Pharmaceuticals and Medical Devices Agency

GMP / GCTP Annual Report

FY 2022

Office of Manufacturing Quality for Drugs

30 November 2023

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Introduction

Statement from Chief Executive

<Message from PMDA>

As a physician, I have been repeatedly struggling with the anxiety over the shortage of drugs that resulted from GMP deficiencies. Providing appropriate medical care to patients can only be achieved when quality assurance and a stable supply to the market by a drug manufacturing site. To this end, we believe that all parties involved in, including pharmaceutical companies and regulatory authorities, need to be aware of their social responsibilities.

In addition to GMP inspection, which is the pillar of GMP monitoring and guidance, PMDA started risk communication initiatives to widely disclose information related to quality of drugs and provide new values to "quality." The initiatives related to risk communication are composed of the following four elements.

1) ORANGE Letter : Publication of observed deficiencies in GMP inspection
2) Information related to drug quality : Announcement of quality-related information including the rating of the drug manufacturing site based on the results from the GMP inspection (under development)
3) GMP Roundtable Meeting : Dialogue between industry, regulatory authorities and academia
4) GMP/GCTP Annual Report : Publication of the performance of PMDA Office of Manufacturing Quality for Drugs

On the occasion of the issuance of the GMP/GCTP Annual Report FY2022, my expectation is that the transparency of the Japanese GMP regulations operated by PMDA will be secured through risk communication, and a quality culture will be fostered so that "Manufacturing sites that stably manufacture and supply good products will be highly evaluated." On the other hand, PMDA may receive opinions related to GMP inspection methods by releasing various information. PMDA will sincerely accept such opinions for continuous improvement.

PMDA will actively promote risk communication efforts so that the Japanese pharmaceutical market and GMP regulations can be perceived as attractive by global market. In addition, we will contribute to ensuring the quality and stable supply of drugs distributed to the market in cooperation with not only Japanese but also global pharmaceutical companies.

November 30, 2023
Chief Executive, Pharmaceuticals and Medical Devices Agency
Yasuhiro FUJIWARA, M.D., Ph.D.

1. Annual Report

PMDA releases*1 the number of GMP inspections (on-site inspections) as the accomplishment for each fiscal year in the GMP field.

The Office of Manufacturing Quality for Drugs (OMQD), PMDA summarizes the Business accomplishment related to GMP inspection, regulatory system, international activities, current issues, future vision, etc., to issue a GMP/GCTP Annual Report. OMQD will make efforts to ensure transparency of regulations and mutual trust between PMDA and companies by proactively providing information on drug quality control. In addition, by preparing the English version, we will collect critiques and advice from overseas through provision of information to pharmaceutical companies, drug manufacturing sites, and regulatory authorities, leading to further strengthening of the operations of OMQD.

*1 https://www.pmda.go.jp/about-pmda/annual-reports/0001.html

2. About us (PMDA)

2-1 About PMDA

The objective of PMDA is to contribute to improvement of public health by providing prompt relief services to patients suffering from adverse health effects caused by adverse drug reactions and infections acquired through biological products (Relief for Adverse Health Effects), providing guidance and reviews regarding the quality, efficacy, and safety of drugs, medical devices, and gene, cellular and tissue-based products through a system that is consistent from pre-clinical research to approval (Approval Review), and collecting, analyzing, and providing post-marketing safety information (Safety Measures).*2

*2 https://www.pmda.go.jp/files/000219906.pdf

2-2 Mission of Office of Manufacturing Quality for Drugs

Mission of OMQD is to conduct its operations with timely decision under the high transparency aiming for 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 for appropriate and effective GMP/GCTP inspections, including the development of quality policies. In addition, the Head of inspectorate (Chief Executive of PMDA) is to conduct management reviews to appropriately maintain the Quality Management System, to improve problems that occur, and to evaluate 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 time of the period (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

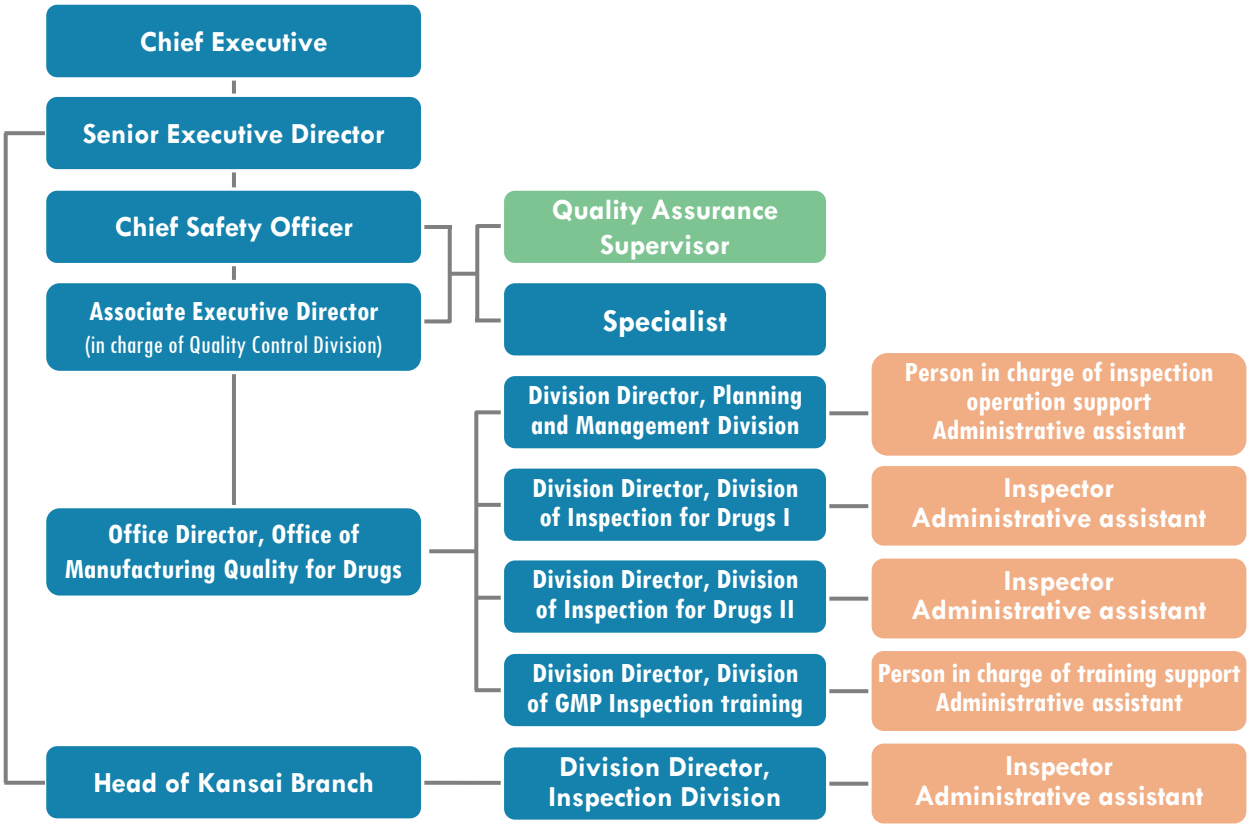
The Office of Manufacturing Quality for Drugs (OMQD) consists of the following 4 divisions (as of March 31, 2023).

