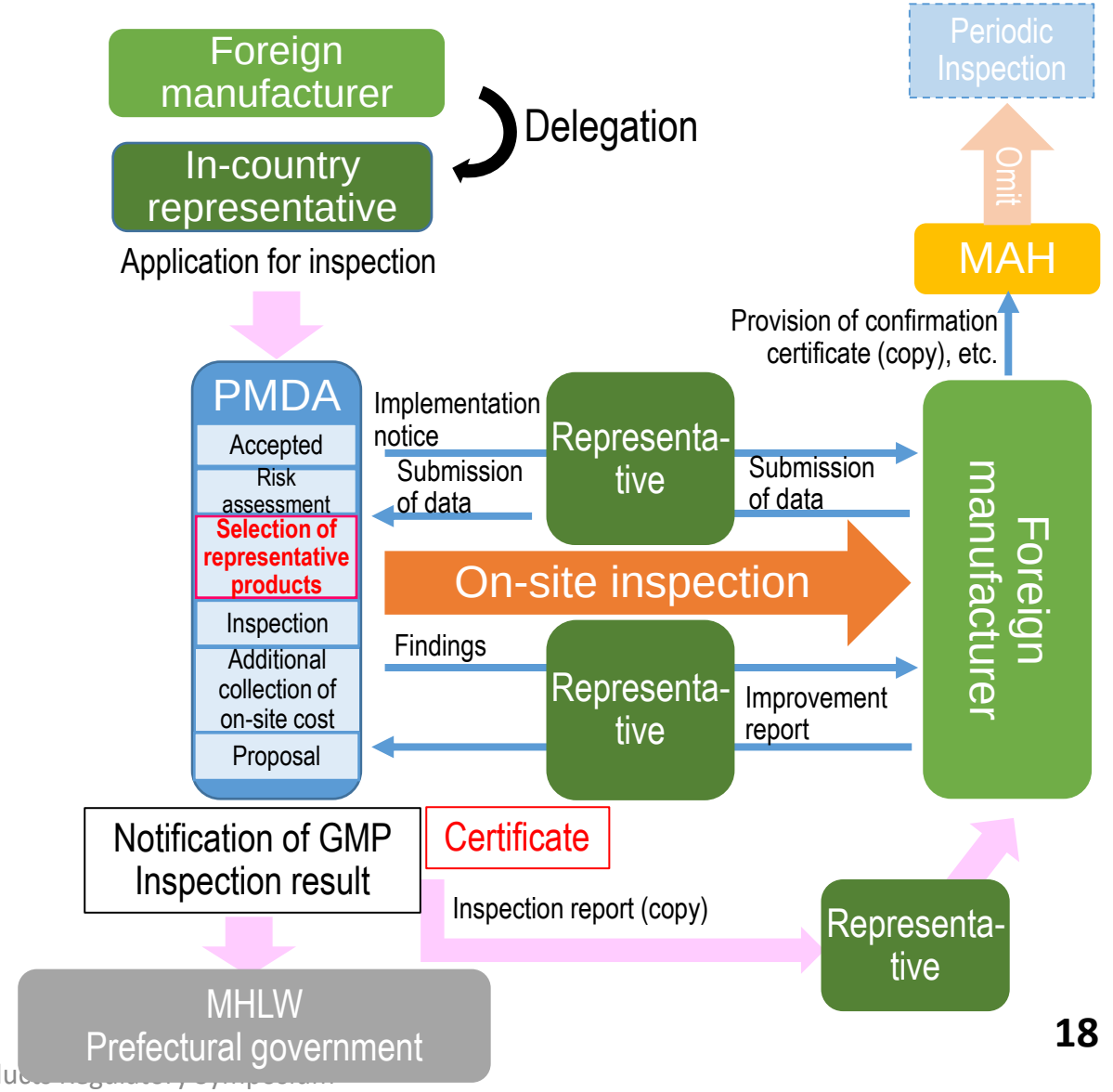
Basic approach	Optional approach (Product category-based Inspection)
Applicant	
Marketing authorization holder	Manufacturer* *Manufacturing sites licensed/certified/registered under the provisions of Article 13, etc. of the Act Manufacturing sites of drug substance intermediates without license, etc., 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

