GMP / GCTP Annual Report
FY 2024

PMDA

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Introduction

GMP/GCTP Annual Report FY 2024
The Director's Statement

<Message from PMDA>

PMDA underwent its first re-assessment by PIC/S(Pharmaceutical Inspection Co-operation Scheme) in March 2025, since acceding to PIC/S in July 2014. The re-assessment team from PIC/S provided favorable feedback, demonstrating that PMDA's GMP inspection capabilities and supporting quality systems meet international standards established by PIC/S. However, in FY (Fiscal Year) 2024, GMP violations were still identified at some domestic manufacturing sites, resulting in administrative actions such as business suspensions. This situation highlights the need for more effective GMP inspections and guidance to ensure the stable supply of safe and reliable pharmaceuticals for the public.

Since FY 2022, PMDA has continued risk communication activities, such as the Orange Letter, GMP Roundtable Meetings, and the GMP/GCTP Annual Report, to widely disseminate information on pharmaceutical quality, encourage internal inspections at manufacturing sites, and promote active discussions among industry, government, and academia. To date, PMDA has issued a total of 20 Orange Letters and held six GMP Roundtable Meetings, including those hosted in regional areas. All related materials are publicly available on the PMDA website for free use.

In the previous GMP/GCTP Annual Report (FY 2023 edition), PMDA published a list of major deficiencies identified during GMP inspections. In preparing this FY 2024 edition of the GMP/GCTP Annual Report, we conducted a questionnaire (anonymous and directly submitted to PMDA) in February to reflect the information most requested by stakeholders. While this edition prioritizes prompt publication and could only partially incorporate your requests, we will continue to consider your feedback for future editions, including the FY 2025 edition.

A QR code linking to the survey site is provided on page 40 of this Annual Report. We encourage you to read this report and share your opinions through the survey. Based on your valuable feedback, PMDA will continue providing information and data that are useful for GMP activities at manufacturing sites.

PMDA remains committed to contributing to the prompt and stable supply of high-quality pharmaceuticals through GMP inspections, training support for local governments, and cooperation with overseas regulatory authorities. We will also continue to advance risk communication, upholding our unwavering mission to protect the health and lives of the public. With this strong sense of duty, we will conduct our operations with speed and high transparency, striving to advance healthcare.

July 7, 2025

Chief Safety Officer, PMDA

Kenji KURAMOCHI

GMP/GCTP Annual Report

The Office of Manufacturing Quality for Drugs (OMQD) at PMDA publishes the GMP/GCTP Annual Report, which compiles information such as achievements in GMP inspection, inspection frameworks, international initiatives, current challenges, and future vision. OMQD aims to enhance regulatory the transparency of GMP inspection operations and strengthen mutual trust between PMDA and pharmaceutical companies by actively disseminating information related to pharmaceutical quality management. OMQD aims to provide information to overseas pharmaceutical companies, manufacturing sites and regulatory authorities, gather feedback and advice from abroad, and further improve its operations.

＜ Past issues ＞

GMP/GCTP Annual Report 2022 （Japanese Version、English Version）

GMP/GCTP Annual Report 2023 （Japanese Version、English Version）

Following the release of the FY 2023 edition, QMQD conducted an anonymous survey*1 targeting all personnel involved in GMP/GCTP operations within companies belonging to the Quality Committee of the Federation of Pharmaceutical Manufacturers' Association of Japan as well as those engaged in pharmaceutical quality assurance as marketing authorization holders or Master File holders. The survey collected responses from 368 individuals, regarding the types of information they hope to see in the Annual Report. The FY 2024 edition reflects some of the key survey results as a priority. Going forward, QMQD plans to continue conducting such surveys to further improve the content of its information dissemination.

*1 Request for cooperation with GMP/GCTP Annual Report survey issued by JPMA on February 5, 2025, No. 083 https://www.toku-seiyakukyo.jp/data/drug_news/2025/1_17387187539139.pdf

Summary of feedback and QMQD response in this Annual Report is as follows:

Summary of feedback	Reflections in this Annual Report
• PMDA's introduction is too detailed. • The report should focus solely on annual activities. • It feels like just a business report with little useful information.	As this Annual Report aims to enhance the transparency of Japan's GMP system and is also published in English for international audiences, we intend to include a certain level of PMDA's organizational introduction. However, we improved the structure by clearly dividing Chapter 1 for organizational overview and Chapter 2 for activity reports, making it easier to locate necessary information. We also enhanced the analysis of observations to provide more valuable insights.
• Desire for more detailed criteria for determining on-site or document-based inspections for GMP/GCTP compliance.	We included information about the selection of inspection methods based on risk assessment under 1-5 Risk-based selection of inspection method. Please note that this may change in the future due to amendments to the Pharmaceutical and Medical Device Act and related laws.
• Want to know which manufacturing sites received observation report or were deemed non-compliant in GMP/GCTP inspections for risk evaluation purposes.	The Annual Report, in principle, does not disclose information that could identify specific manufacturing sites (such as facility names or domestic/overseas status). However, as of March 2025, PMDA has started publishing GMP inspection results on its official website, where you can find information regarding compliance status.
• While a list of major deficiencies was published, the background information was unclear, making it difficult to grasp the context of the observations.	In this year's list of major deficiencies, we included concise background information for each observation after obtaining confirmation from the relevant sites. Please refer to 3-3 List of Identified Deficiencies. Note: In the FY 2023 edition, we included "license/certification categories" as part of the background information; however, this was omitted from this year's edition since we now provide separate background descriptions for each observation.

Summary of feedback	Reflections in this Annual Report
• No information on critical deficiencies was included.	No critical deficiencies were identified in FY 2023. However, one critical deficiency was identified in the current fiscal year. Additionally, we included PMDA's analysis under 3-4 Characteristics of Recent Critical Deficiencies.
• Desire to publish other deficiencies, as is done for major deficiencies. However, there is concern that too many entries would make it difficult to identify important and useful observations.	As you pointed out, the number of other deficiencies is very large. We will continue exploring ways to present such information effectively. In this fiscal year, we analyzed frequently identified categories of other deficiencies, focusing on those related to ministerial ordinance requirements. Please see 2-3-2 Analysis of identified deficiencies for details.
• The Annual Report has been issued late every year—November for FY 2022 and September for FY 2023—making the information outdated.	This year's Annual Report was targeted for publication within approximately three months after the end of the fiscal year.
• The English version of the Annual Report has also been delayed—March 2024 for the FY 2022 edition and February 2025 for the FY 2023 edition—making the information outdated.	For this fiscal year, we aimed to publish the English version within two months of the release of the Japanese version.
• Request to include information on this year's inspection policies, ongoing projects, and PMDA's perspectives on manufacturing sites.	Please refer to Chapter 5: Future vision. We will continue to share PMDA's current policy directions and visions for GMP operations.

Also, the following feedback could not be reflected in this Annual Report, as a result of consideration. Here is the QMQD's policy.

Summary of feedback	QMQD's policy
• While a list of major deficiencies has been published, there is also interest in knowing what improvements were made and how long it took to resolve them.	The time required for corrective actions depends on the nature of the findings. In some cases, improvements may not have been completed by the time of this report's publication. Disclosing such information uniformly is therefore difficult. Additionally, if we were to exclude unresolved cases, the timing of the deficiencies could potentially be inferred. Thus, we decided not to include such information in this report. However, if similar requests continue, we will consider alternative ways to disclose such data.
• Request to publish findings from previous years as well.	Due to the vast volume of data and the need to request masking from many marketing authorization holders or manufacturing sites, we prioritize the publication of observations from the current fiscal year to avoid delays in issuing reports. Nevertheless, if similar requests increase, we will consider alternative approaches for publication.
• While the report shows the number and trends of simple consultations, there is also interest in learning about the actual consultation topics as references.	We will consider including examples of noteworthy simple consultations as a future topic for discussion. For this fiscal year, as in the previous year, we have included an analysis of simple consultation topics in 2-5 Consultation Services.

Additionally, after careful consideration, we decided not to reflect certain other opinions in this Annual Report. The Office's policies regarding those points are explained within this report.
We also received many other valuable suggestions, which we greatly appreciate.

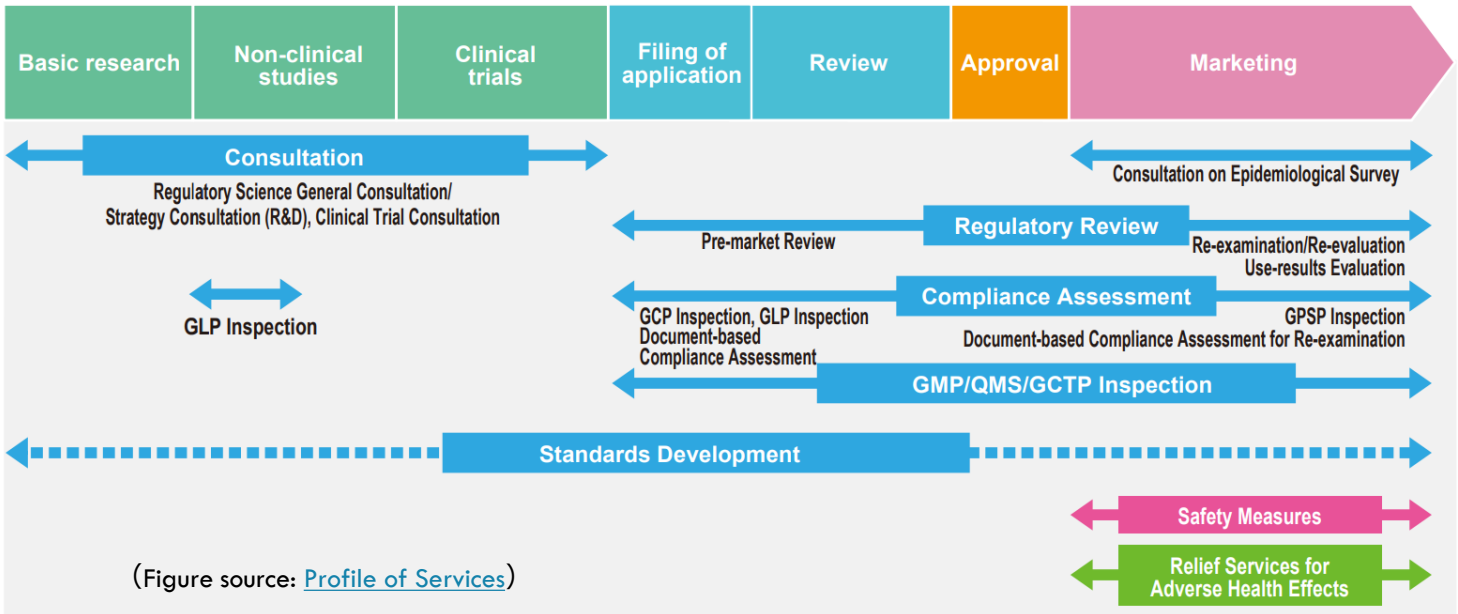
Furthermore, aside from this Annual Report, PMDA regularly publishes annual GMP-related inspection statistics on the number of GMP on-site inspections and other data as part of its annual GMP-related performance reports.

1 PMDA OMQD overview

1-1 About us

1-1-1 About PMDA

One of the key objectives of PMDA is to contribute to the improvement of public health by providing prompt relief services to patients suffering from adverse drug reactions and infections acquired through biological products (Relief for Adverse Health Effects), providing guidance and reviews on the quality, efficacy, and safety of drugs, medical devices, and gene, cellular and tissue-based products through a consistent system from pre-clinical research to approval (Approval Review), and collecting, analyzing, and disseminating post-marketing safety information (Safety Measures). PMDA performs various functions throughout the lifecycle of medical products, from early development to post-marketing. The main categories are shown in the diagram below.



(Figure source: Profile of Services)

1-1-2 Mission of OMQD

The mission of OMQD is to conduct its operations with timely decision-making under a high level of transparency with the goal of ensuring the distribution of high-quality pharmaceuticals, quasi-drugs and gene, cellular and tissue-based products based on its absolute mission to protect citizens' lives and health. To achieve this mission, OMQD has established a Quality Management System to ensure appropriate and effective GMP/GCTP inspections, including the formulation of quality policies. In addition, the Head of inspectorate (Chief Executive of PMDA) conducts management reviews to appropriately maintain the Quality Management System, address arising issues, and to assess the validity of the quality policy.

Quality policy of Office of Manufacturing Quality for Drugs

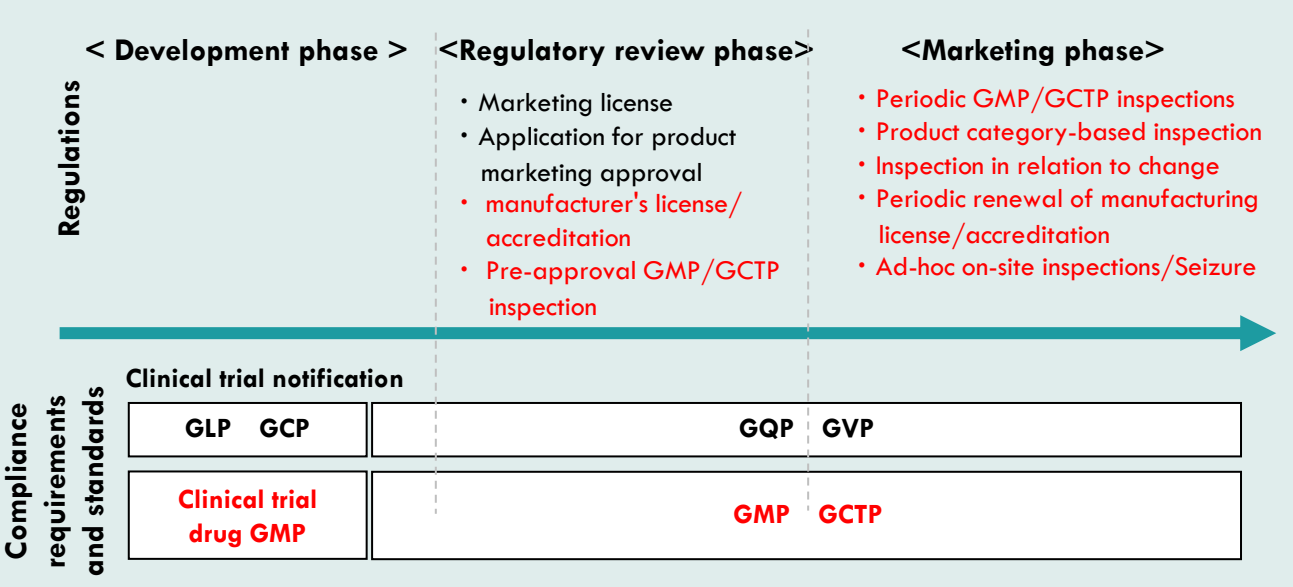
Head of inspectorate (Chief Executive of PMDA) shall ensure the following matters within its quality policy;

- **Quality policy of the PMDA Office of Manufacturing Quality for Drugs, based on its absolute mission to protect citizens' lives and health, aiming for distribution of high-quality pharmaceuticals, quasi-drugs and gene, cellular and tissue-based products shall make its operations be conducted with timely decision making and highly transparency.**
- **Such quality policy should be communicated to and understood by all the GMP inspectors in the PMDA Office of Manufacturing Quality for Drugs.**
- **Sustained effectiveness of such quality policy should be reviewed regularly.**

1-1-3 Scope of responsibilities of OMQD

As part of PMDA's review-related services, OMQD conducts GMP inspections for drugs and GCTP inspections for gene, cellular and tissue-based products. These inspections are intended to assess whether manufacturing sites for such products are operating under appropriate quality management systems and may be conducted either as on-site inspections or as desktop inspections.