- 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 GMP authorities in overseas

In addition to the above, a Division of Inspection has been established at the Kansai Branch and is in charge of GMP inspections in overseas and Japan (mainly Western Japan) in cooperation with OMQD.

Additionally, for the purpose of cooperating with the review divisions of PMDA, the Inspection Director is allocated under Office Director, and for the purpose of reporting 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 monitoring of 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 staffs come from the private sector with experience in manufacturing pharmaceutical products and provide education and support to other inspectors and prefectural government inspectors. For staffs come from the private sector, it is periodically checked through internal audits, etc., that they comply with the PMDA's rules for Conflict of Interests.



2-5 Conflict of Interests

Staffs 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 the duties at the former private sector, they must not be engaged in the duties related to drugs, etc., of the 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 the 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.

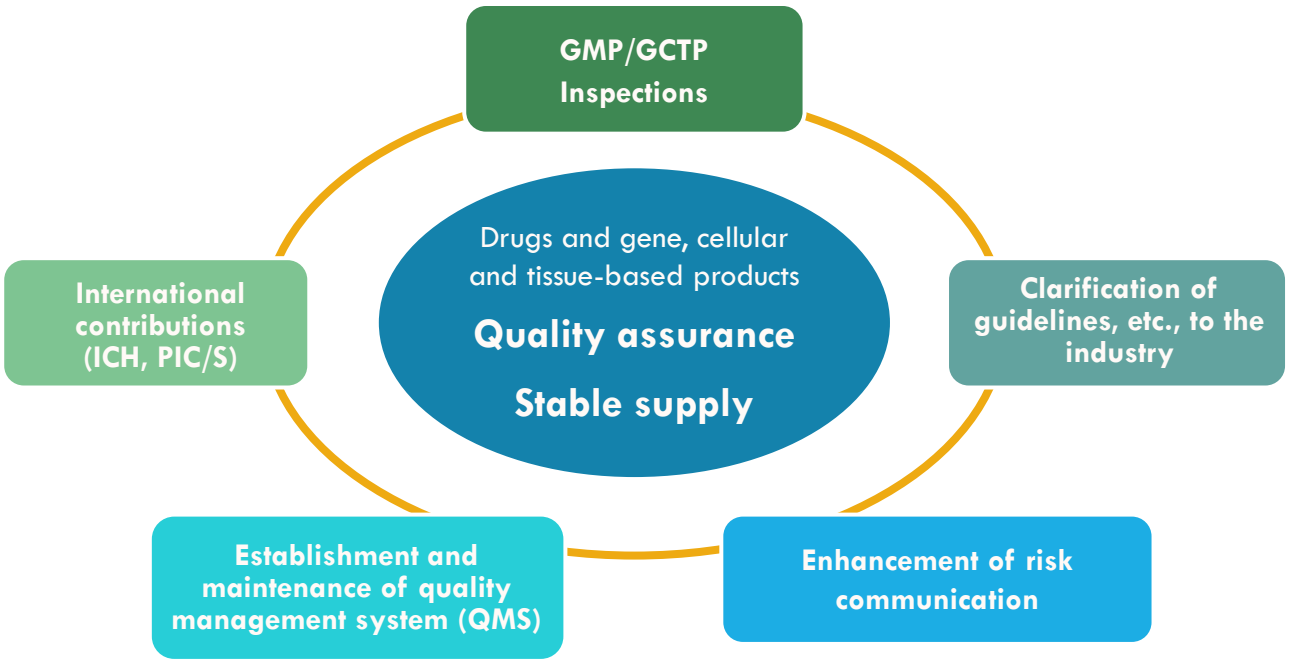
2-6 Operations of the Office of Manufacturing Quality for Drugs

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 "5. Implementation status of inspection operations.")

