GMP / GCTP Annual Report

FY 2023

Pharmaceuticals and Medical Devices Agency

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<Message from PMDA>

The recent issues related to stable drug supply have triggered recognition of the importance of drug manufacturing/quality control once again. PMDA places importance on effective GMP monitoring and guidance that leads to quality assurance for drugs distributed in the Japanese market, as well as consultations and advice that lead to optimization of resources of drug manufacturing sites to improve their quality system operate it functionally. Specifically, PMDA carries on various initiatives based on a belief that cooperation of the regulatory authorities and the manufacturers to mutually build up knowledge and experience, constantly visualize and optimize the level of GMP requirements is key to ensuring a stable good drug supply. We believe that such two-way communication is contributing to the spread of the GMP philosophy.

Since 2022, PMDA has been actively promoting risk communication initiatives related to drug quality, including the issuance of ORANGE Letters, GMP roundtable meetings, and the GMP/GCTP Annual Report. To date, 15 ORANGE Letters have been issued, and 4 GMP roundtable meetings have been held. We will continue to improve these activities while listening to your opinions and develop them into more effective ones. As one of our improvements, we reviewed the information published in the GMP/GCTP Annual Report FY 2022 after its release. In the FY 2023 Report, we decided to publish a list of the major deficiencies reported in the GMP inspections by PMDA.

We believe that the continued publication of the GMP/GCTP Annual Report (in Japanese and English) and presenting specific data such as GMP inspection results will enhance the transparency of PMDA's operations and further boost the trust of the Japanese people, the Japanese and overseas pharmaceutical manufacturers, and the overseas regulatory authorities in the GMP inspections in Japan. We hope the trust gained will also lead the international collaboration in the GMP area to the next level.

PMDA will conduct its operations with timely decision-making and a high level of transparency, driven by its fundamental mission to protect citizens' lives and health, through the promotion of risk communication for drug quality as well as GMP inspections and consultations, training support, and international collaboration to advance the medical care in order to contribute to the realization of a prompt and stable supply of quality-assured drugs.

September 30, 2024

Office Director, Office of Manufacturing Quality for Drugs, PMDA

Kenichi Mikami

1. Annual Report

PMDA publishes[*1] the number of GMP inspections (on-site inspections) conducted as accomplishments for each fiscal year in the GMP field.

The Office of Manufacturing Quality for Drugs (OMQD) at PMDA compiles information on business accomplishments related to GMP inspections, regulatory systems, international activities, current challenges, and future vision into the GMP/GCTP Annual Report. OMQD aims to enhance regulatory transparency and foster mutual trust between PMDA and companies by actively disseminating information on drug quality control. In addition, by preparing an English version, OMQD seeks to gather feedback and advice from overseas stakeholders, including pharmaceutical companies, drug manufacturing facilities, and regulatory authorities, thereby further strengthening its operations.

*1 https://www.pmda.go.jp/about-pmda/annual-reports/0001.html (Only Japanese Version)

< Past issues >

◆ GMP/GCTP Annual Report 2022

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

English Version: https://www.pmda.go.jp/english/review-services/gmp-qms-gctp/0007.html

2. About us (PMDA)

2-1 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).[*2]

*2 https://www.pmda.go.jp/files/000271450.pdf

2-2 Mission of Office of Manufacturing Quality for Drugs

The mission of OMQD is to conduct its operations with timely decisions-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.**

2-3 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

2-4 Organization structure of Office of Manufacturing Quality for Drugs

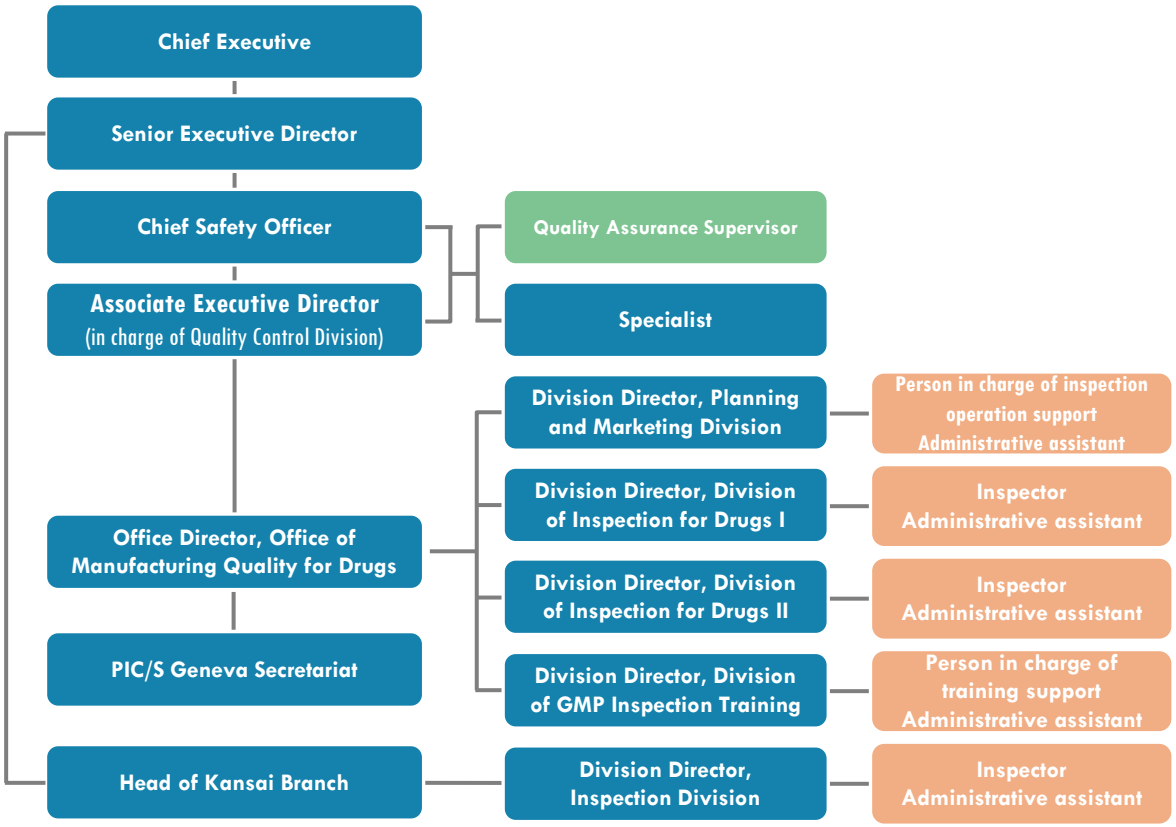
The Office of Manufacturing Quality for Drugs (OMQD) consists of the following 4 divisions (as of March 31, 2024).