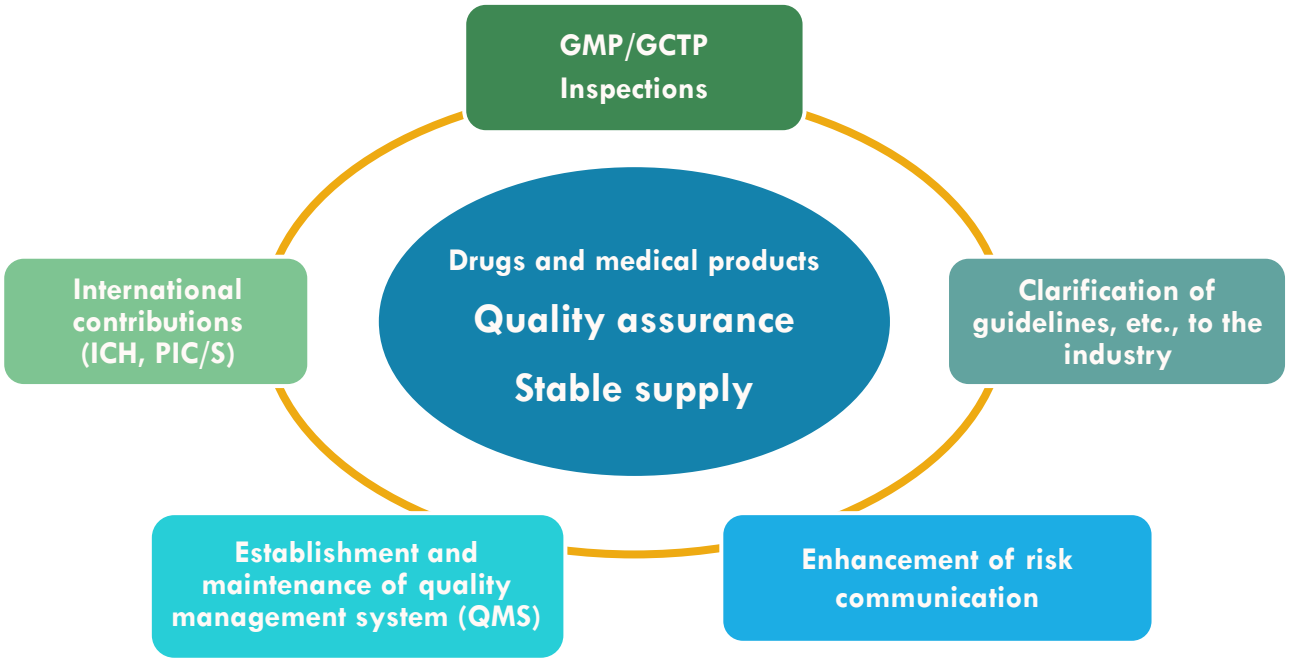
The matters related to OMQD's activities are indicated in red in the diagram illustrating the drug lifecycle below. Details of each matter are shown in 1-2 Type of inspection.



In addition to the above, OMQD are also working on activities for the purpose of global harmonization of pharmaceutical regulations through the provision of information for the pharmaceutical industry, preparation of guidelines, establishment and maintenance of the quality management system in cooperation with prefectural governments, and participation in ICH*2 and PIC/S*3, etc. Details are shown in Chapter3 : Risk communication activities and Chapter 4: International Activities.

*2 International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use https://www.ich.org/

*3 Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme https://picscheme.org/



1-1-4 GMP inspectorate in Japan and scope of inspection

Drugs

Overseas manufacturing site: PMDA
Japanese manufacturing site: PMDA (limited to the following) and prefectural governments

A) GMP inspection of a 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 designated by the Minister of Health, Labour and Welfare as requiring special attention among drugs manufactured using human or other living organisms as raw materials such as blood transfusion preparations
- ✓ Radiopharmaceuticals including contrast media

C) Periodic GMP inspections performed every 5 years specified by a cabinet order, which is not less 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 regular inspections 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).

Gene, cellular and tissue-based products

All manufacturing sites: PMDA

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

Note: Changes resulting from legislative amendments

In accordance with the Act for Partial Revision of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (Law No. 37 of 2025)*4 , the frequency of periodic inspections is currently under review.

Furthermore, the policy was presented in the Summary on the revision of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices and related systems (published on January 10, 2025)*5. Under this policy, PMDA will conduct GMP inspections at the time of marketing approval applications for generic drugs that contain an active ingredient approved for the first time and that are related to the drug product manufacturing process.

*4 The Act for Partial Revision of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (Law No. 37 of 2025)
https://www.mhlw.go.jp/stf/newpage_58083.html#h2_free2

*5 The Summary on the revision of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices and related systems, issued by the Health and Science Council on January 10, 2025. https://www.mhlw.go.jp/content/11120000/001371285.pdf

1-1-5 Organization structure of OMQD

OMQD consists of the following 5 divisions (as of April 1, 2025).

- Planning and Management Division : Support for inspection operations, etc.
- Division of Inspection for Drugs I : Mainly in charge of inspection of biopharmaceuticals and gene, cellular and tissue-based products
- Division of Inspection for Drugs II : Mainly in charge of inspection of chemical products and products other than handled by Division I
- Division of GMP Inspection training : Support for inspections conducted by prefectural governments and overseas GMP authorities
- Division of National Lot Release : National Lot Release operations (Summary Lot Protocol (SLP) review, etc.)

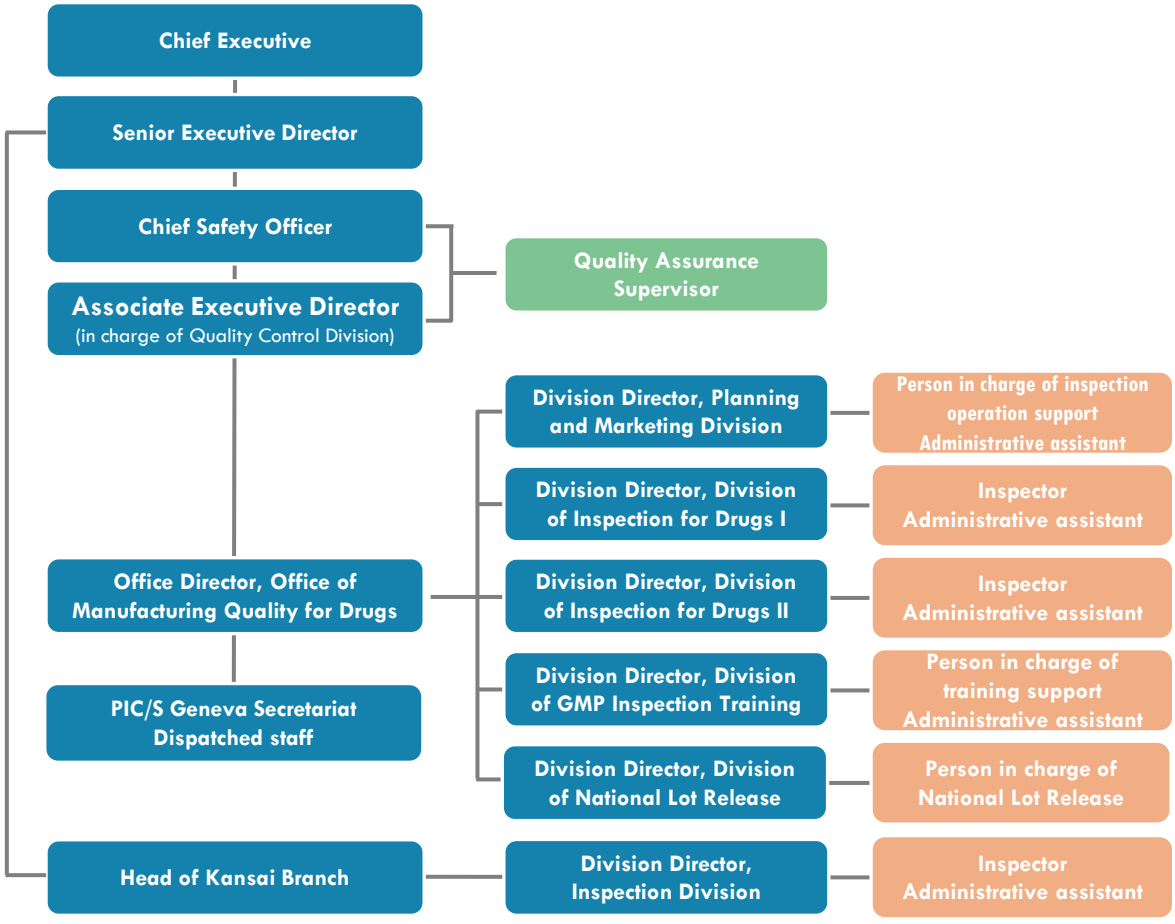
As a result of the review of the National Lot Release implementation methods by the Pharmaceuticals and Medical Devices System Subcommittee, drugs deemed eligible for lot release primarily based on document-based SLP review were transferred from the National Institute of Infectious Diseases (now the Japan Institute for Health Security) to PMDA, thereby establishing a system under which PMDA conducts SLP reviews. Consequently, on April 1, 2025, the Division of National Lot Release was newly established under the OMQD. Information regarding the application procedures for lot release is provided on the PMDA website (National Lot Release operations).

In addition to the above, a Division of Inspection has been established at the Kansai Branch, which is responsible for GMP inspections in Japan and overseas in cooperation with OMQD.

Additionally, to facilitate cooperation with the review divisions of PMDA, the Inspection Director is allocated under Office Director, and to report to the Chief Safety Officer/Associate Executive Director (in charge of the Quality Control Division) who is in charge of safety measures of drugs and quality control of drugs and medical devices, the quality assurance supervisor (independent of the Inspection Division, responsible for monitoring the progress of inspection operations and ensuring compliance) is allocated under such personnel to perform operations.

Furthermore, since FY 2024, a staff member have been dispatched to the PIC/S Geneva Secretariat. For details, please refer 4-4-1 PIC/S Activities (cont'd).

The organizational structure prior to March 31, 2025 is available in the GMP/GCTP Annual Report 2023.



1-1-6 Conflict of interests

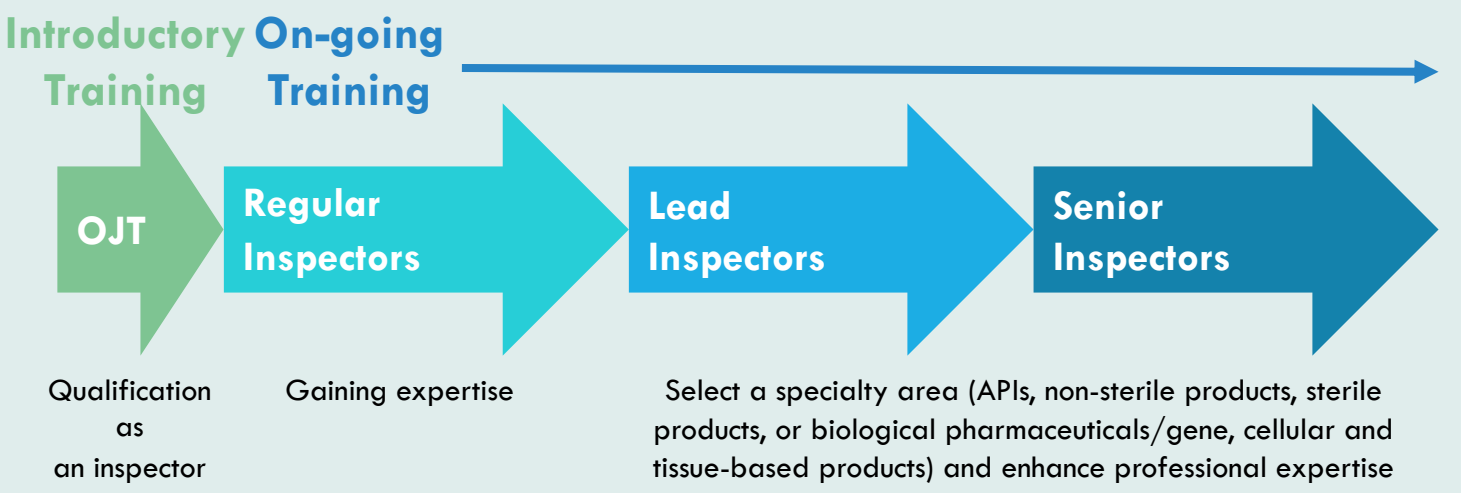
Staff from the private sector are subject to the rules for Conflict of Interests stipulated in the Rules of Employment for Staffs of the Pharmaceuticals and Medical Devices Agency (Regulations No. 2, 2004) and the Detailed Rules on Restriction of Duties for Staffs of the Pharmaceuticals and Medical Devices Agency (Detailed Rules No. 1, 2005).

The rules for Conflict of Interests stipulate that, regardless of whether or not the duties at the PMDA are closely related to their former private-sector duties, they must not be engaged in the duties related to drugs, etc., of their former private sector for 5 years after being employed by PMDA. In OMQD, they shall not be engaged in the inspections of the manufacturing site with interests including their former private sector.

The operating status of the rules for Conflict of Interests in OMQD is checked by the Quality Assurance Supervisor periodically and also by an internal audit (implemented twice a year (half-yearly)) conducted by the PMDA Audit Office.

1-1-7 Training for inspectors

An overview of the training provided to OMQD inspectors is presented below.



Introductory Training

- Gain experience in at least 5 GMP inspections as part of on-the-job training (OJT)
- Theoretical training on the overview of inspection operations, pharmaceutical-related laws and regulations, and necessary procedures to conduct inspections. (Examples include: The PMD Act, Marketing authorization documents and the Japanese Pharmacopoeia, Global trends related to GMP inspections and PIC/S guidelines, Key points and precautions during on-site inspections, Change of clothes procedures, Overall structure, facilities, and support systems, Communication skills required for inspectors, Fundamental attitudes expected of inspectors, The role of GMP in pharmaceuticals, Detailed topics: Quality systems, Quality control, Validation, APIs, Tablets, Sterile pharmaceuticals, biological pharmaceuticals, Cleaning validation, GCTP inspections, fermentation-based APIs, Clinical trial GMP inspections, radiopharmaceuticals, crude drugs, etc.)