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 2022

Main achievements of Office of Manufacturing Quality for Drugs in FY 2022 are as follows:

115 cases
On-site GMP inspection

1,845 cases
Desk-top GMP inspection

614 cases
Facility inspection

48 cases
Ad-hoc on-site inspection

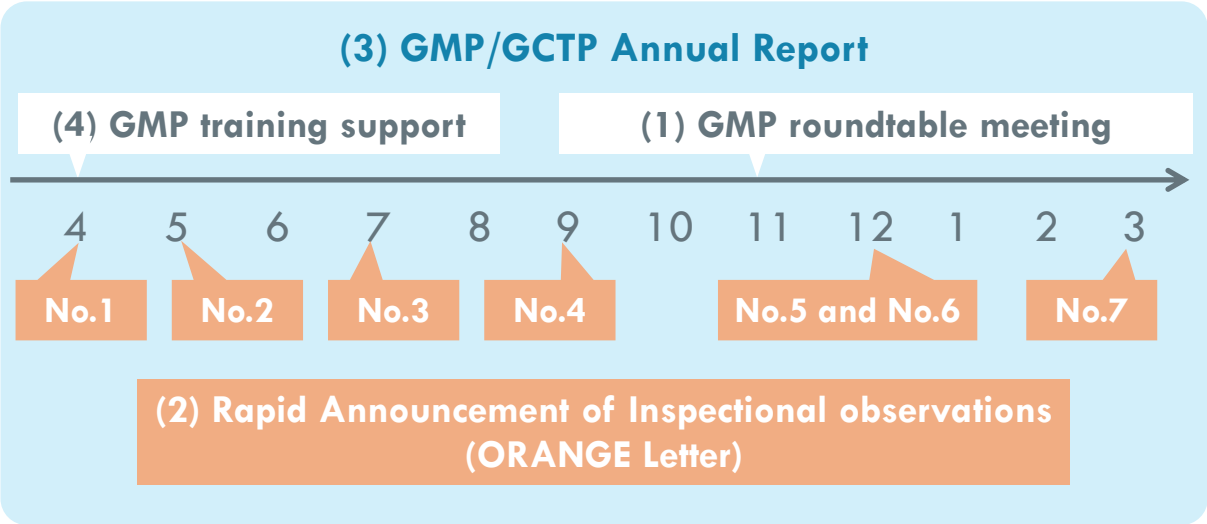
23 cases
Company consultation

4 cases
New project

7 cases
ORANGE Letter

1 case
GMP roundtable meeting

OMQD started 4 new projects in FY 2022 as an effort to ensure quality of drugs.
Chapter 4 provides details of inspection results, and Chapter 5 provides an overview of new projects.

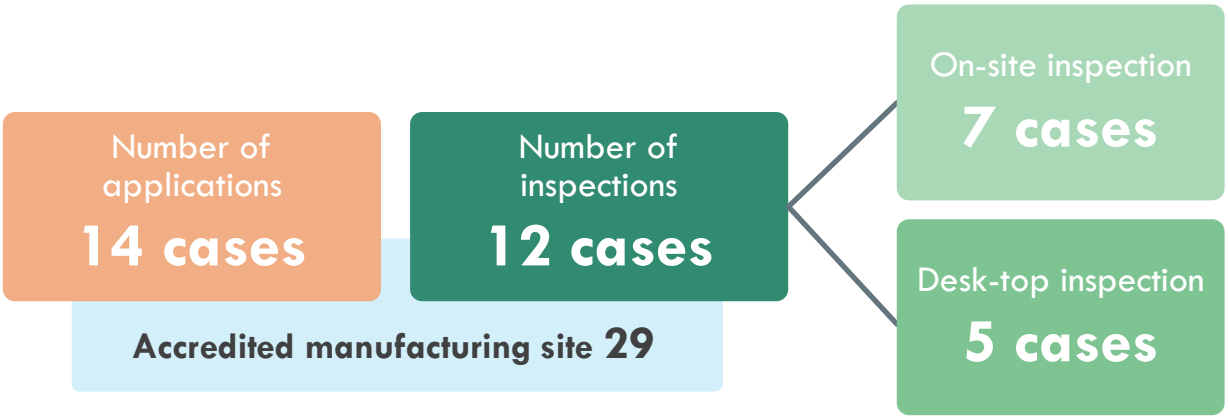


4. Inspection results, etc.

4-1 Inspection implementation status (in FY 2022)

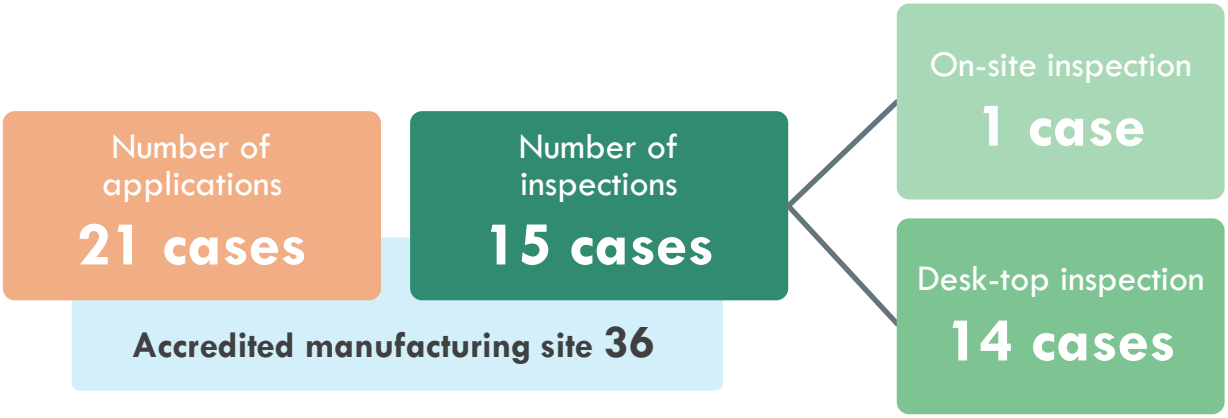
4-1-1 GMP inspection (manufacturing sites for drugs (domestic))

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))