- Planning and Management Division : Support for inspection operations, etc.
- Division of Inspection for Drugs I and : Mainly in charge of inspection of biopharmaceuticals 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

In addition to the above, a Division of Inspection has been established at the Kansai Branch, which is responsible for GMP inspections in Japan (mainly Western 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 are 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) and specialists (technical experts in inspection operations) are allocated under such personnel to perform operations.

Division of Inspection for Drugs I, Division of Inspection for Drugs II, and Inspection Division of the Kansai Branch have staff members with experience in pharmaceutical manufacturing from the private sector and provide education and support to other inspectors and prefectural government inspectors. For staff from the private sector, compliance with PMDA's conflict of Interest rules is periodically verified through internal audits and other measures.



2-5 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.

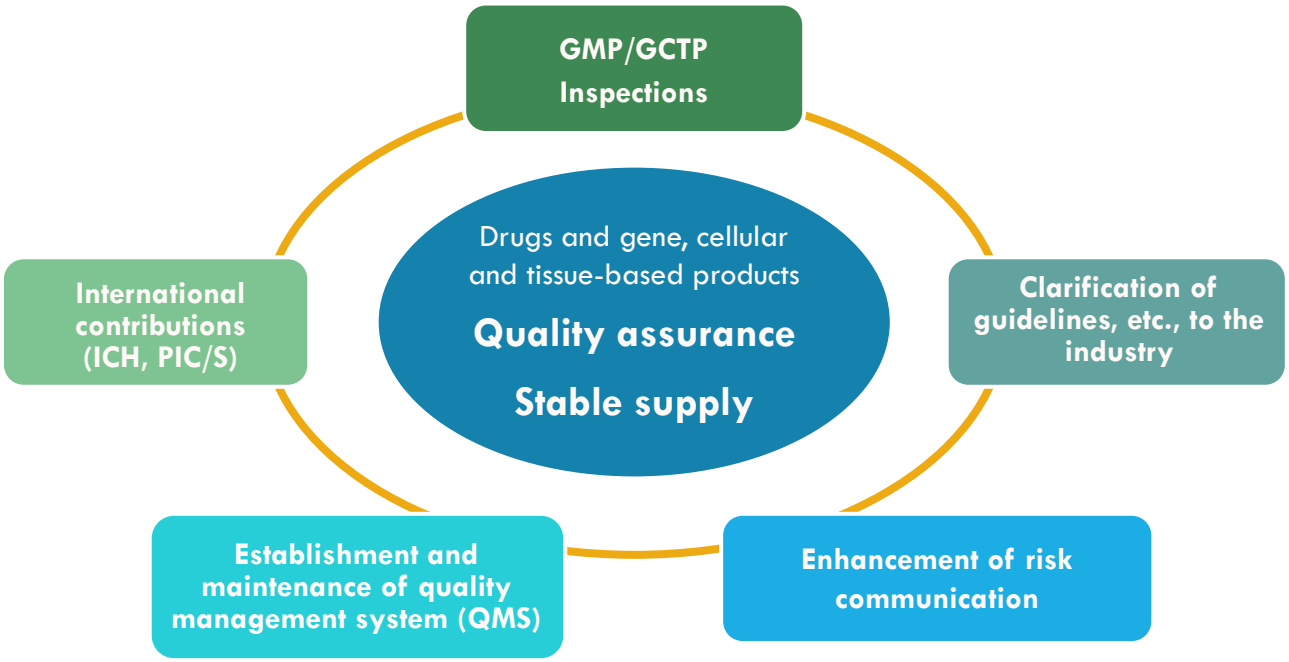
2-6 Operations of the Office of Manufacturing Quality for Drugs

OMQD conducts GMP inspections for drugs and GCTP inspections for gene, cellular and tissue-based products for Japanese and overseas manufacturing sites. (The details are shown in “4. Inspection results, etc. ")

In addition to inspections, 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[*3] and PIC/S[*4], etc. (Details are shown in "9. Collaboration with Overseas Regulatory Authorities and International Organizations").