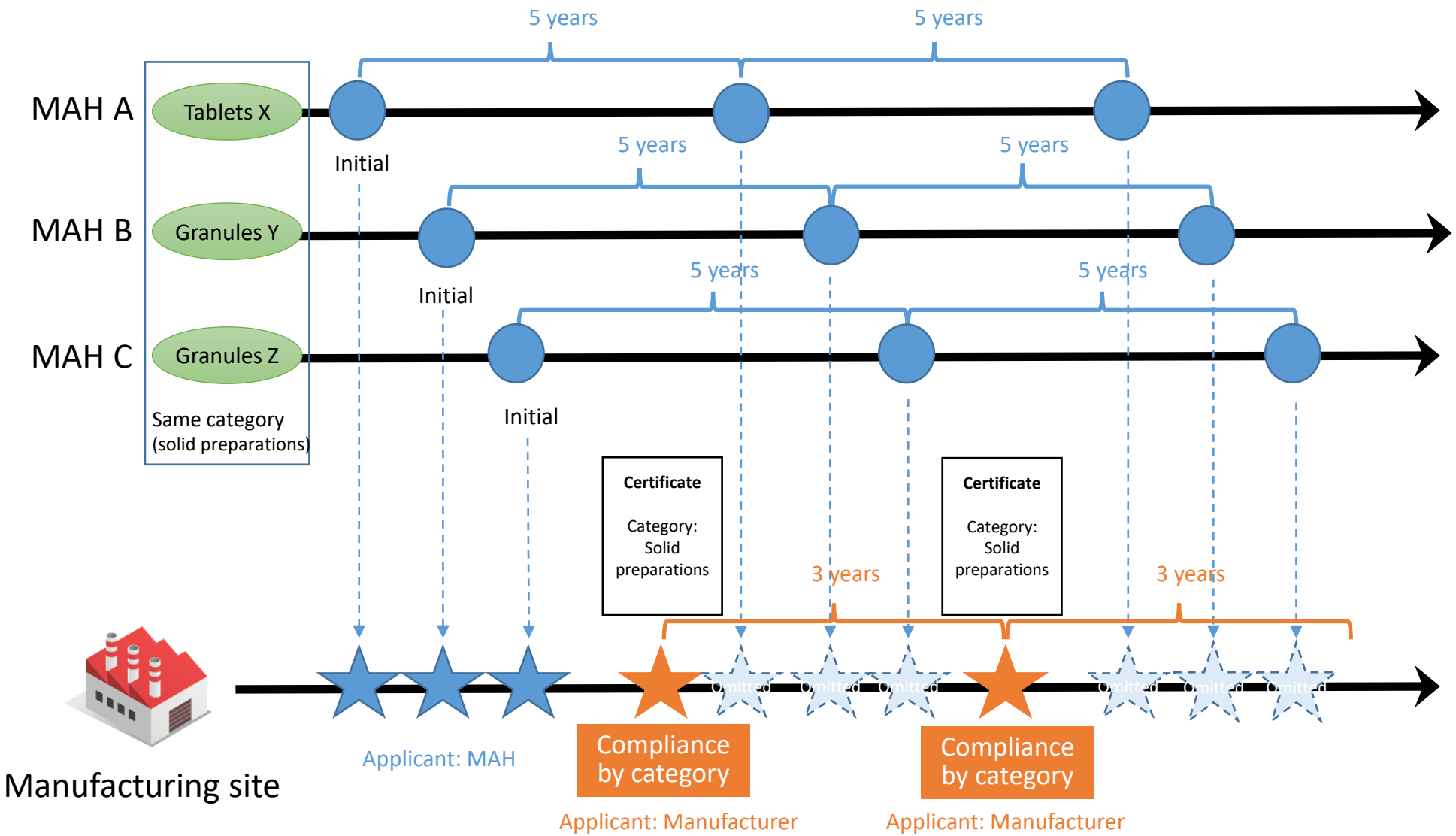


◆Optional approach (Product category-based Inspection)