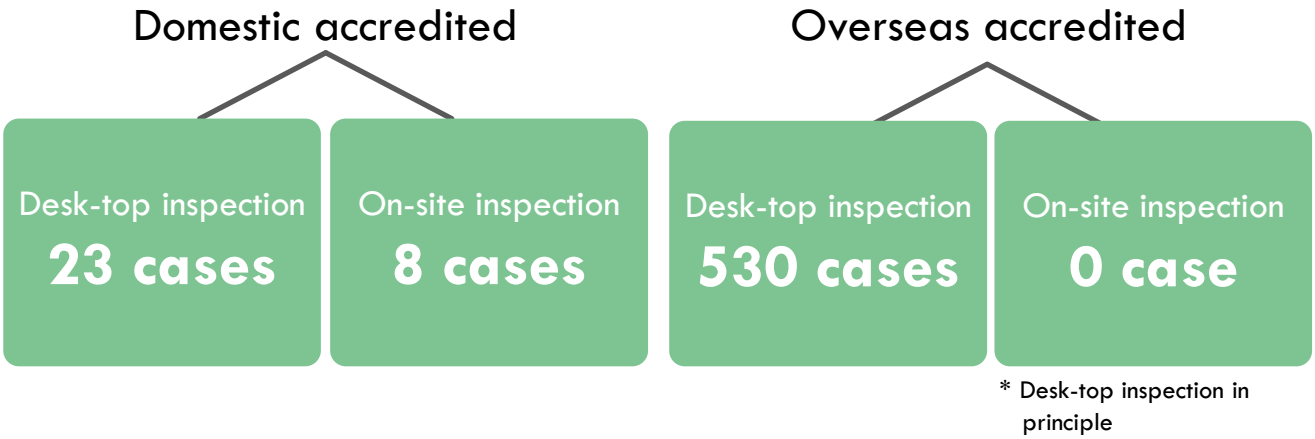
4-1-5 Number of inspections not based on applications (Ad-hoc on-site inspections) and other inspections conducted (on-site)

Ad-hoc on-site inspection (Domestic)	Ad-hoc on-site inspection (Overseas)	Product category-based inspection
47 cases	**1 case**	**3 cases**

* Included in the above number of Compliance Inspection

Inspection in relation to change management protocol	GMP inspection of investigational drugs
0 case	**5 cases**

4-1-6 Facility inspection



* Desk-top inspection in principle

The results of inspection in FY 2022 and the calculation method of each value are as follows.

- Number of applications : Number of applications accepted in FY 2022
- Number of inspections (on-site inspection) : Number of on-site inspections conducted in FY 2022
- Number of inspections (desk-top inspection (document-based inspection))
  : Number of inspections completed in FY 2022
  If a separate inspection was conducted at the same facility, each inspection was counted.
- Accredited manufacturing sites : Number of accredited manufacturing sites (as of March 31, 2022)
  Some manufacturing sites have multiple accredited categories (general, packaging/labeling/storage).

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. Inspections not based on applications (Ad-hoc on-site inspection), etc., are classified into (1) surveillance inspections which are based on the risk analysis and (2) for case inspections depending on the purpose, etc. 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
   Special inspection, such as an inspection on 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 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 conforming 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).

A lead inspector is certified by the qualified persons of OMQDs based on their expertise and experience in each field among persons qualified as regular inspectors.

A senior inspector is certified by the qualified persons of OMQD after their ability as an educator to inspectors is assessed among persons 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" PSEHB/CND Notification No. 0317-5 dated March 17, 2022, issued by the Director of Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health 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 administrative works 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

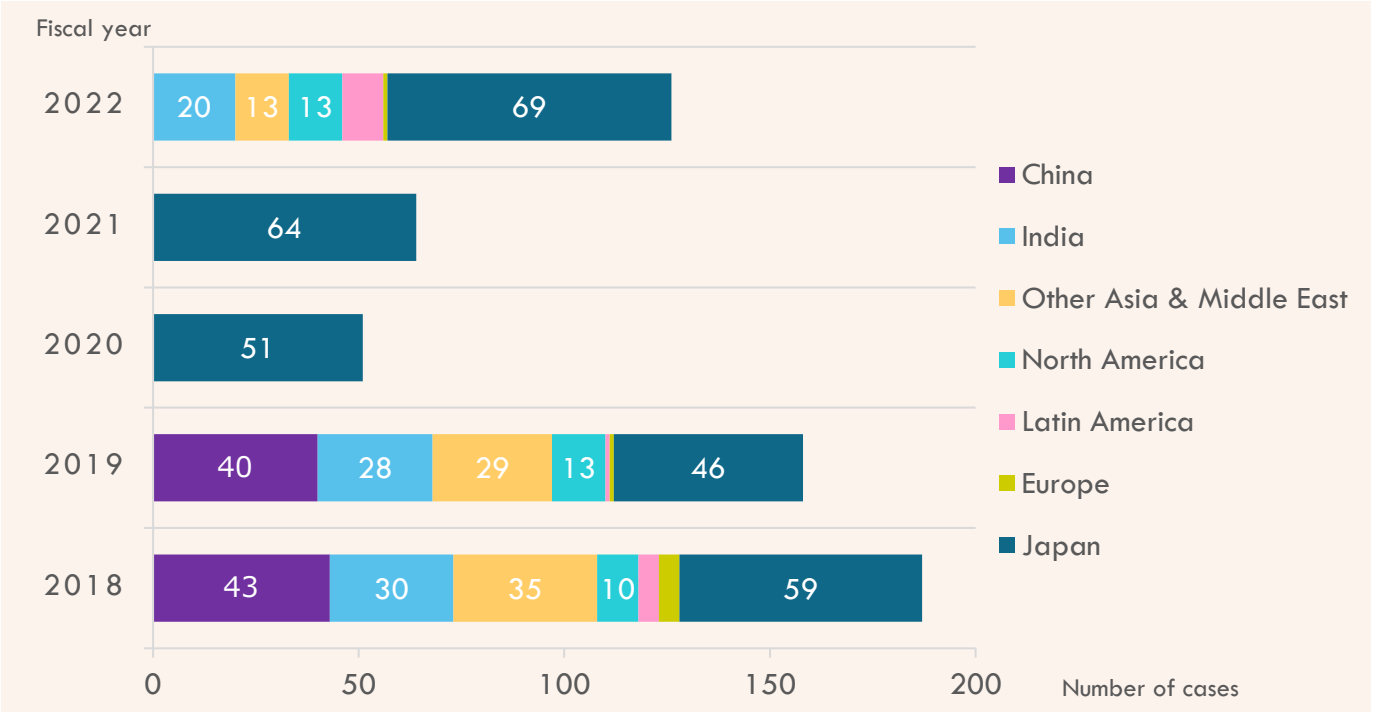
OMQD conducts a risk evaluation of the applied manufacturing site to be inspected and selects the inspection method (on-site inspection or desk-top inspection) based on the results. Key risk factors include:

- 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 are limited to GMP inspections based on applications for inspection and do 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, OMQD conducted inspections only to Japanese manufacturing sites in FY 2020 and FY 2021.