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

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



3. Outline of achievements in FY 2023

Main achievements of Office of Manufacturing Quality for Drugs in FY 2023 are as follows:

233 cases
On-site GMP inspection

1,884 cases
Desk-top GMP inspection

528 cases
Facility inspection

41 cases
Ad-hoc on-site inspection

14 cases
Company consultation

6 cases
ORANGE Letter

2 cases
GMP roundtable meeting

4. Inspection results, etc.

4-1 Inspection implementation status (in FY 2023)

4-1-1 GMP inspection (manufacturing sites for drugs (domestic))

4-1-2 GCTP inspection (manufacturing sites for gene, cellular and tissue-based products (domestic))

4-1-3 GMP inspection (manufacturing sites for drugs (overseas))

4-1-4 GCTP inspection (manufacturing sites for gene, cellular and tissue-based products (overseas))

4-1-5 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
41 cases	0 case	2 cases

* Included in the above number of GMP Inspection

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

4-1-6 Facility inspection

Domestic accredited		Overseas accredited	
Desk-top inspection	On-site inspection	Desk-top inspection	On-site inspection
17 cases	4 cases	513 cases	0 case

* Desk-top inspection in principle

The results of inspection in FY 2023 and the calculation method of each value are as follows.

- Number of applications : Number of applications accepted in FY 2023
- Number of inspections (on-site inspection) : Number of on-site inspections conducted in FY 2023
- Number of inspections (desk-top inspection (document-based inspection)) : Number of inspections completed in FY 2023
  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.

4-2 GMP inspections

Types of GMP inspections and legal basis

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

2. 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 or not, 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.

   (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)
   - (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)
   - (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)
   - (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)

   (2) Post-marketing approval inspection;
   - (a) Periodic inspection concerning an existing marketing approval (as provided in Article 14, paragraph (7) of the PMD Act)
   - (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)
   - (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)
   - (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)

   (3) Product category-based inspection (as provided in Article 14-2, paragraph (2) of the PMD Act)
   (4) Inspection in relation to change management protocol (as provided in Article 14-7-2, paragraph (3) of the PMD Act)
   (5) Inspection on manufacturing of products for export (as provided in Article 80, paragraph (1) of the PMD Act)

3. 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. Ad-hoc on-site inspections are conducted based on Article 69 of the PMD Act by pharmaceutical inspectors or the inspectors of OMQD who have the qualifications specified by the Cabinet Order set forth in Article 69-2, Paragraph (4) of the PMD Act.

   (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

4-3 Product category-based inspection, etc.

(1) Product category-based inspection

An application for GMP inspections is required for each product/manufacturing site.

Manufacturing sites where multiple products are manufactured on consignments from multiple companies may undergo multiple GMP inspections. Having multiple GMP inspections in a short period of time will be a great burden on the marketing authorization holder who applies for the GMP inspections as well as the manufacturing site to be inspected.

In order to reduce burdens on the marketing authorization holder and manufacturing sites and to conduct efficient GMP inspection, a product category-based inspection to confirm whether the methods of manufacturing control or quality control conform to the standards for each type of manufacture process was newly introduced by the revision of the Pharmaceutical and Medical Device Act in 2021.

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.

(2) 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.

4-4 Qualifications for GMP inspectors

4-4-1 GMP/GCTP inspection

OMQD specifies the qualification requirements for inspectors based on the GMP Inspection Guide*5 and GCTP Inspection Guide*6. There are three levels of inspector qualification: Regular inspectors, lead inspectors, and senior inspectors. In the pharmaceutical field, 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.

A 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.

*5 “Notification on the Enactment of the GMP Inspection Guide” PSB/CND Notification No. 0329-9 dated March 29, 2024, issued by the Director of Compliance and Narcotics Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare

*6 "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, Ministry of Health, Labour and Welfare

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

Those who conduct inspections based on Article 69-2 of the Pharmaceuticals and Medical Devices Act (on-site inspections, etc., not based on an application for inspections) must have the qualifications specified by Cabinet Order, and the Enforcement Ordinance of the Pharmaceuticals and Medical Devices 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