On-going Training

- Routine Training : On-going training on inspection operations to acquire or share appropriate interpretations of regulations, the latest scientific knowledge, international regulatory trends, key case studies, and regulatory guidance. The aim is to maintain and enhance inspection methodologies and capabilities. (Held 4 times a month, with sessions lasting 30 to 90 minutes.)
- Specialized Training : Periodic intensive training to gain technical expertise and GMP inspection skills, including case studies, group work, and/or role playing. Additionally, participation is open to prefectural officials and staff from other ministries. (Held 3 times a year, each lasting 3 consecutive days)

Other Training

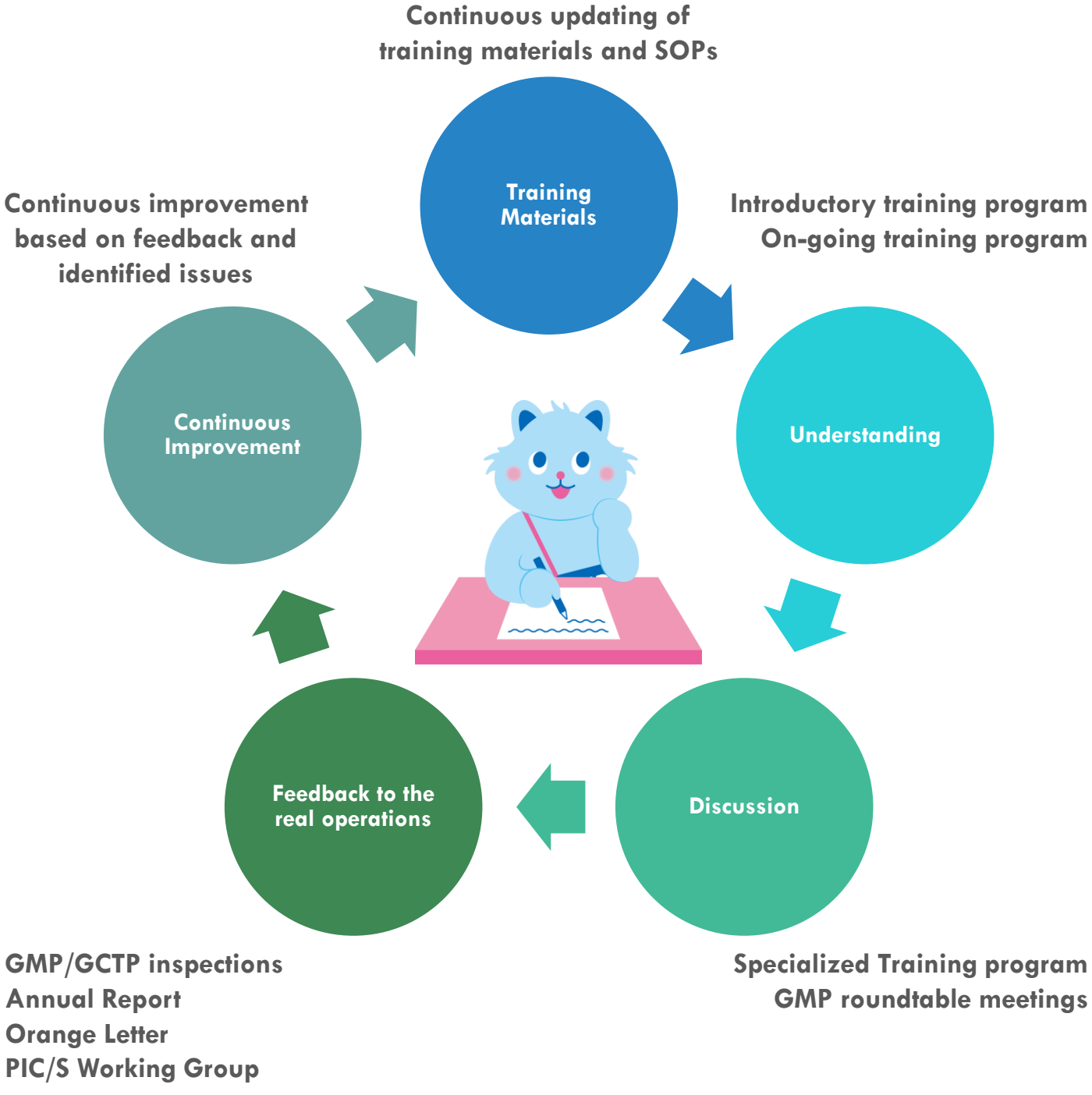
- Temporary training conducted by invited external instructors
- On-site training at manufacturing sites and training facilities, etc.

1-1-7 Training for inspectors (Continued)

The training materials used for introductory and on-going training are developed internally by OMQD and are used to train PMDA inspectors, with the aim of enhancing their understanding of GMP/GCTP. Based on this understanding, inspectors actively participate in discussions with external stakeholders during specialized training sessions and GMP roundtable meetings, in preparation for GMP/GCTP inspections. In addition to this Annual Report, we are also working to publish other materials useful for training purposes, such as the Orange Letters and documents from the PIC/S Working Group.

During GMP/GCTP inspections, we sometimes receive feedback from industry stakeholders, including requests and complaints. Additionally, issues are identified through risk communication activities and the annual management review conducted by PMDA.

Based on such feedback and identified issues, we continuously update the training materials and work to improve our training system. Furthermore, OMQD's standard operating procedures (SOPs) are also regularly reviewed (at least once every five years).



1-2 Type of inspection

1-2-1 GMP / GCTP inspections

The GMP/GCTP inspection is classified into application-based inspections and Inspections not based on applications (Ad-hoc on-site inspections), etc.

GMP / GCTP inspections

Application-based inspections are conducted to confirm whether the actual status of manufacturing and quality control at the facility comply with the Ministerial Order on GMP / GCTP*6 or not, based on the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (hereinafter referred to as the "PMD Act")*7, which are classified further into (1) pre-marketing approval inspection, (2) post-marketing approval inspection, (3) product category-based inspection, (4) inspection in relation to change management protocol, and (5) inspection on manufacturing of a product for export.

*6 The Ministerial Order on GCTP (Order of the Ministry of Health, Labour and Welfare (MHLW) No. 93 of August 6, 2014)
https://www.mhlw.go.jp/web/t_doc?dataId=81ab4197&dataType=0&pageNo=1

*7 The PMD Act (Law No. 145 of 1960) https://laws.e-gov.go.jp/law/335AC0000000145

(1) Pre-marketing approval inspection;

(a) Inspection that is conducted upon the application for product marketing approval (as provided in Article 14, paragraph (7) of the PMD Act for GMP, Article 23-25, paragraph (6) for GCTP)

(b) Inspection that is conducted upon the application for approval for partial changes of any matter prescribed in the existing marketing approval (as provided in Article 14, paragraph (7) as applied mutatis mutandis in Article 14, paragraph (15) of the PMD Act for GMP, Article 23-25, paragraph (6) as applied mutatis mutandis in Article 23-25, paragraph (11) for GCTP)

(c) Inspection that is conducted upon the application for exceptional marketing approval for a product manufactured in a foreign country (as provided in Article 14, paragraph (7) as applied mutatis mutandis in Article 19-2, paragraph (5) of the PMD Act for GMP, Article 23-25 paragraph (6) as applied mutatis mutandis in Article 23-37, paragraph (5) for GCTP)

(d) Inspection that is conducted upon the application for approval for partial changes of any matter prescribed in the existing exceptional marketing approval for a product manufactured in a foreign country (as provided in Article 14, paragraph (7) as applied mutatis mutandis in Article 14, paragraph (15) as applied mutatis mutandis in Article 19-2, paragraph (5) of the PMD Act for GMP, Article 23-25, paragraph (6) as applied mutatis mutandis in Article 14, paragraph (15) as applied mutatis mutandis in Article 23-37, paragraph (5) for GCTP)

(2) Post-marketing approval inspection;

(a) Periodic inspection concerning an existing marketing approval (as provided in Article 14, paragraph (7) of the PMD Act for GMP, Article 23-25, paragraph (6) for GCTP)

(b) Ad-hoc inspection in cases when deemed necessary, concerning an existing marketing approval (as provided in Article 14, paragraph (9) of the PMD Act for GMP, Article 23-25, paragraph (8) for GCTP)

(c) Periodic inspection concerning an existing exceptional marketing approval for a product manufactured in a foreign country (as provided in Article 14, paragraph (7) as applied mutatis mutandis in Article 19-2, paragraph (5) of the PMD Act for GMP, Article 23-25, paragraph (6) as applied mutatis mutandis in Article 23-37, paragraph (5) for GCTP)

(d) Ad-hoc inspection in cases when deemed necessary, concerning an existing exceptional marketing approval for a product manufactured in a foreign country (as provided in Article 14, paragraph (9) as applied mutatis mutandis in Article 19-2, paragraph (5) of the PMD Act for GMP, Article 23-25, paragraph (8) as applied mutatis mutandis in Article 23-37, paragraph (5) for GCTP)

1-2-1 GMP / GCTP inspections (continued)

(3) Product category-based inspection (as provided in Article 14-2, paragraph (2) of the PMD Act for GMP, Article 14-2, paragraph (2) as applied mutatis mutandis in Article 23-25-2, paragraph (1) for GCTP)

(4) Inspection in relation to change management protocol (as provided in Article 14-7-2, paragraph (3) of the PMD Act for GMP, Article 23-32-2, paragraph (3) for GCTP)

(5) Inspection on manufacturing of products for export (as provided in Article 80, paragraph (1) of the PMD Act for GMP, Article 80, paragraph (3) for GCTP)

(6) Inspection for emergency approval(as provided in Article 14-2-2, paragraph (2) of the PMD Act for GMP, Article 23-26-2, paragraph (2) for GCTP)

(7) Inspection for special approval(as provided in Article 14-2-2, paragraph (2) as applied mutatis mutandis in Article 14-3, paragraph (2) of the PMD Act for GMP, Article 23-26-2, paragraph (2) as applied mutatis mutandis in Article 23-28, paragraph (2) for GCTP)

On-site inspections not based on applications (Ad-hoc on-site inspections)

On-site inspections not based on applications (Ad-hoc on-site inspections), etc., Ad-are classified into (1) surveillance inspections based on the risk analysis, and (2) for case inspections depending on the purpose.

(1) Surveillance inspections which are based on the risk analysis Periodic inspection to confirm compliance with the Ministerial Order on GMP

(2) For case inspections such as those addressing a violation of the Ministerial Order on GMP, etc., mainly for the following purposes

(a) Confirmation of the details of corrective/preventive actions (other than those to be performed as an inspection)

(b) Examinations into compliance status with the Ministerial Order on GMP, at the manufacturing sites concerned with those manufactured products which have been recalled, rejected at National Lot Release or complained, etc., and

(c) Others

Product category-based inspection

Product category-based inspection is conducted based on an application by the manufacturing sites. The manufacturing process is classified into 17 types, such as the manufacturing process of specified biological products, manufacturing process of radiopharmaceuticals, and manufacturing process of sterile drug substances.

If the inspection authorities judge that the site is compliant with GMP based on the results of the product category-based inspection, a certificate will be issued to the manufacturing site. The validity period for the certificate is 3 years, and it is possible to omit the second and subsequent periodic inspections for products in the manufacturing category shown in the certificate within the period.

Inspection in relation to change management protocol

In accordance with the principles shown in the ICH Guideline, "ICH Q12 Pharmaceutical Product Lifecycle Management", a system for changing approved items is operated using a protocol for partial change of approved items (change management protocol).

If the marketing authorization holder and PMDA agree in advance about the contents of changes in manufacturing methods, etc., evaluation methods and acceptance criteria for the contents of changes, proposed changes in approved items related to quality, necessity of compliance evaluations of drugs, etc. (confirmation of compliance with the standards specified in the Ministerial Order on GMP), and the expected results are obtained according to the agreed evaluation methods, it is possible to promptly change approved items related to quality by notification.

1-2-2 Manufacturer license / accreditation inspections

When engaging in the commercial manufacture of drugs, quasi-drugs, or gene, cellular and tissue-based products, domestic manufacturing sites are required to obtain a manufacturing license, while overseas manufacturing sites must obtain manufacturing accreditation.

In both cases, an inspection is conducted to determine whether the facility is equipped with the necessary buildings and facilities to obtain the license or accreditation, in accordance with Regulations of Buildings and Facilities of Pharmacies, etc.*8

*8 Regulations of Buildings and Facilities of Pharmacies, etc. (Ministerial Ordinance No. 2 of 1961)
https://www.pmda.go.jp/files/000153560.pdf

1-3 Deficiencies in GMP/GCTP inspection

1-3-1 Process for issuance of the notice of deficiencies

In order to deepen the understanding of the manufacturing sites, subject to inspection in the GMP/GCTP inspections (on-site inspection), OMQD provides comments such as inspection results and summarizes the entire inspection. In addition to this, a violation of the GMP/GCTP Ministerial Ordinance and other deficiencies are communicated during the inspection, and opinions on these matters are exchanged between the inspector and the responsible person of the inspected manufacturing sites.

After completion of the inspection, OMQD's inspectors review the contents of the deficiency again, classify into 3 level (Critical, Major, and Other) in accordance with the criteria for concluding GMP/GCTP conformity, prepare the notice of deficiencies, and the deficiency confirmed (hereinafter referred to as "deficiency") will be issued to the responsible person of the manufacturer, etc., subject to inspection.

1-3-2 Classification of deficiency identified

Deficiencies are classified into 1) critical, 2) major, and 3) other depending on their contents, and the criteria for each classification are specified as follows in the GMP Inspection Guide or in the GCTP Inspection Guide*9.

- **Critical**

  Cases where an identified deficiency that does not comply with any provisions in the GMP/GCTP Ministerial Ordinance fall into any of the following:

  ✓ Any drugs hazardous to patients have been manufactured, or any significant risks which may cause such products has been confirmed, or

  ✓ With regard to products or records, any falsification or false statement or dishonest alteration by the manufacturer has been confirmed.

- **Major**

  Cases where an identified deficiency that does not comply with any provisions in the GMP/GCTP Ministerial Ordinance does not fall into "critical deficiencies" above.

- **Other**

  Cases where an identified deficiency that is not significant to be non-compliance with provisions in the GMP/GCTP Ministerial Ordinance, however, that any rectification is needed for suitable manufacturing control or quality control.

*9 Notification on the Enactment of the GCTP Inspection Guide (PSEHB/CND Notification No. 0730-3 dated July 30, 2021, issued by the Director of Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, the MHLW)
https://www.mhlw.go.jp/web/t_doc?dataId=00tc6091&dataType=1&pageNo=1

1-3-3 Confirmation of the status of improvement

If any deficiency is issued to the manufacturing sites, subject to inspection by the notice for deficiencies identified during a GMP/GCTP inspection, it is necessary to submit a detailed report on corrective/preventive action outcome or a concrete report on corrective/preventive action to OMQD to report the status of improvement within 15 business days after the issuance date of "Critical deficiencies" identified during a GMP/GCTP inspection or within 30 business days after the issuance date of "Major deficiencies".

(1) When only "other deficiencies" are identified

After confirming the content of the report on corrective/preventive action outcome or a report on corrective/preventive action submitted, if any deficiency is properly improved or if it is presumed to be improved promptly, OMQD will notify the manufacturing sites of the conformity status as "compliance."

If the report on corrective/preventive action has been submitted, the report on corrective/preventive action outcome is required to be submitted to confirm that the required corrective actions have been completed, even if the "compliance" inspection results have been notified. In this case, their status of improvement should be examined in the next regular inspection.

(2) When "major deficiencies“ are identified

When the contents of the report on corrective/preventive action outcome or a report on corrective/preventive action are determined to be appropriate, OMQD will notify the inspected manufacturing sites of the conformity status as "compliance."

If the report on corrective/preventive action has been submitted, the report on corrective/preventive action outcome is required to be submitted to confirm that the required corrective actions have been completed, even if the "compliance" inspection results have been notified. In this case, their status of improvement should be examined in the next regular inspection.

If the inspectorate agency cannot judge the corrective/preventive actions to be appropriate, the conformity status is concluded as "non-compliance" in principle, and the results will be notified to the manufacturing sites subject to inspection.

(3) When "critical deficiencies“ are identified

When the appropriate corrective/preventive actions are determined to be completed within 15 business days, OMQD will notify the inspected manufacturer of the conformity status as "compliance."

When corrective/preventive actions to be justified by the inspectorate agency cannot be completed within 15 business days, the conformity status is concluded as "non-compliance" in principle, and the results will be notified to the manufacturing sites subject to inspection.

In addition, the contents of the "critical deficiencies" will be shared with the MHLW, and the presence or absence of an impact on the quality of the product distributed to the market and the necessity of the contents of guidance to the manufacturing sites, will be promptly examined.

1-4 Qualifications for inspectors

1-4-1 GMP/GCTP inspection

OMQD specifies the qualification requirements for inspectors based on the GMP Inspection Guide and GCTP Inspection Guide. As shown in <1-1-7 Training for Inspectors>, there are three levels of inspector qualification: Regular inspectors, lead inspectors, and senior inspectors. The qualification requirements for each inspector are specified in 4 fields of drug substances, a) drug substances, b) non-sterile products, c) sterile products, and d) biological drugs/gene, cellular and tissue-based products.

Regular inspectors are certified by the qualified persons of OMQD based on the level of understanding of the education and training after receiving lectures on related laws and regulations, basic inspection skills, and OJT education (accompanying on-site inspections).

Lead inspectors are certified by the qualified personnel of OMQDs based on their expertise and experience in each field among personnel qualified as regular inspectors.

Senior inspectors are certified by the qualified personnel of OMQD after their ability as an educator to inspectors is assessed among personnel qualified as lead inspectors.

In principle, an inspection team is organized by two or more inspectors from the viewpoint of mutually supplementing the expertise and experience among the inspectors and securing the safety of the inspectors. A responsible inspector for the GMP inspection is designated, who organizes the overall GMP inspection, and comments on the observations, conveys the deficiency report, and documents the inspection report. In addition, the inspection team consists of at least one person who meets the qualification requirements for a lead inspector or a senior inspector for each inspection.