In FY 2022, OMQD resumed on-site inspections in countries/regions where travel restrictions were relaxed.

OMQD conducted GMP inspections as follows: In North America, for US (10), Puerto Rico (2) and Canada (1) sites, in Latin America, Mexico (3) and Argentina (2) sites, in Asia and Middle East excluding India and China, Korea (5), Vietnam (3), Chinese Taipei (2), Singapore (2) and Israel (1) sites, and in Europe, Austria (1) and Italy (1) sites (sites not covered by MRA).

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 summarize 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 inspector review the contents of the deficiency again, classify the deficiencies (deficiencies and their categories, and oral instructions) in accordance with the criteria for concluding GMP conformity, prepare the notice for deficiencies during the GMP inspection, 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" PSEHB/CND Notification No. 0317-5 dated March 17, 2022, issued by the Director of Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health 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 Status of issuance of deficiencies identified

Deficiencies identified issued by PMDA are classified according to their contents and aggregated for each fiscal year. The rankings of frequency of issuance of other deficiencies and major or critical deficiencies are as follows. The contents of the deficiencies identified showed a similar tendency in both Japan and overseas.

Regarding the major or critical deficiencies, deficiencies in organizational management and quality management were increased in FY 2022. This may be because, in the revision of the GMP Ministerial Ordinance in 2021, rules on organizational management such as responsibilities of management and legal compliance system and quality management were clarified, leading to increased opportunities for confirmation and increased cases of deficiency clearly determined to be a violation of the GMP Ministerial Ordinance.

Other deficiencies

	2018	2019	2020	2021	2022
1	Written production directions/records, procedures	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
2	Control of facilities and equipment	Control of facilities and equipment	Control of facilities and equipment	Written production directions/records, procedures	Control of raw materials and intermediates
3	Control of raw materials and intermediates	Sanitation/hygiene control, utility	Test records, test procedures	Control of facilities and equipment	Document management
4	Sampling procedures for testing, management of samples	Control of raw materials and intermediates	DI-related	Document management	Control of facilities and equipment
5	Test records, test procedures	Cleaning, validations for cleaning	Validations	Test records, test procedures	Test records, test procedures
6	Sanitation/hygiene control, utility	Sampling procedures for testing, management of samples	Deviation handling	Sanitation/hygiene control, utility Deviation handling	Sampling procedures for testing, management of samples
7	Document management	Document management	Sampling procedures for testing, management of samples	Sampling procedures for testing, management of samples	DI-related
8	Cleaning, validations for cleaning	Prevention for contamination/ mix-up of products	Document management	Validations DI-related	Control for laboratory reagents/solutions/ reference standards Sanitation/hygiene control, utility Deviation handling
9	Prevention for contamination/ mix-up of products	Test records, test procedures DI-related	Sanitation/hygiene control, utility Prevention for contamination/ mix-up of products	Cleaning, validations for cleaning Supplier control	Prevention for contamination/ mix-up of products
10	DI-related Reviews of product quality	Validations	Control for laboratory reagents/solutions/ reference standards	Handling of laboratory abnormalities, OOS, and OOT	Supplier control

Major or Critical deficiencies

	2018	2019	2020	2021	2022
1	Deviation handling	DI-related	Validations	Deviation handling	Organizational management, quality management
2	DI-related Cleaning, validations for cleaning	Validations Written production directions/records, procedures	Deviation handling	DI-related	Validations Supplier control
3	Change management	Cleaning, validations for cleaning	Test records, test procedures Handling of laboratory abnormalities, OOS, and OOT	Test records, test procedures Sterility assurance	Document management DI-related
4	Control of facilities and equipment	Test records, test procedures	Organizational management, quality management Control of facilities and equipment	Other 5 items	Sterility assurance Reviews of product quality
5	Handling of laboratory abnormalities, OOS, and OOT	Deviation handling Document management	Other 6 items		Other 5 items

5. Outline of new projects in FY 2022

5-1 GMP roundtable meeting

Regarding issues related to manufacturing control/quality control, the opportunity for PMDA and employees of manufacturing sites to individually communicate was limited during the GMP inspections (on-site inspection). The objective of the GMP inspections is to confirm whether the methods of manufacturing control, etc., at the manufacturing site comply with the GMP Ministerial Ordinance. During the GMP inspections (on-site inspection), the time for the PMDA and the manufacturing site to make communications about various problems that occur in daily GMP activities is limited.

Based on these issues, PMDA held a GMP roundtable meeting for solving issues and exchanging opinions among related parties, including pharmaceutical companies, regulatory authorities, and academia, to ensure the quality of drugs.

The outline of the 1st GMP roundtable meeting is as follows. In FY 2023 and thereafter, we plan to continue efforts to solve issues, discussion themes gathered through questionnaires.

Date	: November 2, 2022
Location	: Nadao Hall
Participants	: Approximately 70 (approximately 280 Web participants)
Theme	: Deviation control, stability monitoring

Photo: 1st GMP roundtable meeting

5-2 Rapid announcement of Inspectional observations (ORANGE Letter)

OMQD has presented at lecture meetings the summary and estimates of deficiencies identified which have a large impact on the product quality found in GMP inspections (on-site inspections), and matters for which it was considered beneficial to widely promote awareness.