4-5 Selection of inspection method based on risk evaluation

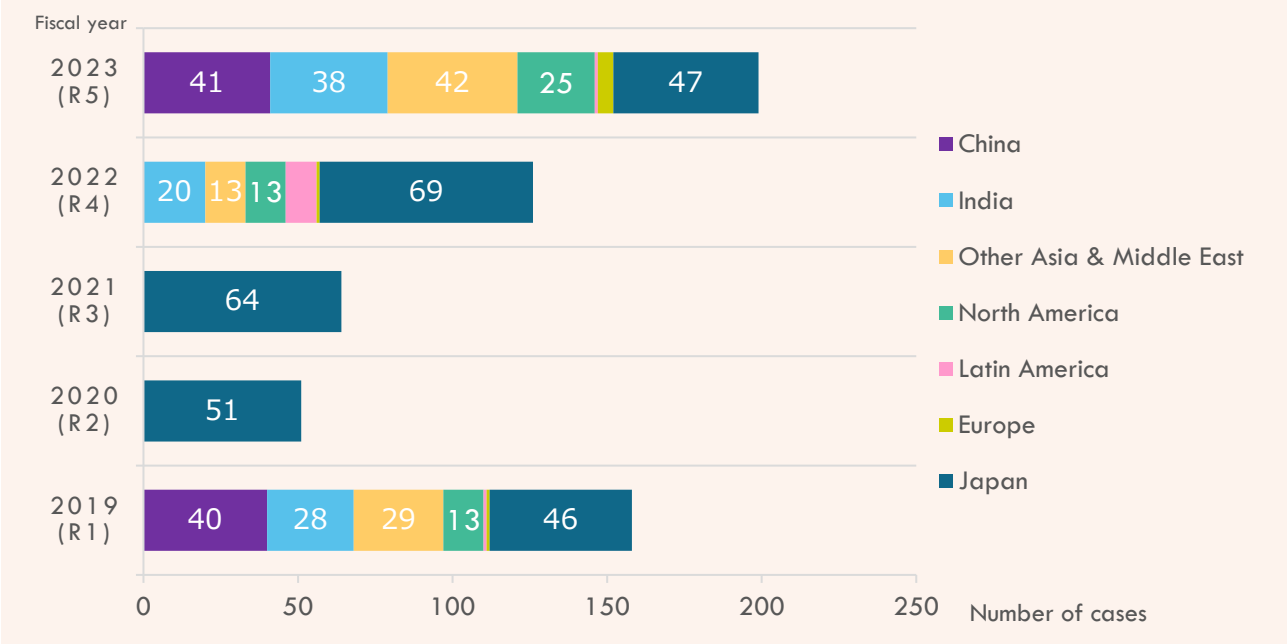
OMQD conducts a risk evaluation of the applied manufacturing site to be inspected and selects the inspection method (on-site inspection or desk-top inspection) based on the results. Key risk factors include:

- Inspection history (PMDA and overseas GMP authorities)
- Results of inspections (PMDA and overseas GMP authorities)
- Manufacturing method and quality characteristics of the product to be inspected
- Status of sharing of the manufacturing equipment to be inspected with other products, etc.

4-6 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 inspections based on applications for inspection and does not include the number of Ad-hoc on-site inspections (30 to 40 cases per year).



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 inspection in China were 41, which are equivalent to the level in FY 2019 before the pandemic of the new coronavirus. 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.

4-7 Issuance of deficiencies, etc.

4-7-1 Classification of deficiency identified

In order to deepen the understanding of the manufacturing sites, subject to inspection in the GMP 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 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, the inspectors review the contents of the deficiency again, classify into 3 level (Critical, Major, and Other) in accordance with the criteria for concluding GMP 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.

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*7.

- Critical

  Cases where an identified deficiency that does not comply with any provisions in the GMP 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 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 Ministerial Ordinance, however, that any rectification is needed for suitable manufacturing control or quality control.

*7 “Notification on the Enactment of the GMP Inspection Guide” PSB/CND Notification No. 0329-9 dated March 29, 2024, issued by the Director of Compliance and Narcotics Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare

4-7-2 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 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 inspection or within 30 business days after the issuance date of "Major deficiencies".

(1) Where identified "other deficiencies" only

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) Where identified "major deficiencies"

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) Where identified "critical deficiencies"

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 Ministry of Health, Labour and Welfare (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.

4-7-3 Trend in 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.

The profile of the identified deficiencies showed a similar tendency in both Japan and overseas.

In FY 2023, a significant proportion of the major or critical deficiencies pertained to deviation handling and validations. Deficiencies related to organizational management and quality management that increased in FY 2022 have decreased. The increase in deficiencies related to organizational management and quality management in FY 2022 can be attributed to the revision of the GMP Ministerial Ordinance, which clarified rules on organizational management such as management responsibilities. This led to increased opportunities for confirmation during on-site inspections. The decrease of such deficiencies is considered to be a result of the progress made by the manufacturing sites in compliance with the GMP Ministerial Ordinance.

Other deficiencies

	2019	2020	2021	2022	2023
1	Written production directions/records, procedures	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
2	Control of facilities and equipment	Control of facilities and equipment	Written production directions/records, procedures	Control of raw materials and intermediates	Control of raw materials and intermediates
3	Sanitation/hygiene control, utility	Test records, test procedures	Control of facilities and equipment	Document management	Control of facilities and equipment
4	Control of raw materials and intermediates	DI-related	Document management	Control of facilities and equipment	Document management
5	Cleaning, validations for cleaning	Validations	Test records, test procedures	Test records, test procedures	Deviation control
6	Sampling procedures for testing, management of samples	Deviation handling	Sanitation/hygiene control, utility Deviation handling	Sampling procedures for testing, management of samples	Sampling procedures for testing, management of samples
7	Document management	Sampling procedures for testing, management of samples	Sampling procedures for testing, management of samples	DI-related	Test records, test procedures
8	Prevention for contamination/mix-up of products	Document management	Validations	Control for laboratory reagents/solutions/reference standards	Change management
			DI-related	Sanitation/hygiene control, utility Deviation handling	Organizational management, quality management
9	Test records, test procedures	Sanitation/hygiene control, utility	Cleaning, validations for cleaning	Prevention for contamination/mix-up of products	Cleaning, validations for cleaning
	DI-related	Prevention for contamination/mix-up of products	Supplier control		
10	Validations	Control for laboratory reagents/solutions/reference standards	Handling of laboratory abnormalities, OOS, and OOT	Supplier control	Sanitation/hygiene control, utility

Major or Critical deficiencies

	2019	2020	2021	2022	2023
1	DI-related	Validations	Deviation handling	Organizational management, quality management	Deviation handling
2	Validations Written production directions/records, procedures	Deviation handling	DI-related	Validations Supplier control	Validations
3	Cleaning, validations for cleaning	Test records, test procedures	Test records, test procedures	Document management	DI-related Document management
		Handling of laboratory abnormalities, OOS, and OOT	Sterility assurance	DI-related	Handling of laboratory abnormalities, OOS, and OOT Supplier control Organizational management, quality management
4	Test records, test procedures	Organizational management, quality management Control of facilities and equipment	Other 5 items	Sterility assurance Reviews of product quality	Other 8 items
5	Deviation handling Document management	Other 6 items		Other 5 items	

5. Risk communication services

5-1 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.