1-4-2 Inspection not based on application (Ad-hoc on-site inspection)

Those who conduct inspections based on Article 69 of the PMD Act (on-site inspections, etc., not based on an application for inspections) must have the qualifications specified by Cabinet Order, and the Enforcement Ordinance*[10] of Article 69-2 paragraph (4) the PMD Act requires that they fall under any of the following:

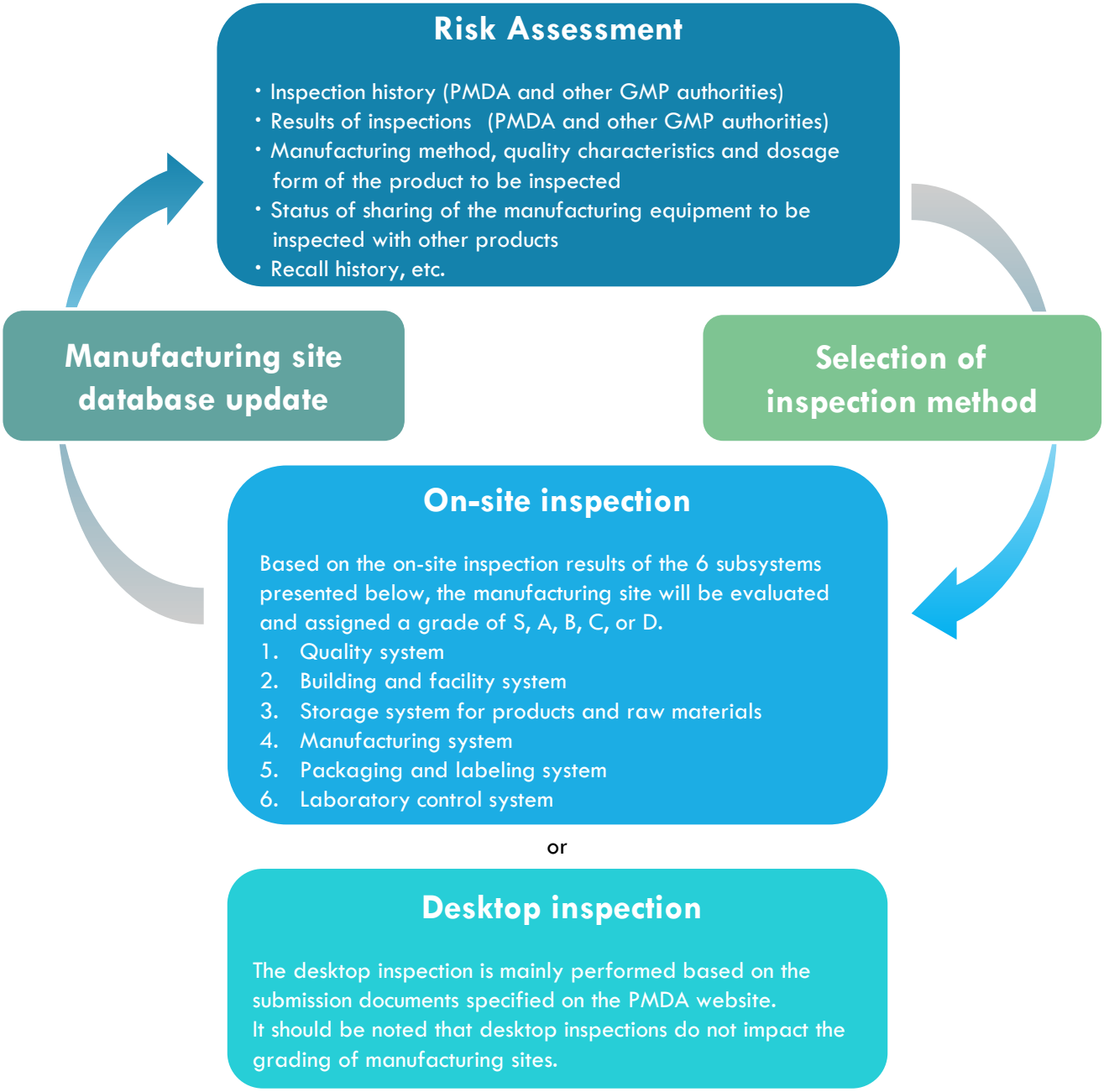
- Pharmacist, physician, dentist or veterinarian
- A person who has completed a specialized course in pharmaceutical science, medical science, medical dentistry, veterinary medicine, science, or engineering at a university or high vocational school and has sufficient knowledge and experience in pharmaceutical inspection
- A person who has been engaged in administration related to pharmaceutical affairs for more than 1 year and has sufficient knowledge and experience in pharmaceutical inspection

*10 Enforcement Ordinance of the PMD Act (Cabinet Order No. 11 of 1961)
https://laws.e-gov.go.jp/law/336CO0000000011

1-5 Risk-based selection of inspection method

OMQD conducts a risk evaluation of the applied manufacturing site to be inspected and selects the inspection method (on-site inspection or desk-top inspection) based on the results.

Inspection methods are selected using a risk-based approach in accordance with the flow outlined below.



1-6 GMP training support

OMQD established the Division of GMP Inspection Training in FY 2022 and operate training support programs for prefectural officials to enhance the training support for prefectural officials who perform GMP inspections. PMDA is making proactive efforts to improve the quality of prefectural GMP inspectors and enhance the inspections.

Our current training programs are as follows:

- ✓ Accept observers from prefectural governments in PMDA's GMP inspection
- ✓ Conduct PMDA-prefectural governments joint GMP inspections without prior notice to generic drug manufacturers under the jurisdiction of the prefectural governments
- ✓ Dispatch PMDA inspectors to GMP inspections conducted by prefectural governments
- ✓ Provide GMP training materials with prefectural governments
- ✓ Dispatch PMDA instructors to mock inspections sponsored by prefectural governments

In FY 2024, we started the following 2 new initiatives:

- **Observer participation of prefectural officials in PMDA planning and decision-making meetings**

  To provide prefectural officials with opportunities to share PMDA inspectors' approach to developing inspection plans and issuing deficiencies.

- **Information collection, accumulation, analysis, and sharing using inspection reports**[*11]

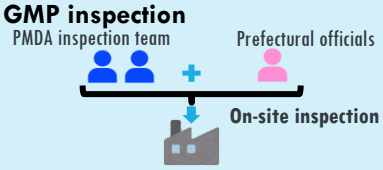
  To maintain and improve GMP inspectors' inspection capabilities, PMDA will collect, accumulate and analyze information of inspection reports prepared both by prefectural governments and by PMDA.

*11 Regarding the Establishment of Operational Procedures for Information Collection, Accumulation, Analysis, and Sharing Using GMP Inspection Report Information (the MHLW, Pharmaceutical and Food Safety Bureau, Surveillance and Narcotics Division, Administrative Notice dated March 29, 2024)
https://www.mhlw.go.jp/web/t_doc?dataId=00tc8409&dataType=1&pageNo=1

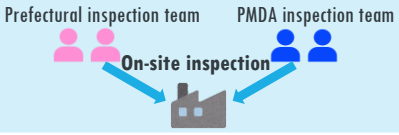
GMP TRAINING SUPPORT FOR PREFECTURAL INSPECTORS
(INITIATIVES UNDERLINED BEGAN IN FY 2024)

1 Support for on-site inspection

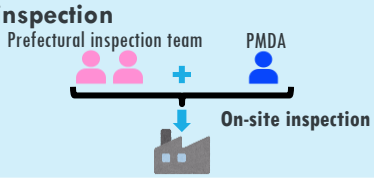
Accept observers in PMDA's GMP inspection



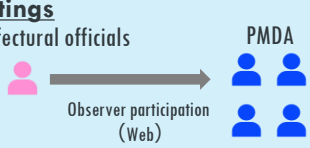
Conduct PMDA-prefectural governments joint GMP inspection



Dispatch of PMDA inspector to prefectural government GMP inspection



Observer participation in planning and decision-making meetings



2 Provision of PMDA training materials, etc.

Introductory GMP training
PMDA provides GMP introductory training which are considered useful for prefectural GMP inspectors.

Lectures on specialized fields of GMP
To make Lectures on specialized fields of GMP by PMDA widely available to prefectural inspectors.

GMP training materials
To provide training slides and videos to prefectural inspectors.

3 Seminars, etc.

GMP Round Table Meeting
Refer to 3-1 GMP roundtable meeting

4 Dispatch of speakers / Consultations

Dispatch of GMP experts to training sessions and mock inspections sponsored by prefectural governments
PMDA GMP experts give basic and advanced lectures, etc.

Consultation on questions regarding GMP inspection
To resolve questions recognized regarding prefectural GMP inspections

Sharing PMDA GMP inspection reports
To strengthen collaboration system including information sharing between domestic inspection authorities

5 Information collection, accumulation, analysis, and sharing using inspection reports

To maintain and improve the inspection capabilities of inspectors, PMDA conducts analysis of the Prefectural and PMDA inspection reports.

1-7 Consultation services

OMQD is in charge of the following consultation services.

(1) Simple consultation

The simple consultation is conducted to confirm matters related to GMP/GCTP inspections, where PMDA is the investigative authority. For more details, please refer to <2-5-1 Simple consultation>.

(2) Consultation on SAKIGAKE(Japan's fast-track designation system for innovative drugs and medical devices) overall evaluation

Consultation on SAKIGAKE overall evaluation is conducted for SAKIGAKE-designated products to promote the development of innovative drugs/medical devices/gene, cellular and tissue-based products.

(3) Consultation on innovative manufacturing technology for drugs

Consultation on innovative manufacturing technology for drugs is conducted to formulate development strategies in anticipation of future commercial production, establishing product control strategies and validation methods when new innovative manufacturing technologies and manufacturing equipment are introduced for future commercial production of drugs.

This consultation is conducted on a trial basis from FY 2020 to date (September 2024), and two consultations concerning "continuous production" were received per year (1 consultation in the first half of the year, 1 consultation in the second half of the year). Consultation on both new drugs and generic drugs can be provided, with OMQD in charge of the consultation.

In this consultation, PMDA's GMP inspectors and reviewers visit the manufacturing sites, and discuss while checking the actual facilities. If the GMP inspectorate agency of the manufacturing site is a prefectural government, inspectors of the prefectural government in charge may accompany the inspection.

(4) Consultation on conformity assessments of reliability criteria

Consultation on conformity assessments of reliability criteria is conducted to provide guidance and advice on the compliance with the reliability criteria for data scheduled to be attached to approval applications for drugs or gene, cellular and tissue-based products.

2 Achievements in FY 2024

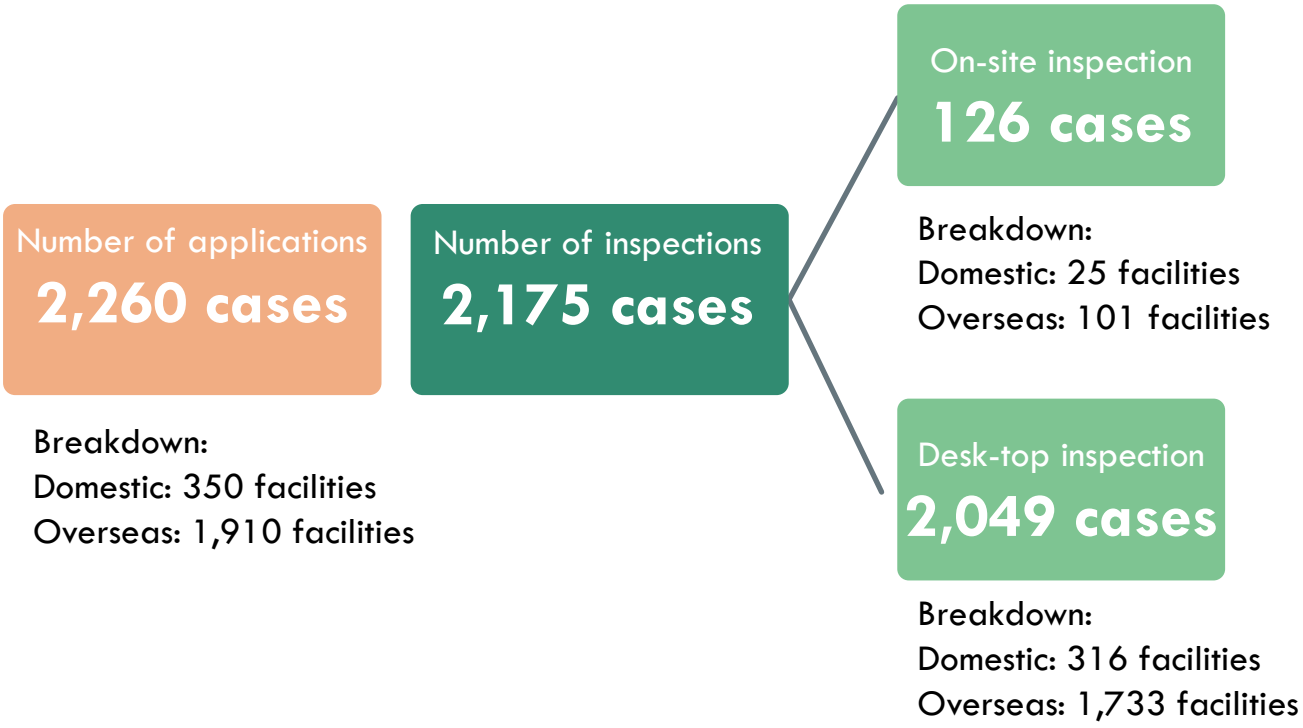
2-1 Overview

Main achievements of Office of Manufacturing Quality for Drugs in FY 2024 are as follows:

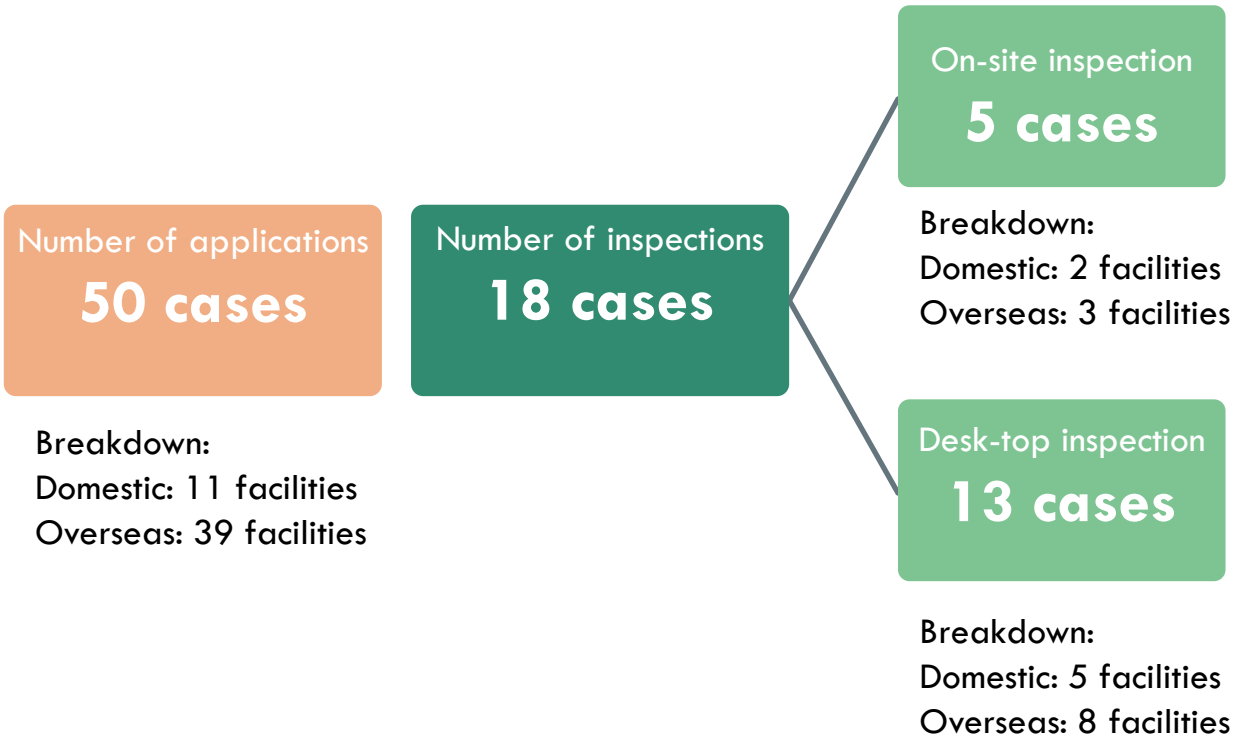
(*An information bulletin issued by OMQD to share important findings and notices regarding GMP inspections)

2-2 Number of inspections, etc.