As part of risk communication activities, in addition to the conventional approach, OMQB has started to post "Rapid announcement of Inspectional observations (ORANGE Letter: Observed Regulatory Attention/Notification of GMP Elements Letter; hereinafter referred to as the "ORANGE Letter") since FY 2022 for which prompt dissemination to the industry would be particularly useful on the PMDA website.

The ORANGE Letter is to be used as a reminder and technical reference to promote voluntary improvement at the drug manufacturing site. Therefore, the deficiencies identified is posted after deleting information that may infringe on intellectual property of a specific company.

A list of ORANGE Letters issued by March 31, 2023 is as follows.

No.	Date of issuance	Title
1	April 2022	Failure to confirm adequacy of raw materials*
2	May 2022	Risks associated with handling substances with unknown pharmacological activities and toxicities*
3	July 2022	Overlooked risks to the quality of products due to insufficient CAPA*
4	September 2022	Importance of thorough management of outsourced activities*
5	December 2022	Improper recording*
6	December 2022	Improper modification of records to align with Instructions*
7	March 2023	Mislabeling of the products caused by the violation of procedures*

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

5-3 Annual Report

OMQD summarizes the performance of operations related to the GMP inspection, etc., international activities, current issues, future visions, etc., to issue a GMP/GCTP Annual Report.

By informing the status related to GMP inspections in Japan, the status of manufacturing control and quality control at the manufacturing site will be detailed to secure the transparency of regulations, mutual trust between PMDA and companies, and mutual trust between PMDA and GMP authorities overseas.

5-4 GMP education support

5-4-1 Regulatory authorities (Domestic)

In 2020, contamination of drug substance during the manufacturing process at the manufacturing site and health hazards occurred for generic drugs. Even after that, several companies reported violations of the GMP Ministerial Ordinance, which had a major impact on the shortage of drugs.

In 2022, OMQD established the Division of GMP Inspection training from the viewpoint of supporting GMP training for the prefectural governments and ensuring manufacturing control and quality control at the manufacturing sites. In addition to planning and development of training support programs for the prefectural governments, it also has started GMP training support for overseas GMP regulatory authorities.

The implementation status of support operations in FY 2022 is as follows:

1 Support for on-site inspection

Participation in PMDA GMP inspection
5 cases
(4 Japanese cases, 1 overseas case)

Implementation of PMDA-prefectural governments joint GMP inspection
11 cases

Dispatch of PMDA inspector to prefectural government GMP inspection
4 cases

2 Provision of PMDA training materials, etc.

GMP training for beginnsers
April : 118 participants

PMDA special education
July (1st) : 32 participants
October (2nd) : 51 participants
March (3rd) : 46 participants

GMP training materials
Provide GMP introduction training videos to prefectures

3 Seminars, etc.

Lecture by external lecturers
July (DI training):
104 participants

Training at the National Institute of Public Health (Wako Training)
May to June:
5 lecturers dispatched

4 Dispatch of lecturers / Consultations

Dispatch of lecturers to training sessions and mock inspections sponsored by prefectural governments 18 cases
Reception of consultation on questions during GMP inspection 3 cases

5 Training support for overseas regulatory authorities (particularly Asian region)

September: Accompanying two Asian GMP authority members (Malaysia) to GCTP inspection of gene, cellular and tissue-based products
October: PMDA-ATC GMP Inspection Webinar 2022 was held (a total of 25 Web participants from 19 countries/regions).

5-4-2 Regulatory authorities (Overseas)

PMDA established the "Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (abbreviated as PMDA-ATC)" on April 1, 2016, based on the "PMDA International Strategic Plan 2015" released in June 2015 as a new international strategy. PMDA-ATC leverages the knowledge and experience the PMDA has gained to date and provides training for representatives of regulatory authorities as required by regulatory authorities in Asian countries. The scope of the training includes the GMP area, and as part of the training in PMDA-ATC, OMQD regularly provides GMP inspectors in Asian countries with training opportunities[*8].

OMQD are also actively in charge of giving lectures at PIC/S training events. In FY 2022, lecturers were dispatched to give lectures at PIC/S Expert Circle on Quality Risk Management held in Brazil and PIC/S Seminar 2022 held in Dublin[*9].

*8 https://www.pmda.go.jp/int-activities/training-center/seminar/0001.html
*9 https://picscheme.org/