An overview of the FY 2023 GMP roundtable meeting is as follows. Based on feedback from the survey conducted after the 1st GMP roundtable meeting, the 2nd meeting was held in Osaka, and the 3rd meeting was held simultaneously in 2 locations: Tokyo and Toyama. More than 95% of the participants in the 2nd and the 3rd meetings said the group discussion was beneficial, indicating that the meetings were highly effective in addressing challenges faced by the pharmaceutical manufacturers.

PMDA plans to continue hosting GMP roundtable meetings from FY 2024 onward as a platform for exchanging opinions with manufacturers.

[The 2nd GMP roundtable meeting]

Date: Thursday; November 2, 2023
Place: HALL-A, 3F, Sunrise Bldg. Osaka
Participants: 102
(web participants: 480 accounts)
Theme: Use of preceding/tailgate sample in acceptance test

[The 3rd GMP roundtable meeting]

Date: Friday; February 16, 2024
Place: Nihonbashi Life Science Hub (Tokyo venue)
Pearl Room, Wohlfahrt Toyama (Toyama venue)
Participants: 84 in Tokyo venue, 36 in Toyama venue
(web participants: 575)
Theme: Appropriate preparation of manufacturing records, management and transfer of knowledge about manufacturing technology

The 2nd GMP roundtable meeting (upper, Osaka venue)
The 3rd GMP roundtable meeting (lower left, Tokyo venue; lower right, Toyama venue)

5-2 Rapid Announcement of Observed Deficiencies (ORANGE Letter)

As part of risk communication activities with pharmaceutical manufacturers, OMQD has been publishing on the PMDA website 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
8	June 2023	Environmental monitoring in aseptic processing areas*
9	July 2023	Handling of stability monitoring results*
10	October 2023	Communication within the organization (from the manufacturing site to the management)*
11	October 2023	Communication within the organization (from the management to the manufacturing site)*
12	January 2024	Risk-based validation planning*
13	March 2024	Handling of products rejected for use or release*

* https://www.pmda.go.jp/english/review-services/gmp-qms-gctp/0007.html
Note that No. 10～13 are only Japanese version. English versions are under preparation.

5-3 List of Identified Deficiencies

PMDA has been striving to support voluntary improvement activities at manufacturing sites by widely sharing the information on drug quality through ORANGE Letters, GMP roundtable meetings, and GMP/GCTP Annual Reports. In the course of the activities, PMDA has received requests to disclose additional information related to drug quality. PMDA held discussion with various stakeholders, including the Quality Committee of the Federation of Pharmaceutical Manufacturers’ Association of Japan, regarding the benefits of disclosing deficiencies identified during PMDA’s GMP inspections on its website. PMDA concluded that disclosing identified deficiencies would effectively promote self inspection at the manufacturing sites.

The list of major deficiencies identified in PMDA’s GMP inspections in 2023 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

6. GMP training support

OMQD established the Division of GMP Inspection Training and started the operation of training support programs for prefectural officials in FY 2022 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 announce on 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's instructors to mock inspections sponsored by prefectural governments

The implementation status of support operations in FY 2023 is as follows:

1 Support for on-site inspection

Accept observers in PMDA's GMP inspection
11 cases (10 Japanese cases, 1 overseas case)

Conduct PMDA-prefectural governments joint GMP inspection
20 cases

Dispatch of PMDA inspector to prefectural government GMP inspection
2 cases

2 Provision of PMDA training materials, etc.

GMP training for beginners
April: 120 participants

PMDA's specialized training
July (1st) : 36 participants
October (2nd) : 17 participants
March (3rd) : 45 participants

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

3 Seminars, etc.

External instructor's lecture
October (DI training): 63 participants

GMP roundtable meeting
November (1st): 20 participants
February (2nd): 23 participants

4 Dispatch of instructors / Consultations

Dispatch of instructors to training sessions and mock inspections sponsored by prefectural governments: 22
Consultation on inquiry regarding GMP inspections conducted by prefectural governments: 3
Sharing PMDA inspection reports: 29 (The status represents the period from December 2023 to March 2024 because this project began in December 2023)