2-2-1 GMP inspection (manufacturing sites for drugs)



2-2-2 GCTP inspection (manufacturing sites for gene, cellular and tissue-based products)



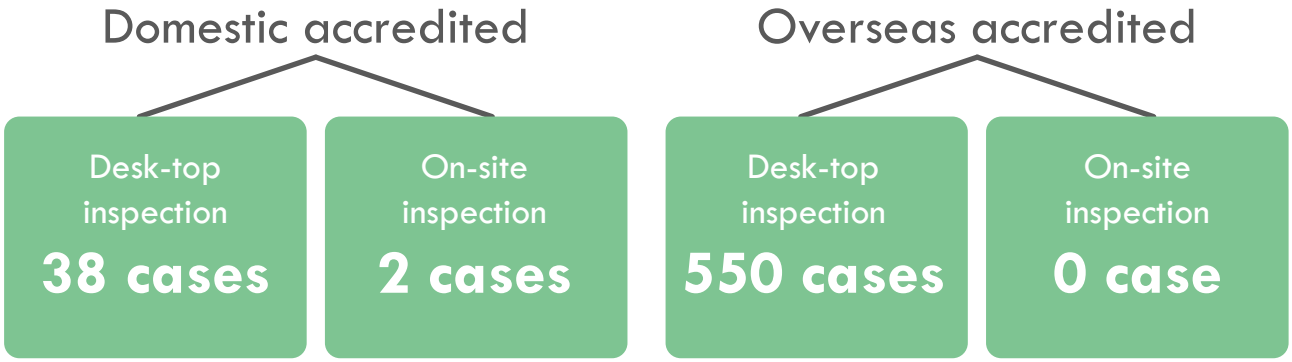
2-2-3 Number of inspections not based on applications (Ad-hoc on-site inspections) and other inspections conducted (on-site)

Ad-hoc on-site inspection (Domestic)	Ad-hoc on-site inspection (Overseas)	Product category-based inspection
45 cases	1 case	0 cases

(already included in the total number of GMP Inspection)

Inspection in relation to change management protocol	GMP inspection of investigational drugs
1 case	2 cases

2-2-4 Facility inspection



(In principle, inspections are desktop-based)

The results of inspection in FY 2024 and the calculation method of each value are as follows.

- Number of applications : Number of applications accepted in FY 2024
- Number of inspections (on-site inspection) : Number of on-site inspections conducted in FY 2024
- Number of inspections (desk-top inspection (document-based inspection))
  : Number of inspections completed in FY 2024
  If a separate inspection was conducted at the same facility, each inspection was counted.

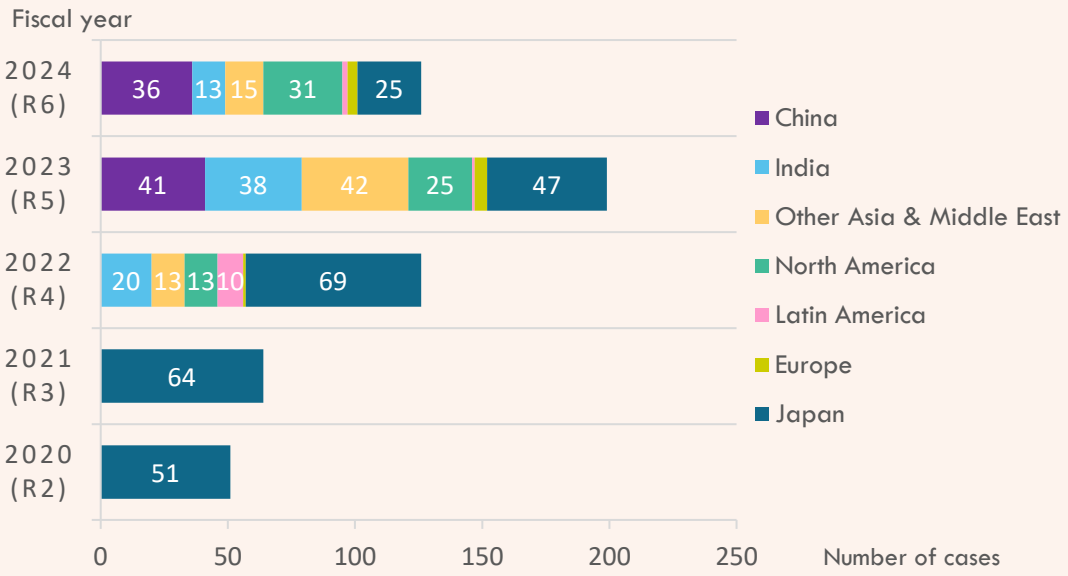
Even if the application was accepted within the fiscal year, it is not possible to complete all inspections within the fiscal year in relation to the period required for inspection. Therefore, the number of applications does not match the number of inspections.

2-2-5 Countries/Regions of On-site Inspection

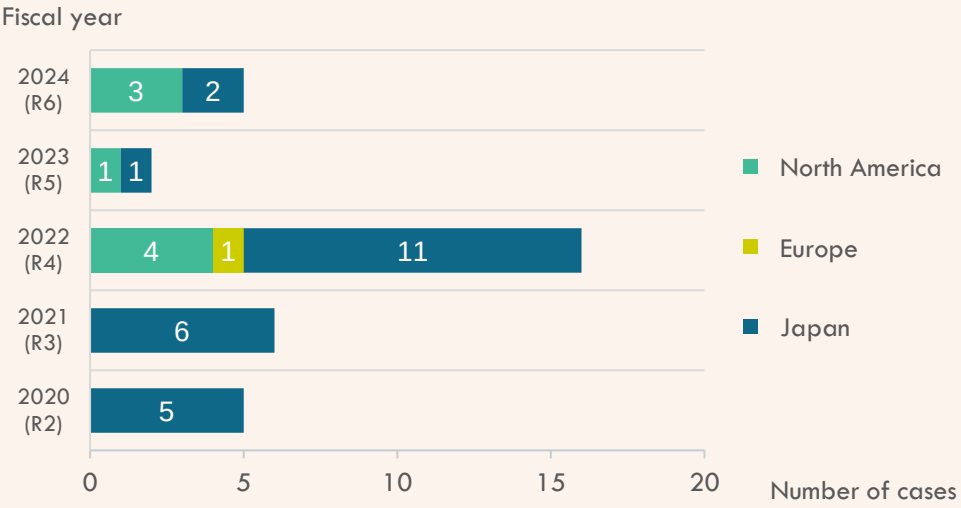
The number of GMP inspections conducted by OMQD by country/region where the sites are located are as follows. (Past 5 years)

The number of inspections is limited to GMP/GCTP inspections based on applications for inspection and does not include the number of other types of inspection, including Ad-hoc on-site inspections (30 to 40 cases as GMP, a few cases as GCTP per year), etc.

GMP inspections :



GCTP inspections :



Due to the new coronavirus pandemic, travel restrictions were imposed in various countries. Consequently, OMQD conducted inspections only to Japanese manufacturing sites in FY 2020 and FY 2021.

In FY 2023, on-site inspections were resumed in China. The number of GMP inspections in China was 41, which are equivalent to the level in FY 2019 before the COVID-19 pandemic. In addition to China, 38 on-site inspections were conducted in India, 42 in Asia/Middle East excluding China and India, 25 in North America, and 5 in Europe (sites not covered by MRA). The number of on-site inspections in all countries/regions increased from FY 2022.

The number of on-site inspections in FY 2024 decreased compared to FY 2023. This is considered to reflect the fact that many of the overseas inspections that could not be conducted temporarily due to travel restrictions following the COVID-19 pandemic from FY 2020 were carried out in FY 2023, resulting in a peak in that year.

2-3 Trend of identified deficiencies

2-3-1 Ranking of identified deficiencies

Deficiencies identified by PMDA are categorized based on their profiles and aggregated for each fiscal year. The rankings of frequency of issuance of other deficiencies and major or critical deficiencies are as follows. Note that multiple deficiencies of the same category identified during a single inspection are counted as one.

Major or Critical deficiencies

	2020	2021	2022	2023	2024
1	Validations	Deviation handling	Organizational management, quality management	Deviation handling	Quality management Management of Documents/Records (including DI) Change management
2	Deviation handling	DI-related	Validations Supplier control	Validations DI-related Document management Handling of laboratory abnormalities, OOS, and OOT	Handling of laboratory abnormalities, OOS(Out of Specification), and OOT
3	Test records, test procedures Handling of laboratory abnormalities, OOS, and OOT	Test records, test procedures Sterility assurance	Document management DI-related	Other 8 items	Cleaning, validations for cleaning
4	Organizational management, quality management Control of facilities and equipment	Other 5 items	Sterility assurance Reviews of product quality		Written production directions/records (including DI)
5	Other 6 items		Other 5 items		Deviation management Satiation Control (Pest, contamination, environment, etc.) Written testing directions/records (including DI)

Other deficiencies

	2020	2021	2022	2023	2024
1	Written production directions/records, procedures Control of raw materials and intermediates	Control of raw materials and intermediates	Written production directions/records, procedures	Written production directions/records, procedures	Deviation management
2	Control of facilities and equipment	Written production directions/records, procedures	Control of raw materials and intermediates	Control of raw materials and intermediates	Written testing directions/records (including DI)
3	Test records, test procedures	Control of facilities and equipment	Document management	Control of facilities and equipment	Written production directions/records (including DI) Management of Documents/Records (including DI)
4	DI-related	Document management	Control of facilities and equipment	Document management	Control of raw materials and intermediates Change management
5	Validations	Test records, test procedures	Test records, test procedures	Deviation control	Control for laboratory reagents/solutions/reference standards Cleaning, validations for cleaning
6	Deviation handling	Sanitation/hygiene control, utility Deviation handling	Sampling procedures for testing, management of samples	Sampling procedures for testing, management of samples	Sampling procedures for testing, management of samples
7	Sampling procedures for testing, management of samples	Sampling procedures for testing, management of samples	DI-related	Test records, test procedures	Handling of laboratory abnormalities, OOS, and OOT
8	Document management	Validations DI-related	Control for laboratory reagents/solutions/reference standards Sanitation/hygiene control, utility Deviation handling	Change management Organizational management, quality management	Supplier/contractors control Control of facilities and equipment
9	Sanitation/hygiene control, utility Prevention for contamination/mix-up of products	Cleaning, validations for cleaning Supplier control	Prevention for contamination/mix-up of products	Cleaning, validations for cleaning	Production procedures
10	Control for laboratory reagents/solutions/reference standards	Handling of laboratory abnormalities, OOS, and OOT	Supplier control	Sanitation/hygiene control, utility	Prevention for contamination/mix-up of products

2-3-2 Analysis of identified deficiencies

Related to Article 14 of the GMP Ordinance (Change Control):

"Change control" ranked fourth in frequency among minor deficiencies. Approximately half of the deficiencies in this category were related to the absence of defined procedures for communication with marketing authorization holders (MAHs) and related parties.

Article 14 of the GMP Ministerial Ordinance stipulates that, in cases where a change causes any actual or potential impact on the product quality or the product authorization requirements, the change must be notified to the relevant MAHs in advance to obtain confirmation, and must also be reported after implementation. Furthermore, records of such communications must be prepared and retained. However, due to insufficient understanding of these requirements, several deficiencies have been identified, including medium-level deficiencies disclosed in the annex, as well as the following examples:

- ✓ Procedures, such as SOPs or quality agreements, did not define how to notify MAHs in advance and after implementation of changes that may impact product quality or approved matters.
- ✓ Change assessments considered impacts on product quality but not on approved matters, resulting in the potential risk that changes deviating from approved matters were not communicated to MAHs.
- ✓ Even in cases where changes could affect product quality, procedures defined that notifying the MAHs was not required as long as the change did not affect approved matters or require regulatory filing.
- ✓ Procedures did not specify that records of communications with MAHs must be prepared when changes affecting product quality or approved matters were communicated.

Related to Article 15 of the GMP Ordinance (Deviation Management):

"Deviation management" ranked first in frequency among minor deficiencies. Approximately half of the deficiencies identified were related to inadequate root cause investigations for individual deviations. Additionally, approximately 20% of the deficiencies were due to the absence of defined procedures for notifying MAHs.

Article 15 of the GMP Ministerial Ordinance requires that, when a significant deviation occurs (e.g., when it affects product quality or deviates from approved matters), the relevant MAHs must be promptly notified and records of such notifications must be prepared and retained. However, due to insufficient understanding of these requirements, the following deficiencies have been observed:

- ✓ Procedures, such as SOPs or quality agreements, did not define how to notify MAHs in the event of a significant deviation.
- ✓ Deviation assessments considered the impact on product quality but not on approved matters, potentially leading to unreported deviations that violate or may violate the approved conditions.
- ✓ The procedure designated the deviation management responsible person to decide whether notifying the MAHs was necessary, but did not define clear criteria, raising concern that significant deviations might not be reported.
- ✓ Although the manufacturing site had procedures in place (under a quality agreement) to report significant deviations, the MAH had entered into a quality agreement not with the manufacturing site but with the domestic MAH representative (MF local manager). The agreement between the manufacturing site and the MF local manager did not include provisions for reporting significant deviations, creating a situation where such deviations might not be reported to the MAH.
- ✓ There were no procedures in place for preparing records of communications with MAHs when significant deviations were reported.

2-3-2 Analysis of identified deficiencies (continued)

Related to Article 20 of the GMP Ordinance (Document/Record Management):

"Document/record management (including DI)" ranked third in frequency among minor deficiencies. The most common issue in this category was related to errors in the specified retention period for documents and records.

Article 20 of the GMP Ordinance stipulates the retention periods for documents and records. In addition, for APIs, Article 22 applies; for biological products, Article 30; and for regenerative medical products, the corresponding Article 22 of the GCTP Ministerial Ordinance must also be followed. However, due to insufficient understanding of these requirements, the following deficiencies have been identified:

For biological products or regenerative medical products, documents and records that must be retained for the product's shelf life plus 10 years were incorrectly set to be retained for only 10 years.

The scope of records subject to the GMP-specified retention period was misunderstood as applying only to manufacturing records, while other important records (e.g., quality information records, equipment cleaning records, inventory records of raw materials and products, equipment usage logs, etc.) were retained for shorter periods.

For Japanese-destined lots, test samples were prepared together with those for non-Japanese markets, and the preparation records were retained as part of the non-Japanese lot records. As a result, the records were subject to a shorter retention period than required under Japan's GMP Ministerial Ordinance.

Summary

In GMP inspections, inspectors assess facilities in accordance with the requirements of the GMP Ministerial Ordinance. Therefore, deficiencies frequently arise from non-conformance with the Ordinance, as illustrated above.

Notably, a large proportion of the above deficiencies were identified at overseas manufacturing sites. PMDA is actively promoting greater transparency of Japan's GMP regulations to overseas stakeholders. As part of these efforts, the English translation of the latest GMP Ministerial Ordinance was published on PMDA's official website on June 21, 2024. Moving forward, we aim to strengthen external communication by, for example, preparing English translations of important documents such as the Ordinance's enforcement notification and the GMP Case Study Collection.