*2 MHLW: Ministry of Health, Labour and Welfare

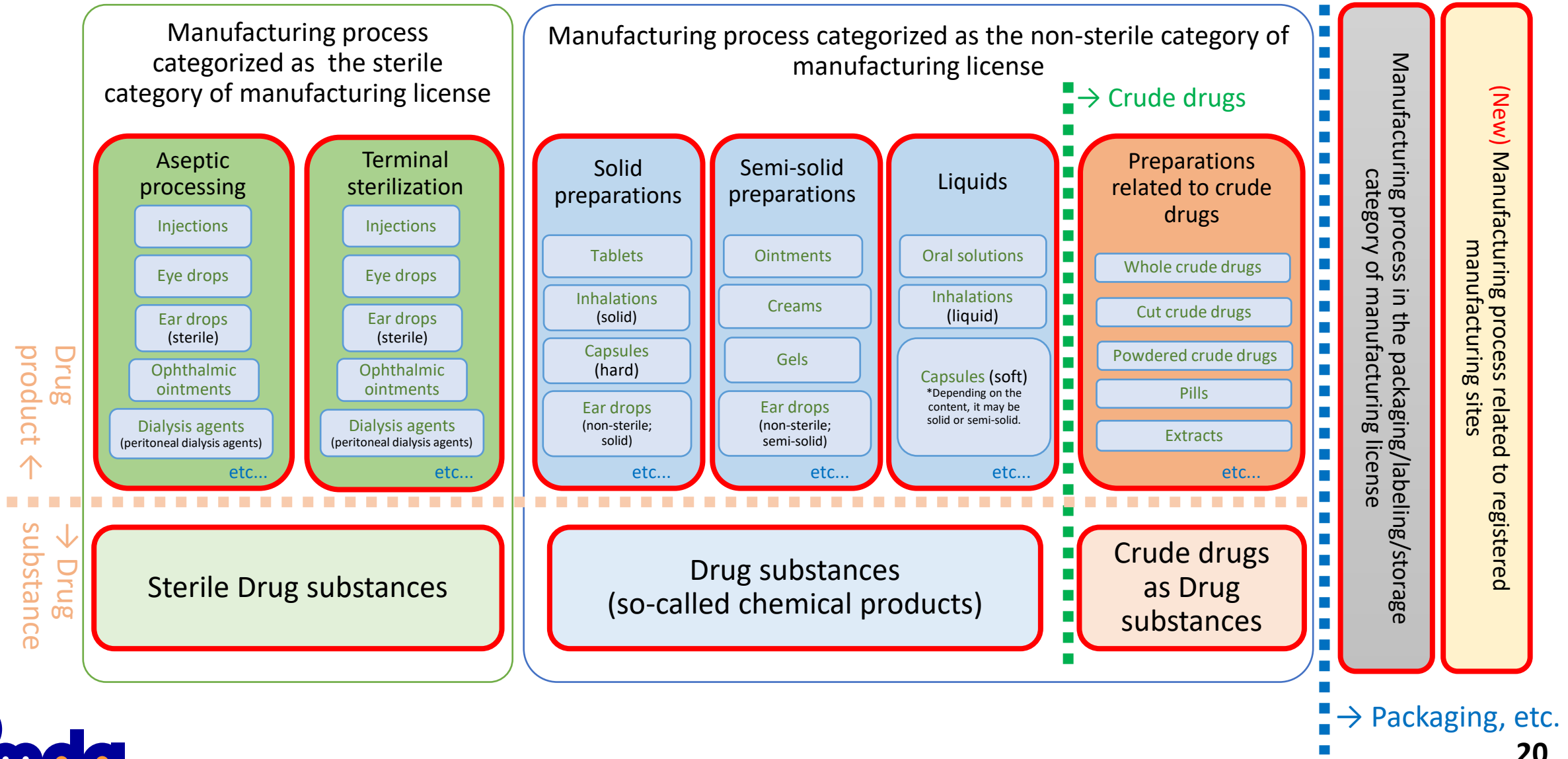
Example of omission of periodic Inspection based on the Certificate