7. Consultation services

7-1 Simple consultation

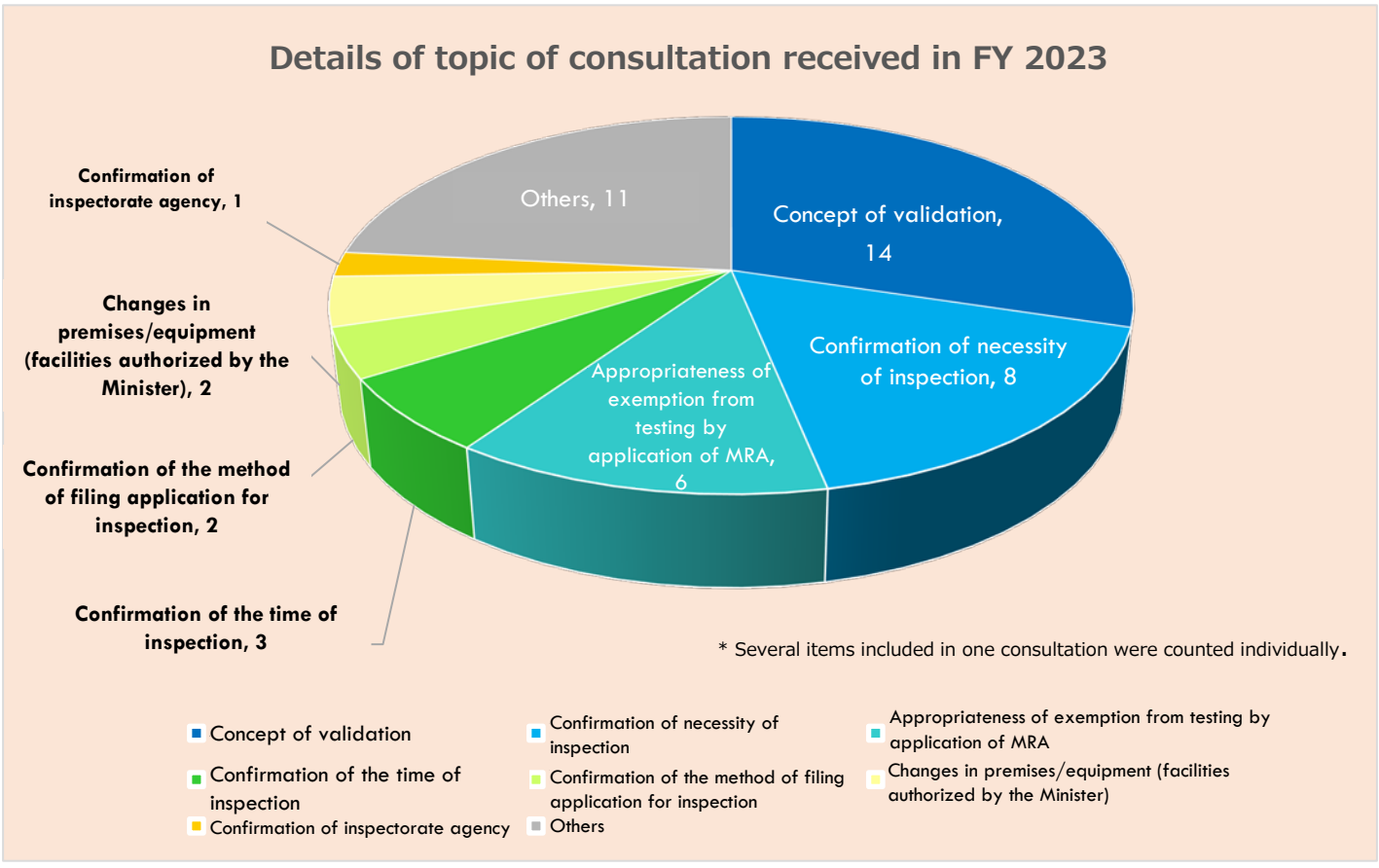
OMQD is in charge of consultations related to GMP and GCTP inspections among Simple consultations based on “Implementation Guideline, for Face-to-Face Consultations and Examinations Confirm Certification Conducted by Pharmaceuticals and Medical Devices Agency" (PFSB/ELD/OMDE Notification No. 0302070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

The numbers of receipt and meetings of Simple consultations related to GMP and GCTP inspections in the past 3 years are shown below.

Fiscal year	Number of receipt[1]	Number of meetings[2]
2021	46	20
2022	43	20
2023	42	13

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

The most frequent topic of consultation is the “Concept of validation," which includes consultation on acceptance of concurrent validation and grouping of products with different concentration (or content) or volume. Consultation on the appropriateness of each process validation is outside the scope of Simple consultation because it needs to be confirmed in GMP inspections.



7-2 Other consultations

The outlines and results of various consultations other than “Simple consultations” in FY 2023 are as follows.

Number of consultations in FY 2023

* The number of consultations completed in FY 2023 was tabulated

1 case	0 case	1 Case	0 case
(1) Consultation on PACMP	(2) Consultation on SAKIGAKE overall evaluation	(3) Consultation on innovative manufacturing technology for drugs	(4) Consultation on conformity assessments of reliability criteria

(1) Consultation on PACMP

OMQD is in charge of quality and GMP consultations for applicants who seek to utilize the Post-Approval Change Management Protocol (PACMP). Based on the revised Pharmaceutical and Medical Device Act enforced in 2021, the PACMP consultation system was terminated, and a new system for the application of PACMP confirmation was started.

(2) Consultation on SAKIGAKE 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.

No application was made for consultation on the SAKIGAKE overall evaluation (GMP/GCTP) in FY 2023. One consultation applied before FY 2023 regarding the SAKIGAKE overall evaluation (GCTP) is ongoing.