As stated in Annex 3 of the GMP Inspection Procedures, deficiencies that violate a provision of the GMP Ministerial Ordinance but do not constitute a critical deficiency are generally classified as medium-level deficiencies. However, in some cases, if the relevant procedures were not documented but were implemented in practice, such context may justify classification as a minor deficiency.

2-4 GMP training support

The achievement of support operations in FY 2024 is as follows:

1 Support for on-site inspection

Accept observers in PMDA's GMP inspection

9 cases (8 Japanese cases, 1 overseas cases)

Conduct PMDA-prefectural governments joint GMP inspection

17 cases

Dispatch of PMDA inspector to prefectural government GMP inspection

3 cases

Observer participation in planning and decision-making meetings

38 participants

2 Provision of PMDA training materials, etc.

Introductory GMP training

April : 148 participants

Lectures on specialized fields of GMP

July(1st) : 19 participants
March(3th) : 17 participants

GMP training materials

GMP training for beginners' videos/slides (renewals), PMDA's specialized training slides (renewals)

3 Seminars, etc.

GMP Round Table Meeting

September : 13 participants (Shizuoka Prefecture Co-host)
February : 3 participants (Miyazaki Prefecture Co-host)
March : 11participants (Aichi Prefecture Co-host)

4 Dispatch of speakers / Consultations

Dispatch of GMP experts to training sessions and mock inspections sponsored by prefectural governments

21 cases

Consultation on inquiry regarding GMP inspections conducted by prefectural governments

3 cases

Sharing PMDA GMP inspection reports

29 cases

2-5 Consultation services

2-5-1 Simple consultation

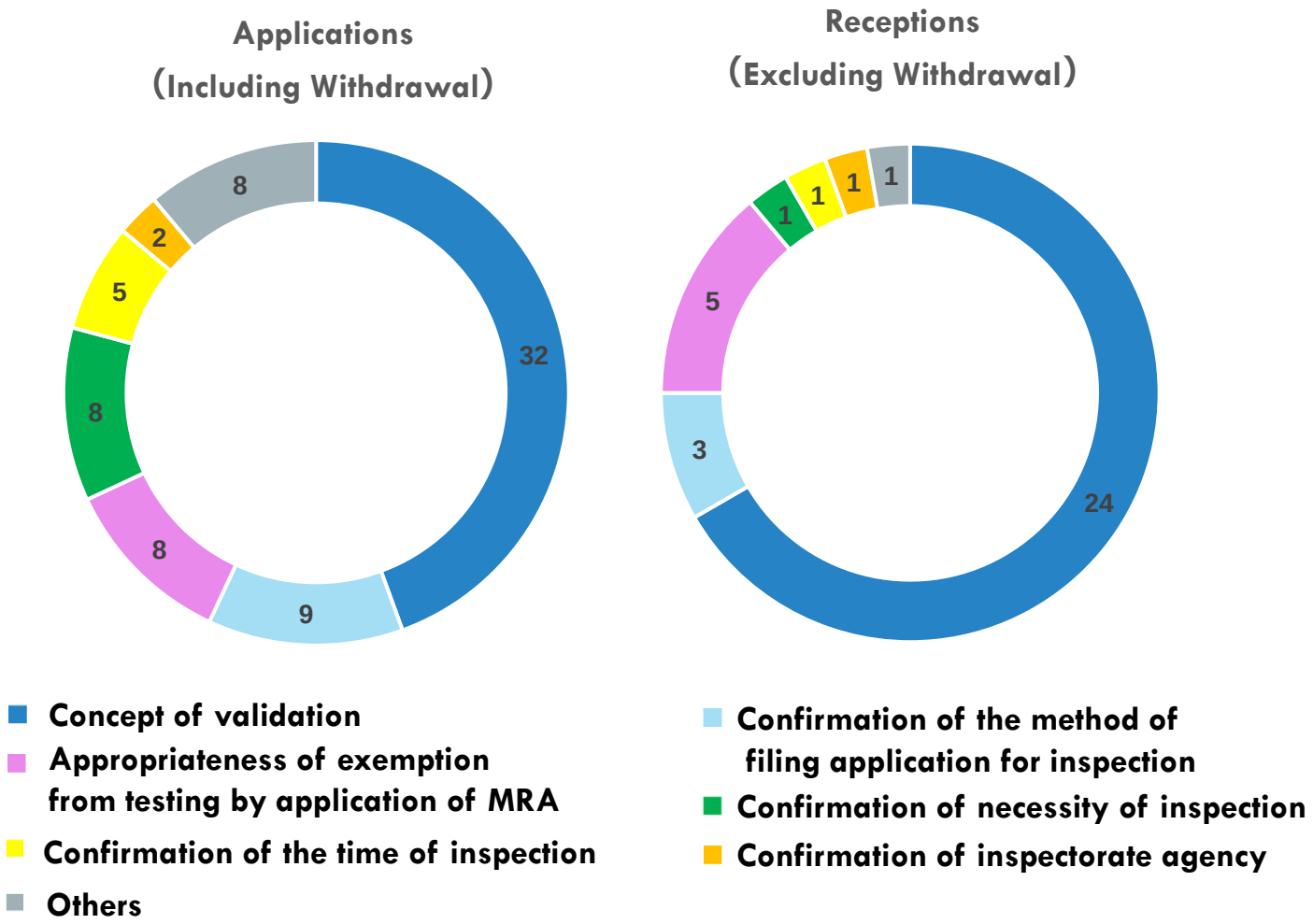
OMQD is in charge of consultations related to GMP and GCTP inspections among Simple consultations based on “Implementation Guideline, for Face-to-Face Consultations and Examinations Confirm Certification Conducted by Pharmaceuticals and Medical Devices Agency" (PFSB/ELD/OMDE Notification No. 0302070 dated March 2, 2012; hereinafter referred to as the "Implementation Guideline").

The numbers of receipt[1] and meetings[2] of simple consultations related to GMP and GCTP inspections in the past 3 years are shown below.

Fiscal year	Number of receipt	Number of meetings
2022	43	20
2023	42	15
2024	62	33

1) Number of Simple consultations received
2) Number of Simple consultations (meetings) conducted

The breakdown of the simple consultation applications and reception details for the fiscal year 2024 is as follows. Several items included in one consultation were counted individually.



2-5-1 Simple consultation (continued)

In FY 2024, as in previous years, the most frequent topic of consultation is the "Concept of validation." Additionally, compared to previous years, the total number of receipt increased significantly this fiscal year, while the proportion of consultations that were withdrawn decreased. One possible reason for the decline in the withdrawal rate is that examples of withdrawn cases were posted on the PMDA, allowing applicants to check in advance whether their consultation topics fall within the scope of simple consultations.

Among the consultations on the "Concept of validation," 8 out of 32 receipt cases were withdrawn. A common reason for withdrawal was the lack of sufficient explanation as to whether the validation plan could be deemed scientifically valid. Examples include insufficient justification for the appropriateness of using grouping or bracketing methods, or for substituting verification for validation.

The second most common type of consultation after Concept of validation is the "Appropriateness of exemption from testing by application of MRA". MRA refers to a Mutual Recognition Agreement between Japan and foreign countries. In the context of pharmaceutical GMP, it generally refers to the agreement between Japan and the European Union (EU)*12, hereafter referred to as the "Japan-EU MRA."

Under the Japan-EU MRA, mutual acceptance of batch certificates issued by manufacturing sites that have been confirmed by the authorities of Japan or EU member states is stipulated. This allows for the partial omission of tests that importers are required to conduct for each batch, thereby contributing to optimization of resources for both companies and regulatory authorities. However, due to increasing complexity in the supply chain, it has become more difficult to determine whether the MRA is applicable in certain cases, and the PMDA continues to receive regular inquiries on this matter.

Regarding the applicability of MRA and similar exceptions, for cases among the inquiries received by the PMDA that are deemed appropriate to be shared more broadly, we will consider actions such as presenting them in lectures and issuing Q&A documents, in collaboration with industry organizations and the MHLW.

*12 Notification on Partial Revision of the Implementation of the Agreement on Mutual Recognition between Japan and the European Community (PSEHB/CND Notification No. 0718-1 dated July 18, 2018, issued by the Director of Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, the MHLW)
https://www.mhlw.go.jp/web/t_doc?dataId=00tc3504&dataType=1&pageNo=1

2-5-2 Other consultations

The outlines and results of various consultations other than "Simple consultations" in FY 2024 are as follows.

Number of consultations in FY 2024

* The number of consultations completed in FY 2024 was tabulated

0 case	1 case	0 case
Consultation on SAKIGAKE overall evaluation	Consultation on innovative manufacturing technology for drugs	Consultation on conformity assessments of reliability criteria

For Consultation on innovative manufacturing technology for drugs, on-site inspections and face-to-face guidance were conducted for the consultations applied for in fiscal year 2023.

3 Risk communication activities

3-1 GMP roundtable meeting

Since FY 2022, PMDA has been holding GMP roundtable meetings to address challenges and facilitate opinion exchange pharmaceutical companies, regulatory authorities, and academia to ensure the quality of drugs.

In FY 2024, PMDA convened the 4th GMP Roundtable Meeting which was cooperated with Shizuoka Prefecture, with venues established in both Tokyo and Shizuoka with web-connecting. The meeting featured extensive discussions on the topic of "Quality Culture," culminating in a panel discussion involving distinguished experts from industry, academia, and regulatory authorities.

As with the previous session, both the lecture segment and the panel discussion were broadcast online to facilitate broader participation.

Feedback from participants indicated that over 90% found the group discussions and the panel discussion to be valuable. These results suggest that the session was highly beneficial in addressing various questions and challenges faced by pharmaceutical manufacturers, including strategies for cultivating a robust quality culture and identifying practical solutions to ongoing issues.

Furthermore, as a new initiative, PMDA launched regional GMP Roundtable Meetings, wherein staff members travel to prefectures that request hosting such events. In FY 2024, these regional meetings were held in Miyazaki and Aichi Prefectures.

PMDA remains committed to fostering dialogue with manufacturers and will continue to actively organize GMP Roundtable Meetings in FY 2025 and beyond, thereby contributing to enhanced mutual understanding and continuous improvement in pharmaceutical quality practices.

[The 4th GMP roundtable meeting]

Date:	Tuesday; September 2024
Place:	Nihonbashi Life Science Hub (Tokyo venue) Couple (Shizuoka venue)
Participants:	59 in Tokyo venue, 32 in Shizuoka venue (web participants: 420)
Theme:	Fostering a Quality Culture Together Through Shared Learning

Tokyo venue

Shizuoka venue

Panel Discussion

3-2 Rapid announcement of observed deficiencies (ORANGE Letter)

As part of risk communication activities with pharmaceutical manufacturers, OMQD has been publishing on the PMDA website(Quality Assurance Activities) information on deficiencies found during GMP inspections, which is deemed useful for prompt dissemination and raising awareness across the entire industry as "Rapid Announcement of Observed Deficiencies" (ORANGE Letter: Observed Regulatory Attention/Notification of GMP Elements Letter; hereinafter referred to as "ORANGE Letter") since FY 2022.

The primary purpose of ORANGE Letter is to encourage voluntary efforts of pharmaceutical manufacturers to improve quality. Information that may infringe on intellectual property of a specific companies is withheld from publication.

The list of ORANGE Letters issued in FY 2023 is as follows (No. 8 to 13; 6 issues in total). No. 1 to 7 were issued in FY 2022.

No.	Date of issuance	Title
14	June 2024	Who should assess whether change control is required?
15	September 2024	Deficiencies identified in generics manufacturing sites
16	October 2024	Non-compliance with product authorization requirements / Falsification of records
17	December 2024	Risk-based validation planning (Part 2)
18	January 2025	Deficiencies identified in manufacturing sites handling multiple products
19	March 2025	Handling of stability monitoring results (Part 2)

3-3 List of identified deficiencies

In response to requests from the pharmaceutical industry to disclose additional information related to drug quality, PMDA began disclosing major deficiencies identified during GMP inspections in GMP/GCTP Annual Report 2023. Subsequently, PMDA conducted a survey and received considerable feedback including comments such as "publishing only the deficiencies does not provide sufficient context to understand the background, making it difficult to utilize the information for voluntary improvement activities at manufacturing sites." Taking this feedback into account, GMP/GCTP Annual Report 2024 includes concise background descriptions behind each deficiency within the list of identified deficiencies to enhance its usefulness.

The list of major deficiencies identified in PMDA's GMP inspections in 2024 has been published as shown in the Attachment.

*The Attachment is posted as an Excel file at the following URL.
https://www.pmda.go.jp/english/review-services/gmp-qms-gctp/0007.html

There was one critical deficiency issued by PMDA during GMP inspections in FY 2024. Since the details of the violation of the PMD Act and the GMP Ministerial Ordinance have already been disclosed on the Tokushima Prefecture website (*13), and because the manufacturing site could easily be identified —even if anonymized— by cross-referencing with administrative actions such as business improvement orders, it was determined that disclosure of deficiencies while maintaining the anonymity of the manufacturing site to which it was issued would not be feasible. Therefore, this critical deficiency, along with the two associated major deficiencies issued at the same time, is excluded from the list of deficiencies.

*13: *Regarding administrative actions against pharmaceutical manufacturers in Tokushima Prefecture*
https://www.pref.tokushima.lg.jp/sp/kenseijoho/hodoteikyoshiryo/7302993/

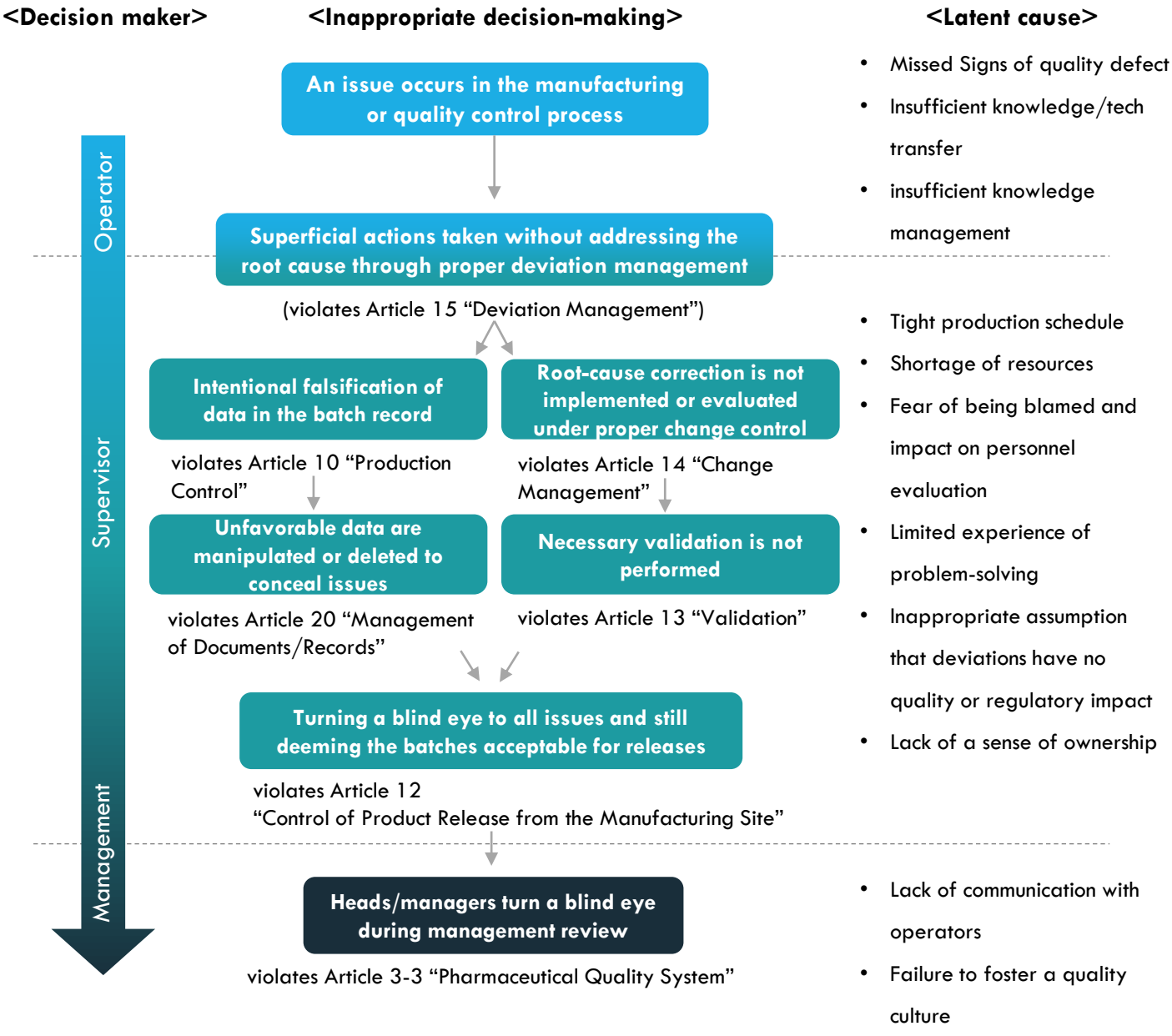
3-4 Characteristics of recent critical deficiencies

Regarding recent quality issues involving generic drugs, the Ministry of Health, Labour and Welfare is currently examining measures to ensure appropriate manufacturing and quality control systems through the "*Expert Committee on the Ideal Industrial Structure for Ensuring Stable Supply of Generic Drugs*".