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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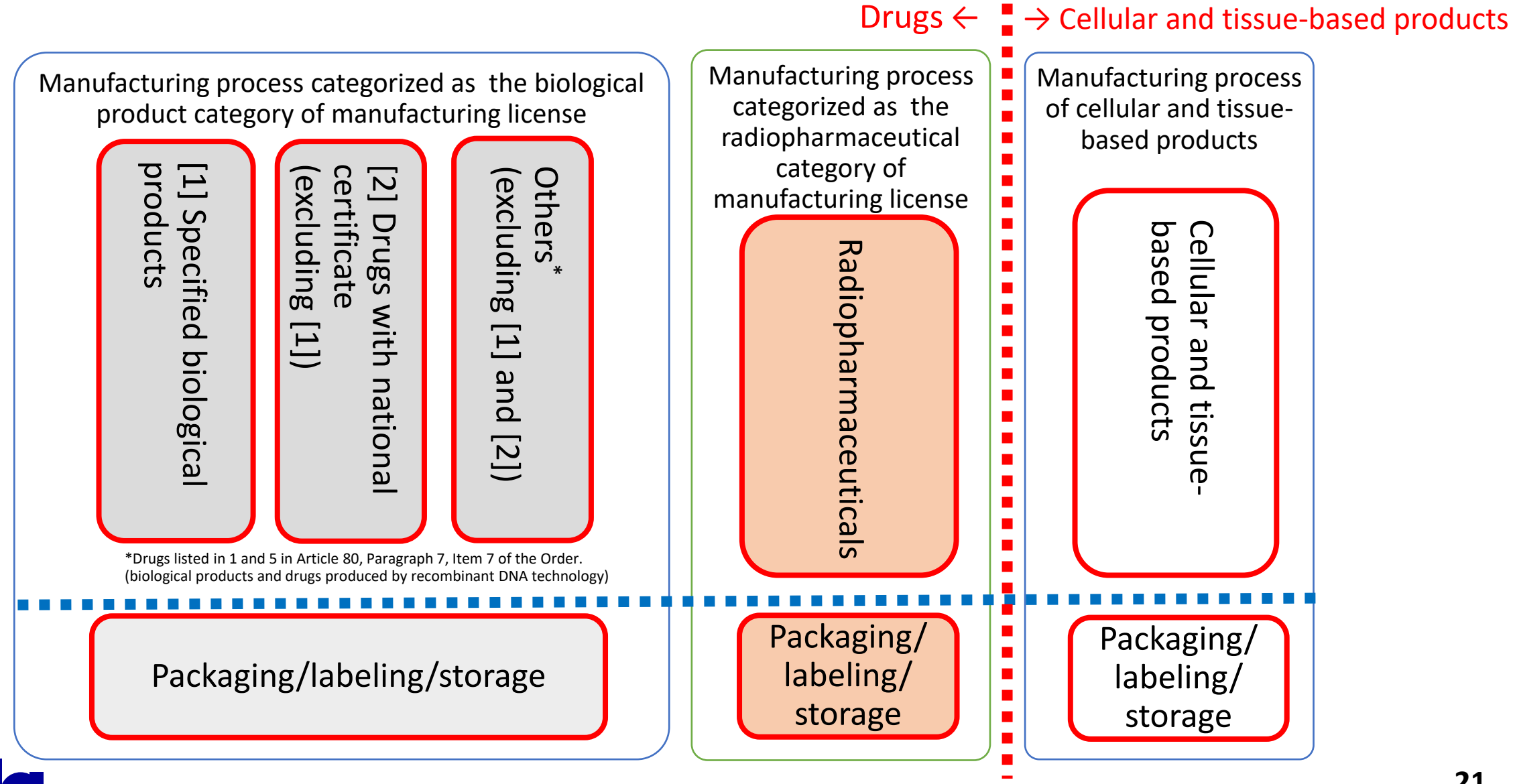
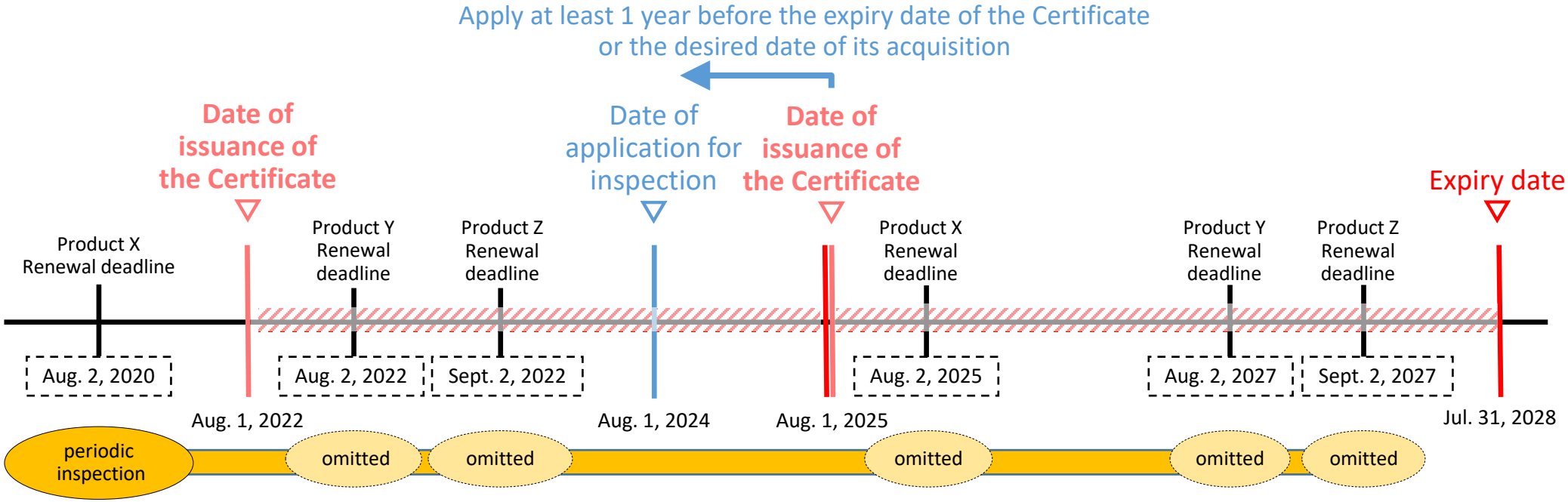