6. Consultation services

6-1 Simple consultation

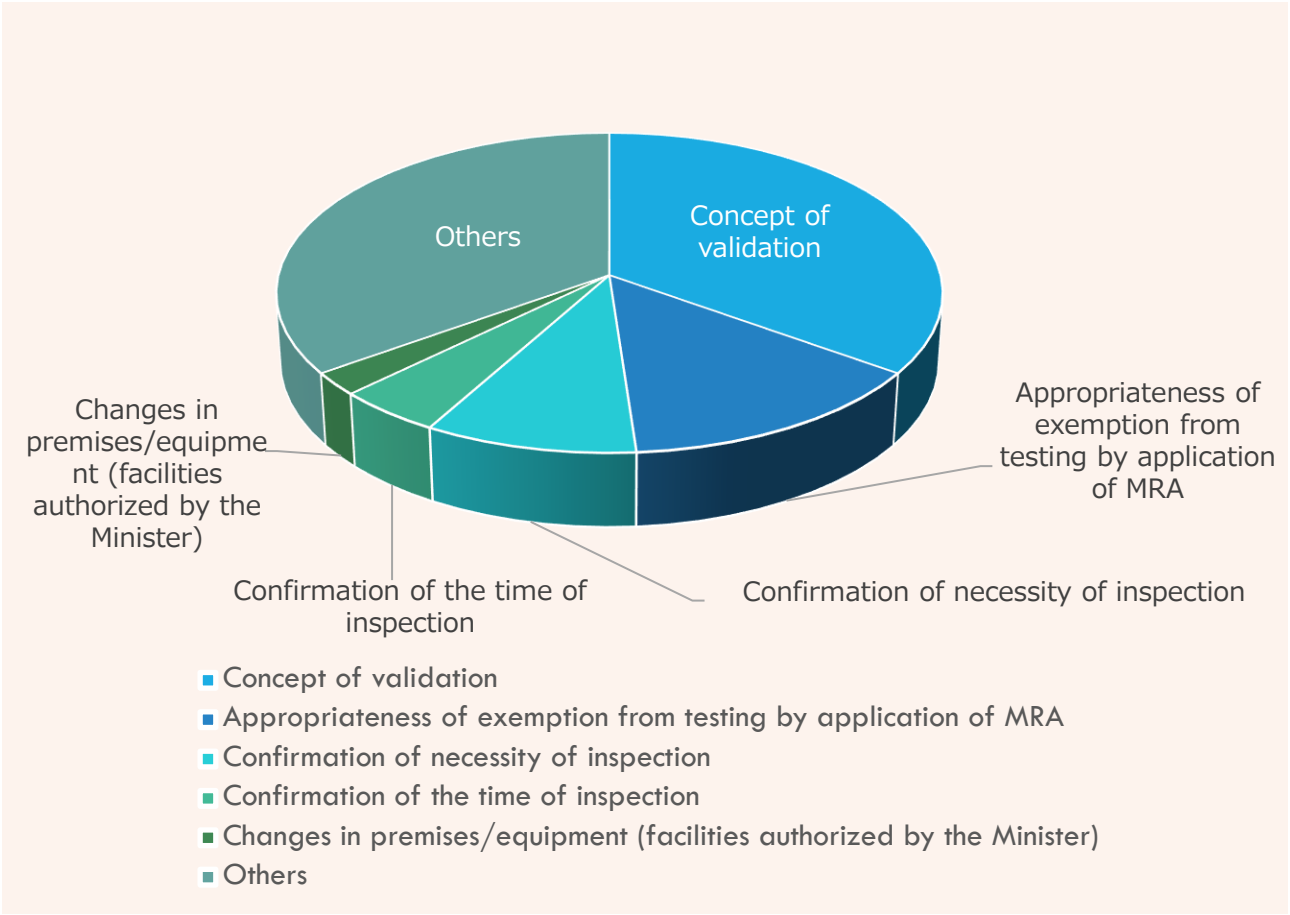
OMQD is in charge of consultations related to GMP and GCTP inspections among Simple consultations based on "Implementation Guideline, for Face-to-Face Consultations and Examinations Confirm Certification Conducted by Pharmaceuticals and Medical Devices Agency" (PFSB/ELD/OMDE Notification No. 0302070 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]
2020	54	29
2021	46	20
2022	43	20

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.



6-2 Other consultations

The outlines and results of various consultations other than “Simple consultations” in FY 2022 are as follows.

Number of consultations in FY 2022

* The number of consultations completed in FY 2022 was tabulated

(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 case	0 case	1 case	1 case

(1) Consultation on PACMP

OMQD is in charge of quality and GMP consultations for applicants who seek to utilize Post-Approval Change Management Protocol (PACMP).

(2) Consultation on SAKIGAKE (Forerunner-designated products) 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 2022. One consultation applied before FY 2022 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. In FY 2023, two consultations concerning "continuous production" were received (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 2022.

(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.

One consultation was concluded in FY 2022.

7. International activities

7-1 Cooperation with overseas regulatory authorities and international organizations

(1) Importance of international activities

The supply chain of drugs is becoming increasingly complex, and the manufacturing sites producing drugs delivering to Japan are located all over the world. Therefore, it is extremely difficult for each regulatory authorities to comprehensively inspect all the manufacturing sites.

PMDA is proactively collecting information on inspections conducted by overseas regulatory authorities for the implementation of highly accurate risk assessment of manufacturing sites to focus on the high-risk manufacturing sites and prioritize allocation of inspection resources to the corresponding manufacturing sites.

When utilizing the inspection information of overseas regulatory authorities, it is necessary that the criteria and inspection capability of the reference overseas regulatory authorities for GMP inspection are standardized. For this reason, PMDA is actively promoting collaborative relationships with overseas regulatory authorities by actively working on activities related to international harmonization of GMP standards in PIC/S.

(2) PIC/S activities

PIC/S is an international organization mainly aiming at international harmonization of GMP standards and improvement of inspection capability of inspectors. Japanese GMP regulatory authorities (PMDA, MHLW, and 47 prefectural governments) joined PIC/S in 2014 and are conducting international activities centering on PIC/S activities. The main activities are as follows:

1) Participation in PIC/S Executive Bureau

PIC/S has established six Sub-committees which operate under the committee meeting, the final decision-making body. One of the PMDA's staff members has been elected as Chairperson of Sub-committee of Communication (SC COM) and executive bureau (EB) member (Term of service: January 2022 to December 2023, January 2024 to December 2025).

The SC COM promotes cooperation between PIC/S participating authorities and between PIC/S and other organizations, and plays a core role in promoting information sharing and public relations activities inside and outside PIC/S.

2) Participation in PIC/S Sub-committee

In addition to the activities in SC COM, staff members of PMDA participated in Subcommittee on Training (SCT) to review PIC/S educational materials, hold PIC/S seminars and PIC/S Expert Circle, etc.

3) PIC/S Seminar

PIC/S seminars are annual training events organized by volunteer participating authorities. It is the most important event in PIC/S training in which almost all PIC/S member countries participate. Since joining PIC/S in 2014, PMDA has been continuously participating in all PIC/S seminars, receiving training, and actively dispatching lecturers.

PMDA held the PIC/S seminar at Toyama in 2019 on the theme of sterility assurance of drugs and achieved great contributions to the training of inspectors of PIC/S participating authorities.