Many cases of misconduct related to quality stem from so-called "upstream issues," such as inadequate development or insufficient technology transfer to manufacturing departments—ultimately leading to the inability to produce products according to specifications. Contributing factors often include poor corporate governance and a lack of maturity in quality culture.

PMDA's recent on-site inspections have also identified cases where such upstream problems triggered quality or manufacturing failures, which in turn led to multiple and interconnected violations of the Pharmaceutical and Medical Device Act (PMD Act) and GMP Ministerial Ordinance due to the absence of root-cause resolution. One example is illustrated below:

※14 Expert Committee on the Ideal Industrial Structure for Ensuring Stable Supply of Generic Drugs
https://www.mhlw.go.jp/stf/shingi/other-isei_ryutsu-yakka_00002.html

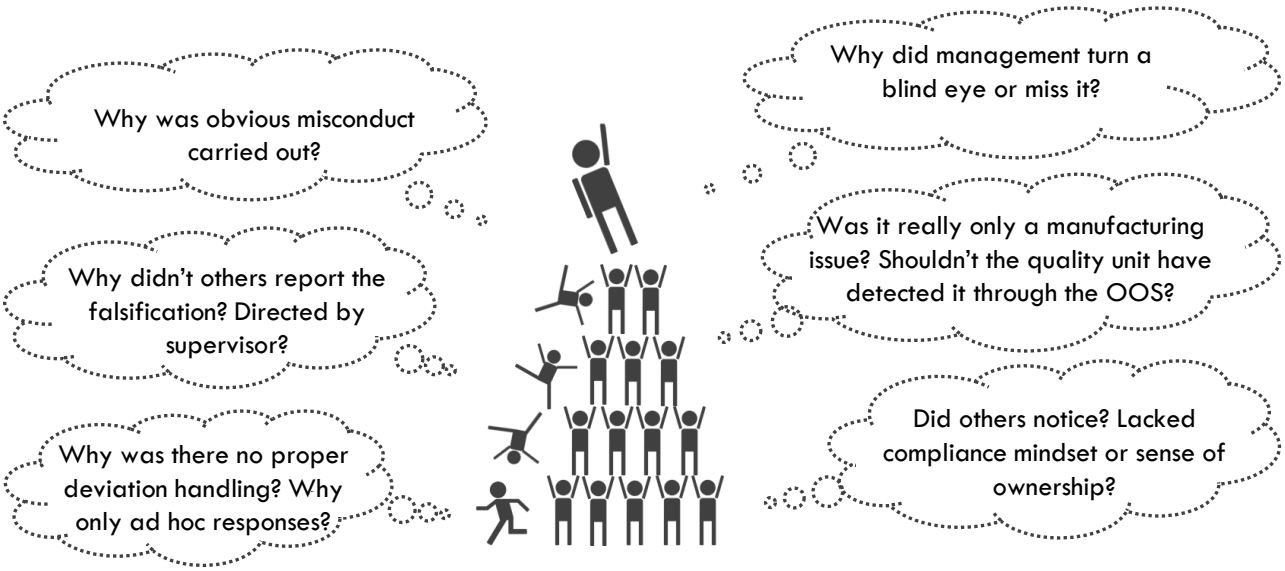


Knowledge management, which was a central theme of the 3rd GMP Roundtable Meeting, plays a crucial role when identifying the root cause of quality defects. Please refer to the presentation slides and discussion output available on "GMP Roundtable Meetings" under PMDA's website.

As illustrated in the figure "Collapse of the Quality-Supporting Pyramid," it is essential not to view quality issues merely as problems caused by an individual department or person, but to recognize that the root causes may lie within the organization's structure, decision-making processes, and communication pathways.

Companies must proactively address and resolve the specific challenges faced at each manufacturing site.

Figure: Collapse of the Quality-Supporting Pyramid



Technical problems may sometimes be unavoidable.
However, many past pharmaceutical quality defects have been exacerbated by a corporate culture of turning a blind eye and an environment where employees felt discouraged from reporting issues. This in turn led to a cascade of regulatory violations and ultimately resulted in serious quality failures.

- If something is unclear, clarify it.
- If something feels off, report it to your supervisor without hesitation.
- If a serious regulatory violation is identified, promptly report it to the competent authority.

Each individual's awareness and initiative become the foundation that safeguards quality—and ultimately protects patients.

Systems alone cannot ensure quality.
What is crucial is the professional mindset of the operators and responsible individuals who implement the system, as well as the cultivation of shared values within the organization.

4 International activities

4-1 Importance of international activities

In recent years, the pharmaceutical supply chain has become increasingly globalized, and the number of overseas manufacturing sites supplying pharmaceuticals to Japan to grow. In this context, regulatory authorities are required to respond appropriately within an international oversight framework.

On the other hand, regulatory authorities face limitations in human resources, making rapid staffing increases unrealistic. Even under such constraints, it is necessary to maintain a certain level of operational quality while carry out their duties reliably.

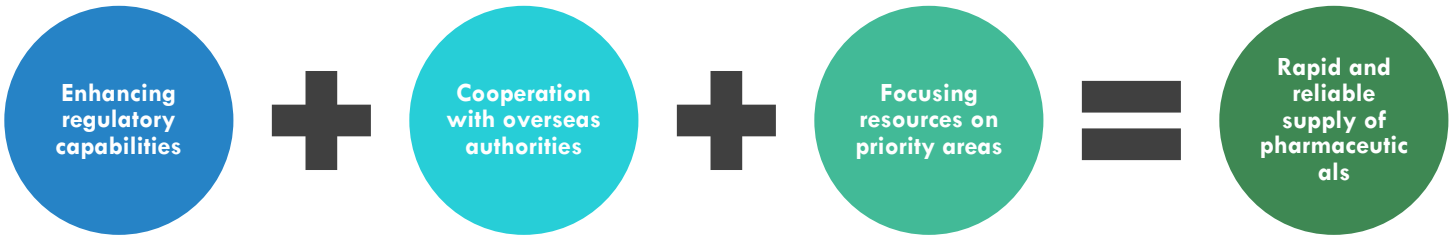
To address these challenges, it is effective to enhance regulatory capabilities, cooperate with overseas authorities, and focus resources on priority areas. In particular, strengthening international cooperation and collaboration with foreign regulatory authorities are essential measures.

Specifically, by actively collecting inspection information conducted by overseas regulatory authorities and conducting risk assessment of manufacturing sites with higher accuracy, on-site inspections are carried out at high-risk manufacturing sites. When utilizing overseas inspections information, it is premised on the alignment of the inspected authority's GMP standards and inspection capabilities with the PIC/S standards.

Therefore, QMQD is actively engaged in activities related to the international harmonization of GMP standards at PIC/S, simultaneously promoting the building of cooperative relationships with overseas authorities and enhancing its own inspection capabilities.

Many benefits gained through international activities serve as an important foundation for continuously and stably conducting GMP inspection operations. Utilizing overseas inspections results, avoiding duplicate inspections, and achieving internationally harmonized and prompt responses contribute not only to operational efficiency but also to ensuring the quality of pharmaceuticals.

As a result, it becomes possible to deliver necessary pharmaceuticals to patients who need them more quickly and reliably.



- Joint training with overseas authorities
- Guideline development in PIC/S working groups
- Information gathering on advanced technologies

- Information sharing with PIC/S participating authorities
- Participation in EMA（European Medicines Agency） GMDP Inspectors Working Group※15
- Participation in API Programme※16

- Mutual acceptance of trusted overseas inspection results
- Concentration of resources on high-risk manufacturing sites

※15 EMA GMDP Inspectors Working Group
https://www.ema.europa.eu/en/human-regulatory-overview/research-development/compliance-research-development/good-manufacturing-practice/good-manufacturing-practice-gmp-distribution-practice-practice-gdp-inspectors-working-group

※16 Programme to rationalise international GMP inspections of active pharmaceutical ingredients/active substances manufacturers https://www.ema.europa.eu/en/documents/other/programme-rationalise-international-good-manufacturing-practice-inspections-active-pharmaceutical-ingredient-active-substance-manufacturers-terms-reference-and-procedures-participating-authorities_en.pdf

4-2 Strategy of QMQD in international activities

QMQD formulates its international activity policies in a coherent manner, taking into account the national basic policies, measures of relevant administrative agencies, trends and mid- to long-term directions in international organizations, as well as the strategic objectives of PMDA as a whole (PMDA the fifth mid-term strategic plan). The specific strategy policies are as follows:

- **Enhancing Regulatory Capabilities**
  - ✓ Improve PMDA's inspection capabilities
  - ✓ Analyze the gaps between Japanese GMP regulations and global GMP regulations to identify PMDA's technical vulnerabilities
  - ✓ Continue all activities centered on PIC/S (see subsequent pages for details)
- **Cooperation with Overseas Authorities**
  - ✓ Aim to strengthen the cooperative framework, especially with Asian countries, to further accelerate pharmaceutical regulatory harmonization
- **Focusing Resources on Priority Areas**
  - ✓ Establish GMP inspection regulatory reliance (i.e., the act of one regulatory authority considering and giving weight to another authority's inspection outcomes when making its own decisions) framework in Asia
  - ✓ Enroll the activities that would be helpful for Japanese Pharmaceutical industry.

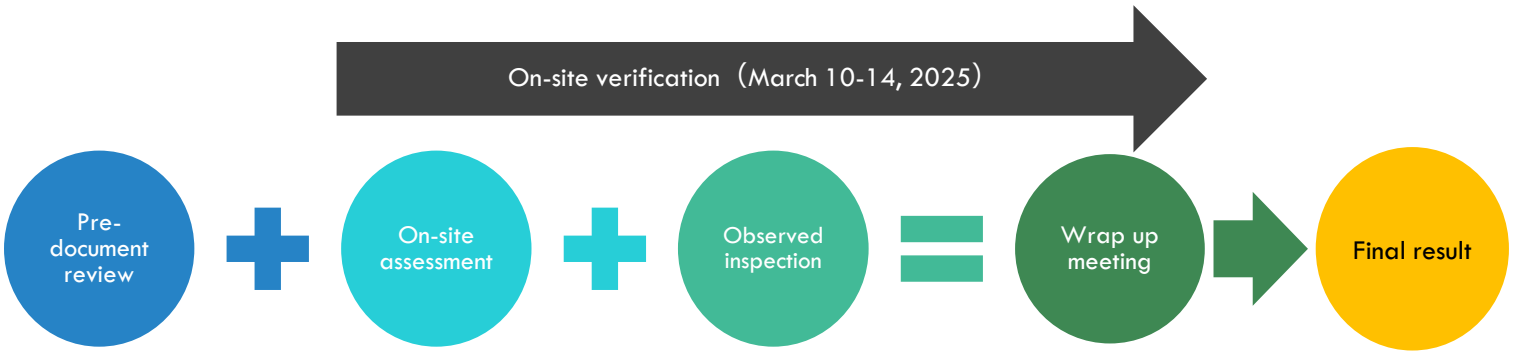
4-3 Highlights of FY 2024

4-3-1 Re-assessment for continued PIC/S Membership

From March 10 to 14, 2025, Japanese regulatory authority underwent the first re-assessment of its membership qualification in PIC/S (Pharmaceutical Inspection Cooperation Scheme) since joining in 2014.

Prior to the re-assessment, explanatory materials regarding Japanese GMP inspection system were submitted to PIC/S. During the on-site verification, the "on-site assessment" was conducted, wherein Japanese regulatory authority, centered around the Ministry of Health, Labour and Welfare, explained the common system. Additionally, the "observed inspection" was performed, where rapporteurs dispatched from PIC/S observed GMP inspections conducted by PMDA and prefectural authorities to assess their inspection capabilities.

At the final day of the re-assessment, the rapporteur team provided feedback, which was favorable. The Final result of the re-assessment (compliance/non-compliance) is expected to be approved at the PIC/S Committee scheduled for November 2025.



4-3-2 PIC/S Seminar 2024 in Brazil –Annex1-

The PIC/S Seminar is an annual educational training event for GMP inspectors hosted by different PIC/S member countries each year. The seminar focuses on specific GMP-related themes, aiming to harmonize training content and inspection methodologies among countries. Lectures, case studies, and workshops are held during the seminar.

In 2024, from November 6 to 8, the seminar titled “PIC/S SEMINAR 2024 - Annex I Unveiled: Shaping the Future of Sterility” was hosted by Brazil’s regulatory authority ANVISA in Brasilia. Discussions centered on the assurance of sterility focusing on the revised Annex 1.

At this seminar, the Pharmaceutical Quality Management Division delivered a lecture on the implementation status of the revised Annex 1 in Japan and PMDA’s perspective, receiving valuable feedback from various regulatory authorities.

4-4 Collaboration with overseas regulatory authorities and international organizations

4-4-1 PIC/S activities

PIC/S is an international organization aimed at the international harmonization of GMP standards and improvement of inspector competencies. Japan’s GMP regulatory authorities (PMDA, Ministry of Health, Labour and Welfare, and prefectural governments) joined PIC/S in 2014, and since then have been promoting international initiatives centered on PIC/S activities. The main activities are as follows:

4-4-1 PIC/S activities (continued)

Participating in PIC/S Executive Bureau

PIC/S has a committee composed of representatives from each member country. Under the committee, seven subcommittees (SC) have been established, each supported by the PIC/S Executive Bureau (EB) and the PIC/S Secretariat: SC COM (Communication and Information Sharing), SC SD (Strategic Development), SC H (GMDP Harmonisation), SC B (Budget), SC EC (Expert Circle), SC T (Training) and SC COMPL (Compliance)

QMQD successfully ran for and was elected as the chair of SC COM. As chair, the division also serves as a member of EB (term: January 2022 to December 2025). SC COM promotes collaboration among PIC/S member authorities and between PIC/S and other organizations, playing a central role in information sharing and public relations activities both inside and outside PIC/S.

Cooperating PIC/S subcommittee and expert circle activities

QMQD actively cooperates in the activities of SC COM and SC T. In SC COM, PMDA staff serve as chairpersons and contribute to strengthening information sharing and collaboration through leading related projects and organizing teleconferences. Meanwhile, PMDA personnel participate as members of SC T, engaging actively in educational activities such as reviewing PIC/S training materials and supporting the organization of PIC/S seminars.

Contributing to PIC/S Seminar

PIC/S Seminar is one of the most important educational events of PIC/S, attended by nearly all PIC/S member authorities. Since Japan's PIC/S accession in 2014, PMDA has consistently participated in every seminar, attending training sessions and actively dispatching instructors. In 2019, PMDA hosted a PIC/S seminar in Toyama with the theme of "Sterility Assurance of Medicinal Products," significantly contributing to training member authority personnel. The achievements for FY 2024 are described in section <4-3-2 PIC/S Seminar 2024 in Brazil – Annex 1>.