Standard paperwork period, etc. for Product Category-based Inspection

- 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.

Japanese GMP Regulations (English translation)

As soon as English translations of the guidelines and notices become available, we will publish them on PMDA website.

On PMDA website
https://www.pmda.go.jp/english/review-services/gmp-qms-gctp/0001.html

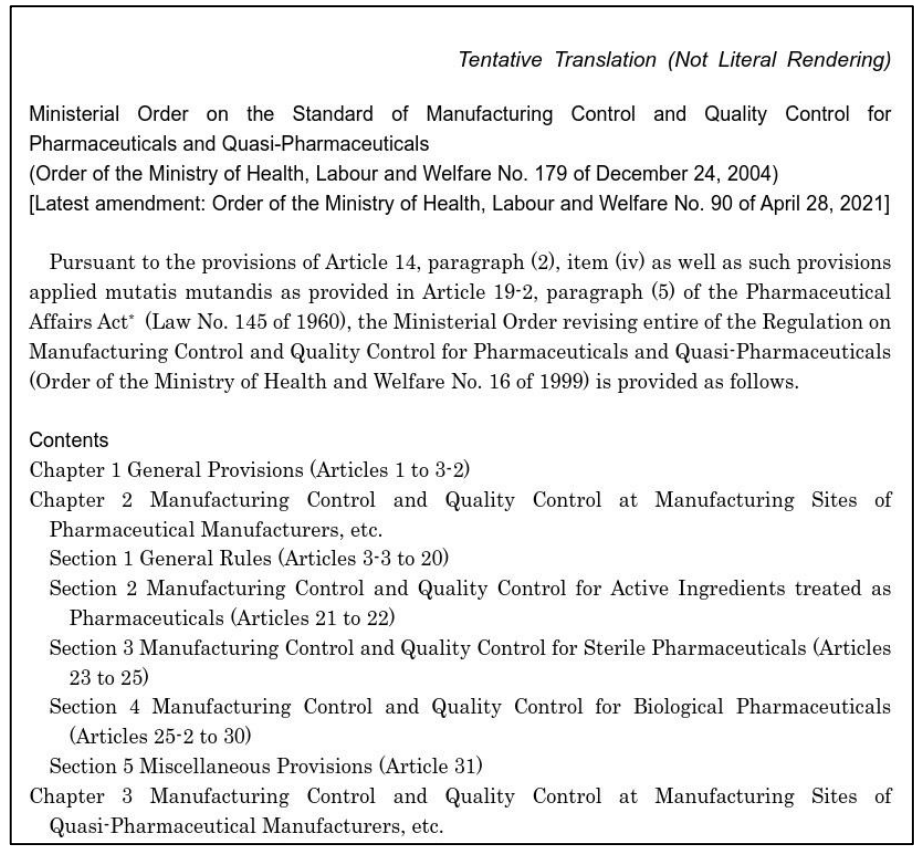
GMP compliance inspection

Add this pa

1. Regulations and Guidelines

Regulations

- GMP Ministerial Ordinance (Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs) [309.6KB] (Tentative Translation updated Jun 21, 2024)
- GQP Ministerial Ordinance (Ministerial Ordinance on Standards for Quality Assurance for Drugs, Quasi-drugs, Cosmetics and Medical Devices) [586.63KB]
- Regulations of Buildings and Facilities of Pharmacies, etc. [1.02MB]
- Notification Concerning Partial Amendment of the Ministerial Ordinance on Standards for Manufacturing Control and Quality control for Drugs and Quasi-drugs (April 28, 2021) [668.60KB] (English version is under preparation.)



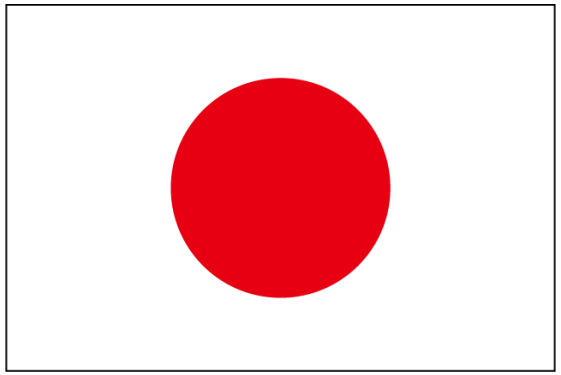
Tentative Translation (Not Literal Rendering)

Ministerial Order on the Standard of Manufacturing Control and Quality Control for Pharmaceuticals and Quasi-Pharmaceuticals
(Order of the Ministry of Health, Labour and Welfare No. 179 of December 24, 2004)
[Latest amendment: Order of the Ministry of Health, Labour and Welfare No. 90 of April 28, 2021]

Pursuant to the provisions of Article 14, paragraph (2), item (iv) as well as such provisions applied mutatis mutandis as provided in Article 19-2, paragraph (5) of the Pharmaceutical Affairs Act* (Law No. 145 of 1960), the Ministerial Order revising entire of the Regulation on Manufacturing Control and Quality Control for Pharmaceuticals and Quasi-Pharmaceuticals (Order of the Ministry of Health and Welfare No. 16 of 1999) is provided as follows.

Contents

GMP Ministerial Order (English translation) is now on PMDA website



Thank you