(3) Consultation on innovative manufacturing technology for drugs

Consultation on innovative manufacturing technology for drugs is conducted for formulation of development strategy 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 made, and OMQD is 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.

One consultation was concluded in FY 2023.

(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.

No application for consultation on conformity assessments of reliability criteria was received in FY 2023.

8. International activities

8-1 Cooperation with overseas regulatory authorities and international organizations

(1) Importance of International Activities

The pharmaceutical supply chain is becoming increasingly complex, with manufacturing sites producing drugs for Japan located across the globe. It is extremely challenging for individual regulatory authority to conduct on-site inspections at all these sites.

PMDA actively collects inspection information from overseas regulatory authorities and conducts high-precision risk assessments of manufacturing sites. This allows us concentrate GMP resources on high-risk manufacturing sites.

To utilizing the inspection information from overseas regulatory authorities, it is essential that GMP standards and inspection capabilities of these authorities are standardized. Therefore, we actively participate in activities related to the international harmonization of GMP standards under PIC/S, thereby strengthening cooperative relationships with overseas authorities.

(2) PIC/S activities

PIC/S is an international organization aimed at harmonizing GMP standards and enhancing the skills of inspectors. Japan's GMP regulatory authorities (PMDA, MHLW, and 47 prefectural governments) joined PIC/S in 2014 and have since engaged in international activities centered around PIC/S. The main activities include the following:

1) Participation in PIC/S Executive Bureau

PIC/S operates under the General Assembly, its highest decision-making body, with six subcommittees. An PMDA's officer has been elected as chair of the Sub-committee of Communication (SC COM) and serves as a member of the Executive Bureau (EB) (term: January 2022 to December 2025). This subcommittee focuses on promoting collaboration among PIC/S member authorities and other organizations, playing a key role in information sharing and public relations within and outside of PIC/S.

2) Participation in PIC/S Sub-Committee

In addition to SC COM, we also participate in Subcommittee on Training (SCT). Activities include reviewing PIC/S educational materials, organizing PIC/S seminars, and conducting Expert Circle meetings.

3) PIC/S Seminar

The annual PIC/S seminar is a major training event attended by nearly all member authorities. Since joining in 2014, we have continuously participated in these seminars, both as attendees and lectures. In 2019, we hosted a seminar in Toyama, focusing on aseptic processing, significantly contributing to the training of PIC/S member authority personnel.

4) Secondment to PIC/S Secretariat

On April 1, 2024, we dispatched a specialist from OMQD to the PIC/S Secretariat in Geneva, Switzerland, for a two-year term. The specialist is responsible for activities related to the harmonization of GMP standards and the training of GMP inspectors among member authorities.

5) PIC/S Expert Circle

PIC/S Expert Circle is group dedicated to promoting specialized training in specific technical fields. Activities include organizing an Expert Circle meeting and developing training materials. We hosted the Expert Circle meeting on Quality Risk Management (QRM) in Tokyo in 2014. Recently, we have been actively involved in the following activities:

- Control of Cross-Contamination in Shared Facilities (CCCISF)
  Updating the Aide Memoire on Cross-Contamination in Shared Facilities (PIC/S Document PI 043-1)
- Human Blood, Tissues, Cells & ATMPs
  Participating in training on PIC/S GMP Guide Annex 2A hosted by Italy (AIFA) and Austria (AGES) from March 14 to 16, 2023
- PIC/S Expert Circle on Human Blood, Tissues, Cells & ATMPs hosted by Malaysia (NPRA) from August 20 to 22, 2024

6) Information sharing with PIC/S Participating Authorities (April 2023 to March 2024)

We provided information such as GMP inspection reports and deficiencies to the following overseas authorities:

A total of 22 cases to European Medicines Agency (EMA), Singapore (HSA), European Directorate for the Quality of Medicines & Healthcare (EDQM), South Korea (MFDS), Canada (Health Canada), Brazil (ANVISA), and WHO

Additionally, we also received information such as GMP inspection reports and deficiencies from the following overseas authorities:

A total of 20 cases from the US (US FDA), Argentina (ANMAT), EDQM, MFDS, Germany (BfArM) , Hungary (NIPN), Singapore (HSA), and Taiwan (TFDA)

7) Observed inspection (April 2023 to March 2024)

The number of GMP inspections conducted by PMDA with the observing of overseas regulatory authority inspector is as follows:

5 cases in MFDS, 10 cases in TFDA, 2 cases in HSA, and 1 case in South Africa (SAHPRA).

Additionally, the number of GMP inspections conducted by overseas authorities with observing of PMDA's inspector is as follows:

2 cases in US FDA, 1 case in TFDA, 1 case in MFDS

8-2 Other International Activities

(1) Educational Support for Overseas Regulatory Authorities (particularly Asian region)

1) PMDA-ATC GMP Seminar

The Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC) provides training for regulatory authorities, utilizing PMDA's accumulated knowledge and experience. These seminars are conducted with the support of PIC/S and include lectures on regulatory requirements for manufacturing and quality control, as well as mock inspections conducted in collaboration with actual manufacturing sites.

The latest seminar information is as follows:

- PMDA-ATC GMP Inspection Webinar 2023 (February 6 to 7, 2024)
- PMDA-ATC GMP Inspection Seminar 2024 (October 8-10, 2024)

2) PIC/S training event

We actively participate in PIC/S seminar. In FY2023, we delivered lectures at the PIC/S Seminar 2023 held in Bangkok.