Secondment a specialist staff to PIC/S secretariat

On April 1, 2024, PMDA dispatched a specialist staff member QMQD to the PIC/S Secretariat in Geneva, Switzerland. The dispatch period is two years, during which the staff member is responsible for Secretariat duties related to international harmonization of GMP standards within PIC/S member organizations and training of GMP inspectors (auditors). This dispatch is expected to facilitate understanding of the latest international trends in GMP, secure a Japan-led GMP inspection framework for pharmaceutical manufacturing sites in the Asia region, strengthen collaboration with overseas regulatory authorities, and promote strategic initiatives toward building reliance systems.

PIC/S Expert Circle

The PIC/S Expert Circles promote training in specific technical fields. Their main activities include holding Expert Circle Meetings and preparing training materials.

These meetings are recognized as key events within PIC/S for exchanging technical expertise. Japan hosted the first Expert Circle Meeting on the theme "Quality Risk Management (QRM)" in Tokyo upon joining PIC/S in 2014.Currently, Expert Circles cover many specialized areas.

Recent activities in which PMDA has participated include:

- Revision work on the Aide Memoire for "Control of Cross-Contamination in Shared Facilities (CCCISF)" (PIC/S document PI 043-1)
- Expert Circle Meeting on "Human Blood, Tissues, Cells & ATMPs" held from March 14 to 16, 2023, hosted by Italian (AIFA) and Austrian (AGES) authorities
- Training on PIC/S GMP Guide Annex 2A
- Expert Circle Meeting on "Human Blood, Tissues, Cells & ATMPs" held from August 20 to 22, 2024, hosted by Malaysian authority (NPRA)

4-4-1 PIC/S activities (continued)

Information sharing with PIC/S member authorities

Based on PMDA's 5th Mid-Term Plan, PMDA is actively promoting information exchange on GMP inspections to strengthen cooperation with overseas regulatory authorities.

The performance over the past five years is shown in the table below. Especially since FY 2023, the COVID-19 pandemic caused disruptions and delays in GMP inspection activities due to overseas travel restrictions, limitations on inspectors' access to manufacturing sites, and infection prevention measures for inspectors. Consequently, regulatory authorities worldwide have increasingly engaged in risk assessments and information sharing based on GMP inspection results from other countries, highlighting the importance of information exchange.

	FY	2020	2021	2022	2023	2024
Information provided from Japan to overseas	Count	3	5	9	22	15
	Authorities	Taiwan, Australia, USA	USA, EMA	EMA, EDQM(European Directorate for the Quality of Medicines), Italy, Germany, Canada, Argentina, Ukraine	EMA, Singapore, EDQM, Korea, Canada, France, WHO	EMA, Canada, Switzerland, Taiwan, USA、EDQM, Peru
Information provided from overseas to Japan	Count	12	11	13	20	3
	Authorities	Italy, USA, Belgium, Germany, UK, Switzerland, Spain, Taiwan, EMA, Netherlands	USA, EMA, Korea, Brazil	USA, Canada, Argentina, Germany, EMA	USA, Argentina, EDQM, Korea, Germany, Hungary, Singapore, Taiwan	EMA、Korea, Taiwan

Mutual observer programs

To promote mutual understanding and enhance inspection capabilities with overseas regulatory authorities, PMDA conducts mutual observer programs during GMP inspections (on-site inspections).

The achievements over the past three years are summarized in the table below. During the COVID-19 pandemic, various restrictions such as travel bans and limitations on access to manufacturing sites severely constrained GMP inspections. As a result, the importance of reliance on inspection results from overseas authorities was internationally re-recognized, accelerating efforts toward mutual utilization of information.

Following the resolution of the COVID-19 pandemic, there was an increased need to smoothly proceed with backlogged GMP inspections. This led to further utilization of overseas inspection results, and concurrently, the number of cases in which overseas regulatory authorities accompanied PMDA inspections to deepen understanding of Japan's GMP inspection system also increased.

	FY	2022	2023	2024
Observing inspections by PMDA	Count	8	7	5
	Authorities	USA	USA, Korea, Taiwan	USA, Korea, Taiwan
Observing inspections by Overseas	Count	4	19	8
	Authorities	Malaysia, Taiwan, Singapore	Taiwan, Korea, Singapore, South Africa	Canada, Thailand, Malaysia, Korea, Taiwan

4-4-2 Other international activities

Training support to Asian regulatory authorities (PMDA-ATC(Asia Training Center) GMP Seminar)

The Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC) utilizes the knowledge and experience accumulated by PMDA to provide training for regulatory authority personnel in Asian countries, supported by PIC/S, in response to their requests.

QMQD delivers lectures on inspection systems and regulatory frameworks related to pharmaceutical manufacturing and quality control. In addition, with cooperation from actual manufacturing facilities, it provides practical programs that allow participants to experience simulated on-site inspections.

Recent seminar achievements are as follows:

- PMDA-ATC GMP Inspection Webinar 2023 (February 6–7, 2024)
- PMDA-ATC GMP Inspection Seminar 2024 (October 8–10, 2024)
- PMDA-ATC GMP Inspection Seminar 2025 (scheduled for September 17–19, 2025)

API Programme (Active Pharmaceutical Ingredient Programme)

The API Programme was launched in 2012 to streamline international GMP inspections of active pharmaceutical ingredient manufacturers. PMDA has participated in this program since 2016. The current participants comprise 14 organizations: AIFA, ANSM, ANVISA, DKMA, US FDA, Health Canada, HPRA, MHRA, PMDA, TGA, EDQM, EMA, WHO, and EC.

Under this program, all GMP inspection information (inspection plans and results) of API manufacturers already inspected or scheduled to be inspected by participating authorities is registered and shared in a master list (database) under confidentiality agreements. Monthly web meetings allow authorities to utilize this information to identify overlapping inspection targets, coordinate inspection schedules, plan joint inspections, and mutually use inspection results, thereby enhancing efficiency and international reliability of inspections.

PMDA uses information obtained through this program to identify issues at inspection target manufacturing sites in advance, set prioritized confirmation items, and allocate inspection resources preferentially to high-risk facilities. Additionally, joint inspections with other authorities are conducted as needed to improve efficiency and quality of inspections. Furthermore, sharing inspection information via the API Programme also serves as a means to verify GMP inspection capabilities of participating authorities, thereby strengthening the foundation of mutual trust among organizations.

EMA GMDP Inspectors Working Group

The EMA GMDP Inspectors Working Group (EMA GMDP-IWG(Inspectors Working Group)) is a group mainly composed of EU member states and MRA partner countries, holding meetings every three months for information sharing among participants. QMQD participates in these meetings as an observer under the Japan-EU MRA.

QMQD regularly attends these meetings to stay informed of the latest regulatory trends related to pharmaceutical manufacturing and quality control in the EU, and actively promotes international mutual understanding and cooperation by sharing information on Japan's pharmaceutical regulatory system and engaging in discussions.

5 Future vision

The key points of the amendments to the Pharmaceuticals and Medical Devices Act (PMD Act) were clarified in the notification issued on May 21, 2025[*4], titled "The Act for Partial Revision of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (Law No. 37 of 2025)". With respect to GMP, the amendments aim to strengthen the assurance of pharmaceutical quality. Key measures include the exemption of periodic inspections for manufacturing sites deemed low-risk, as well as the introduction of a new framework that allows PMDA to conduct additional inspections in conjunction with conformity assessments carried out by 47 prefectural authorities.

Furthermore, the summary document published on January 10, 2025[*5], titled "The Summary on the revision of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices and related systems, issued by the Health and Science Council on January 10, 2025.", outlines specific directions for implementation, such as shortening the inspection cycle from five years to three, and assigning PMDA to conduct GMP conformity inspections at the time of new approval for generic drugs that contain active ingredients being approved for the first time and involve formulation processes.

In response to these developments, it is recognized that PMDA inspectors are now expected to possess a higher level of risk assessment capability and technical guidance skills than ever before.

PMDA is committed to its mission of ensuring "timely and stable delivery of high-quality pharmaceuticals to patients," and continuously seeks to strengthen its role as a GMP inspection authority. Under the new legal framework, it becomes increasingly important to enhance inspection skills/capabilities, maintain and strengthen effective training programs, enrich risk communication activities, and optimize resource allocation to achieve these goals.

In this context, PMDA launched a new initiative titled "*Publication of GMP inspection results*" on its official website in March 2025, based on the MHLW notification[*17]. Publishing GMP inspection results for the public is already becoming a global standard among major regulatory authorities from the perspective of transparency. Making such results visible not only heightens quality awareness within Japan's pharmaceutical industry, as well as within PMDA itself, but also contributes to strengthening international confidence in Japanese pharmaceuticals.

Looking ahead, the introduction of Warning Letter system[*18] is being considered, which would serve as a deterrent to strengthen the GMP inspection framework. At the same time, it will continue to provide technical support through the "Orange Letter" publication. This two-pronged approach is aimed at further reinforcing GMP compliance systems at manufacturing sites.

*17 "Notification on the Trial Publication of GMP Inspection Results" PSB/CND Notification No. 0321-1 dated March 21, 2025, issued by the Director of Compliance and Narcotics Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare; https://www.pmda.go.jp/files/000274617.pdf

*18 Theme 2: Strengthening Risk-Based Post-Marketing Safety Measures for Pharmaceuticals and Other Products in Response to Emerging Technologies, and Enhancing Regulatory Compliance and Quality Assurance Based on Cases of Legal Violations; https://www.mhlw.go.jp/content/11121000/001271801.pdf

Enhancing regulatory transparency is also expected to facilitate mutual reliance in the area of GMP between Japan and overseas regulatory authorities. As described in <Chapter 4: International Activities>, PMDA continues to promote regulatory reliance in close collaboration with foreign authorities and international organizations. After COVID-19 pandemic, stabilizing international networks has become even more crucial. Mutual use of inspection results based on reliance frameworks is expected to improve the precision of risk assessments for manufacturing sites, streamline regulatory procedures, and enable optimal allocation of resources.

Furthermore, as discussed in <2-3-2 Consideration of identified deficiencies>, analysis and disclosing of inspection results and trends of deficiencies can provide opportunities to identify and address challenges faced by both regulators and industry. It is essential not to stop at simply sharing information — what matters is taking concrete action. For instance, if similar deficiencies are identified across multiple manufacturing sites, possible responses may include raising the issue at a GMP Roundtable Meeting or organizing a new type of stakeholder dialogue to explore solutions together. We intend to continue such reflections to maximize the impact of our risk communication activities.

Through these initiatives, PMDA continue to enhance the quality and effectiveness of inspections, with the aim of building a quality oversight system that earns the trust of stakeholders both in Japan and abroad.

What's on your mind now? Let us know!
-PMDA Annual Report 2024 Survey-

QR code
Scan here using your mobile device.
The survey is also accessible from here.

The content of GMP/GCTP Annual report is continuously improved based on feedback collected through surveys from our readers. For example, the FY 2023 edition began publishing a list of major deficiencies. The latest edition includes an analysis of minor deficiencies related to provisions in the GMP Ministerial Ordinance.

As we consider the contents of future GMP/GCTP Annual Reports, we kindly ask for your cooperation in completing a short survey so that we can better address your needs and provide more useful information. The summary of the survey results will be shared with the Quality Committee of the Federation of Pharmaceutical Manufacturers' Association of Japan and will be used as a reference in discussions about the future direction of the Annual Report. Please be assured that individual responses will remain anonymous.

We sincerely appreciate your honest and constructive feedback.

PMDA GMP / GCTP Annual Report FY 2024

Issued on September 5, 2025
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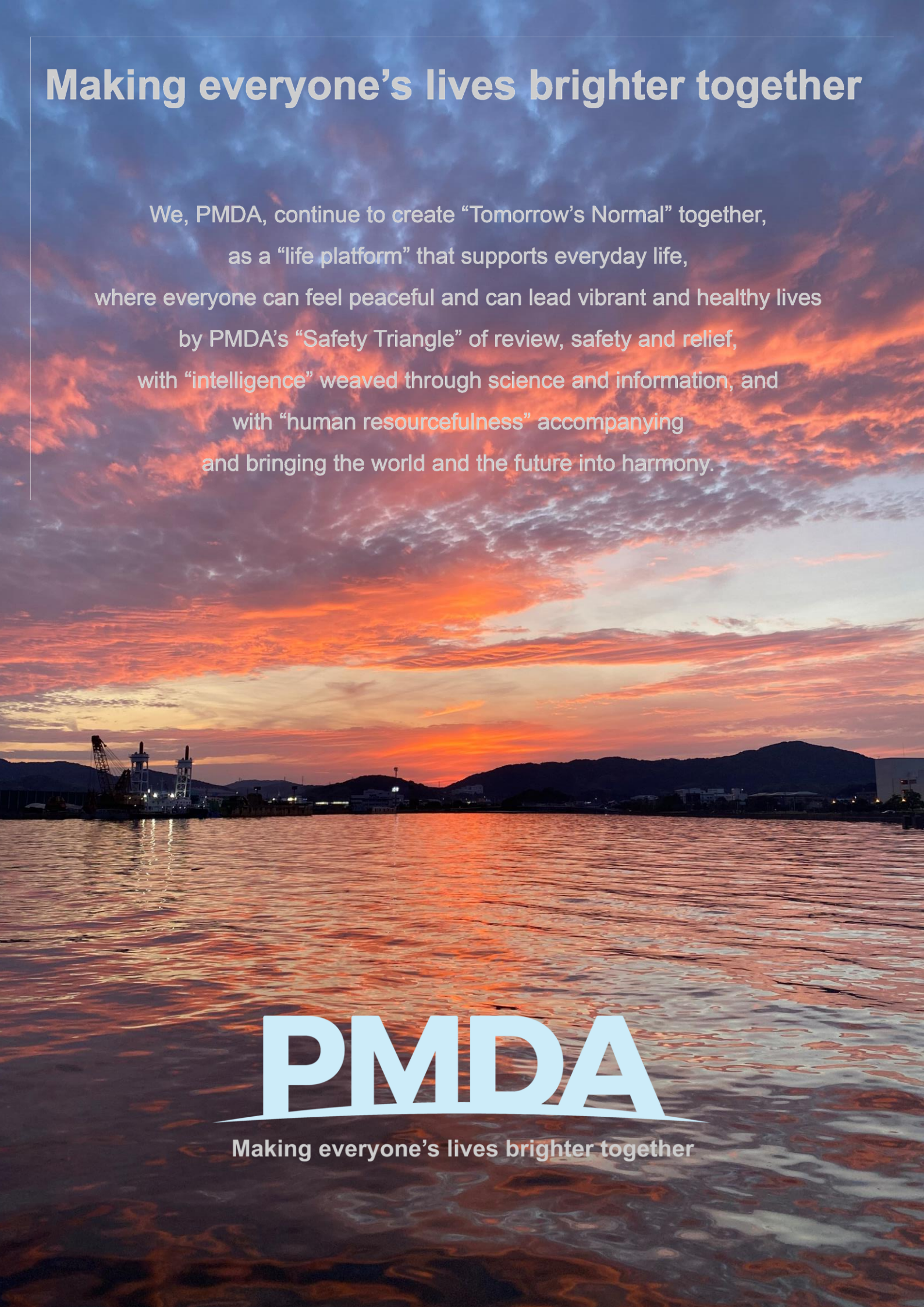
Making everyone’s lives brighter together
We, PMDA, continue to create “Tomorrow’s Normal” together,
as a “life platform” that supports everyday life,
where everyone can feel peaceful and can lead vibrant and healthy lives
by PMDA’s “Safety Triangle” of review, safety and relief,
with “intelligence” weaved through science and information, and
with “human resourcefulness” accompanying
and bringing the world and the future into harmony.
PMDA
Making everyone’s lives brighter together