4) PIC/S Expert Circle

PIC/S Expert Circle is a group to promote training in specialized fields, and the main activities include holding of Expert Circle Meeting and development of training materials.

Expert Circle Meeting is a forum for exchange of information on technical expertise in PIC/S and is one of the major events of PIC/S. PMDA held PIC/S Expert Circle Meeting in Tokyo on the theme of Quality Risk Management (QRM) in 2014 when Japan joined PIC/S.

Currently, Expert Circles are established in many specialized fields, and PMDA has recently participated in the following activities.

- Quality Risk Management (QRM)
  Dispatch of lecturers to Expert Circle Meeting hosted by Brazilian Authority (ANVISA) from November 29 to December 2, 2022
- Control of Cross-Contamination in Shared Facilities (CCCISF)
  Participated in the revision work of Aide Memoire on Cross-Contamination in Shared Facilities (PIC/S Document PI 043-1)
- Human Blood, Tissues, Cells & ATMPs
  Participated in training on PIC/S GMP Guide Annex 2A hosted by Italian Authority (AIFA) and Austrian Authority (AGES) from March 14 to March 16, 2023

5) Information sharing with PIC/S Participating Authorities (April 2022 to March 2023)

OMQD has provided information on GMP inspection reports and deficiencies with overseas authorities as follows.

2 cases to the US FDA, and to the European Medicines Agency (EMA) respectively, 1 case to the European Directorate for the Quality of Medicines and Healthcare (EDQM), to Canada (Health Canada), to Germany (BfArM), to Ukraine (SMDC), to Singapore (HSA) and to Argentina (ANMAT) respectively

We received information on GMP inspection reports and deficiencies from overseas authorities as follows.

12 cases from the US FDA, 1 case from the European Medicines Agency (EMA), from Canada (Health Canada), from Germany (BfArM), from Argentina (ANMAT), and from Singapore (HSA) respectively

6) Observed inspection (April 2022 to March 2023)

Members of overseas regulatory authorities have observed PMDA inspections (on-site inspection) as follows.

Observed inspection in Japan: 1 case from Malaysia (NPRA)
Observed inspection overseas: 2 cases in Chinese Taipei (TFDA) and 1 case in Singapore (HSA)

PMDA inspectors observed inspections conducted by overseas authorities as follows.

Observed inspections by overseas authorities in Japan: 8 cases from the US (US FDA)

7-2 Other international activities

(1) PMDA-ATC GMP seminar

The Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC) leverages the knowledge and experience that PMDA has gained and provides training for regulators in Asia in response to the demands made by them.

PMDA provides lectures on information necessary for establishing regulations in each country related to GMP inspections, as well as mock inspection trainings with the cooperation of manufacturing sites.

The latest seminar information is as follows:

- PMDA-ATC GMP Inspection Webinar 2022 (October 25 to 26, 2022)
  Training for GMP inspectors of overseas regulatory authorities (19 countries/25 inspectors)
- PMDA-ATC GMP Inspection Webinar 2024 (February 6 to 7, 2024)

(2) API Program

API Program "Programme to rationalise international GMP inspections of active pharmaceutical ingredients/active substances manufacturers" has launched in 2012 and PMDA has been participating in the program since 2016. The current participating authorities are 13 authorities (AIFA, ANSM, ANVISA, DKMA, US FDA, Health Canada, HPRA, MHRA, PMDA, TGA, EDQM, EMA, WHO).

In the program, participating authorities share a database (master list) of GMP inspection information of manufacturing sites of drug substances and update periodically. This program enables participating authorities to share the GMP inspection plans and results promptly. Participating authorities can obtain and utilize GMP inspection plans and results, etc., under confidentiality agreements.

PMDA has been working to improve the efficiency and quality of GMP inspections by utilizing inspection results by other authorities through API program, narrowing down important matters to be inspected by prior confirmation of issues at the manufacturing site to be inspected, and planning joint inspections with other authorities. Information sharing between authorities through API program also contributes to confirming the GMP inspection capability of each authority which is the basis of mutual trust between organizations.

(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. PMDA participates in the meeting as an observer based on MRA between Japan and the EU.

By participating in the meeting, OMQD is able to obtain the latest information on regulations related to manufacturing control and quality control of drugs in the EU and to disseminate information of Japanese pharmaceutical regulations.

8. Future vision

In recent years, suspension of shipments of many generic drugs due to the violations of laws and regulations at manufacturing sites has led to drug shortage in Japan. In the background, various problems related to the manufacturing and distribution of generic drugs have been pointed out, such as the industrial structure resulting from small-scale production of multiple products and frequent cycles of new application and marketing of new generic drugs. Currently, countermeasures for these issues are under consideration at the review meeting in Japan.

PMDA enhances the following efforts to improve the quality of drugs distributed in Japan and to secure a stable supply through various risk communication activities, which fosters convincing regulations and bridge support from development to manufacturing, etc.

(1) Deepening of communication among stake holders

In order to improve the quality of the life-related drug products, OMQD is planning to deepen communication among all stake holders such as patients, healthcare professionals, manufacturers, and government. Specifically, OMQD enables manufactures to widely utilize drug quality-related information for securing the quality of drugs through GMP roundtable meetings, Rapid announcement of Inspectional observations (ORANGE Letter), Annual reports, etc.

Such information shall be made available on the PMDA website with the aim of making it readily available to stake holders including related regulatory authorities as much as possible.

(2) Tightening of international collaboration initiatives

OMQD continues to actively participate in PIC/S activities such as dispatching of lecturers to seminars, and obtaining the latest information on manufacturing control and quality control and knowledge on the international situation in the field of GMP. In addition, in order to perform risk assessment of manufacturing sites in the world efficiently, OMQD selects and concentrates inspection resources by deepening information sharing with PIC/S participating authorities and promoting mutual utilization of inspection results, and OMQD also promotes international harmonization activities.

PMDA GMP / GCTP Annual Report FY 2022

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Notice

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