(2) API Program

The API Program, an initiative to streamline international GMP inspections of active pharmaceutical ingredient (API) manufactures, has been ongoing since 2012, with PMDA joining in 2016. Currently, 13 authorities participate in the program, including AIFA (Italy), ANSM (France), ANVISA (Brazil), DKMA (Denmark), US FDA (USA), Health Canada (Canada), HPRA (Ireland), MHRA (United Kingdom), TGA (Australia), EDQM, EMA, WHO, PMDA.

The program maintains a shared database (Master List) of GMP inspection information, which is regularly updated and enables authorities to efficiently plan inspections and share results in a timely manner. Under confidentiality agreements, participating authorities can access and utilize GMP inspection plans and results, fostering mutual trust among organizations and contributing to the verification of each authority's GMP inspection capabilities. PMDA leverages this data to identify key issues in advance, streamline the scope of inspections, and improve the efficiency and quality of GMP inspections, including planning joint inspections with other authorities.

(3) GMP/GDP Inspectors Working Group Meeting

GMP/GDP Inspectors Working Group (GMP/GDP IWG), a group organized around EU countries and their MRA partner countries, holds meetings quarterly for the purpose of sharing information among participating countries. We participate as an observer based on Japan-EU MRA, acquiring the latest regulatory updates from the EU, and promoting awareness of Japan's regulations.

(4) Joint Inspection

In October 2023, we conducted the joint inspection with EDQM. Joint inspection allows regulatory authorities to share methodologies and best practices, thereby improving reliance on inspection results. It also reduces the burden on manufactures by avoiding redundant inspections. We plan to continue promoting a joint inspection.

9. Future vision

The report of the "Expert Panel on Comprehensive Measures to Achieve Rapid and Stable Supply of Pharmaceuticals" (June 9, 2023) highlights the critical public health issues of essential drugs failing to reach the public. This issue is considered to have been brought to light not only due to individual factors, such as corporate scandals and a declining development capabilities, but also to systemic and environmental challenges within Japan's pharmaceutical industry, as well as broader issues affecting the industry as a whole stemming from these factors. The importance of stakeholders collaborating to reform the current environment has been reaffirmed, and various discussions focused on improvement are ongoing.

The report of the "Debate toward Establishing an Industrial Structure that Ensures Stable Generic Supplies" (May 22, 2024) suggests that corporate information related to stable drug supply, such as manufacturing capacity, production plans, and production output should be made transparent (disclosed) to serve as a basis for discussion on optimal drug pricing. It also suggests that this measure will enable manufacturers capable of ensuring a stable supply of quality-assured generic drugs to gain recognition and achieve a competitive advantages in the market.

Additionally, it also states, "all manufacturers should have a system for manufacturing and quality control in place (ensuring a manufacturing and quality control system)", as the first of three conditions for how the generic drug industry should be. It also states that reinforcement of the manufacturing and quality control system is essential to restore reliability of generic drugs and prevent the recurrence of uncertain supply.

The GMP compliance status of the manufacturing site is information on manufacturing and quality control that forms a foundation for stable supply-related information (e.g., manufacturing capacity, production plan, production output). In addition to the corporate information released by the manufacturer (e.g., manufacturing capability, production plan, production output), for example, new values will be added to the information on the drug quality if PMDA visualizes the information on the GMP compliance status. There are various arguments over what information should be presented as a GMP compliance status. Wide publication of information on the characteristics of individual manufacturing sites, for example, having a robust pharmaceutical quality system, an optimal for aseptic operation and so forth, may become a new tool to show the manufacturer's commitment to stable supply. Showing the manufacturers' commitment to appropriate manufacturing and quality control to ensure quality to the public and healthcare professionals through such visualization of corporate information may lead to cultivation of trust in the stable drug supply.

PMDA will continue to build a vision of future risk communication activities, looking ahead to various impacts of visualization of corporate information and publication of drug quality information on the pharmaceutical industry in Japan and expected outcomes.

The GMP/GCTP Annual Report FY 2023 presents the major deficiencies reported in the GMP inspections issued by PMDA in a list. PMDA is considering to continue providing a wide range of knowledge to the public according to their needs.

PMDA has accumulated extensive knowledge through past operations, including GMP inspections of domestic and overseas drug manufacturing sites. By initiating risk communication activities to share this knowledge with society, while ensuring that the intellectual property rights of manufacturers are not infringed, PMDA aims to enhance synergy with efforts to improve quality through GMP inspections. This initiative also represents a new approach to utilizing PMDA's knowledge as part of its technical support for drug manufacturing sites.

On the other hand, any recurrence of a critical deficiency at a manufacturing site due to insufficient GMP control needs to be widely publicized as soon as possible once it is determined no appropriate improvement for risk reduction is expected. It will be necessary to discuss with MHLW and the prefectural governments about the implementation of the Japanese version of the Warning Letter system to publish the names of specific manufacturers, manufacturing sites, and products with quality risks.

As above, the various risk communication activities performed by PMDA are part of the efforts to "ensure stable supply of quality-assured drugs" in Japan. In the global trends in the GMP area, various changes and needs are occurring every day. PMDA will keep track of the changes without delay and continue to improve its operations to protect the lives and health of Japanese people by ensuring the quality of drugs.

PMDA GMP / GCTP Annual Report FY 2023

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