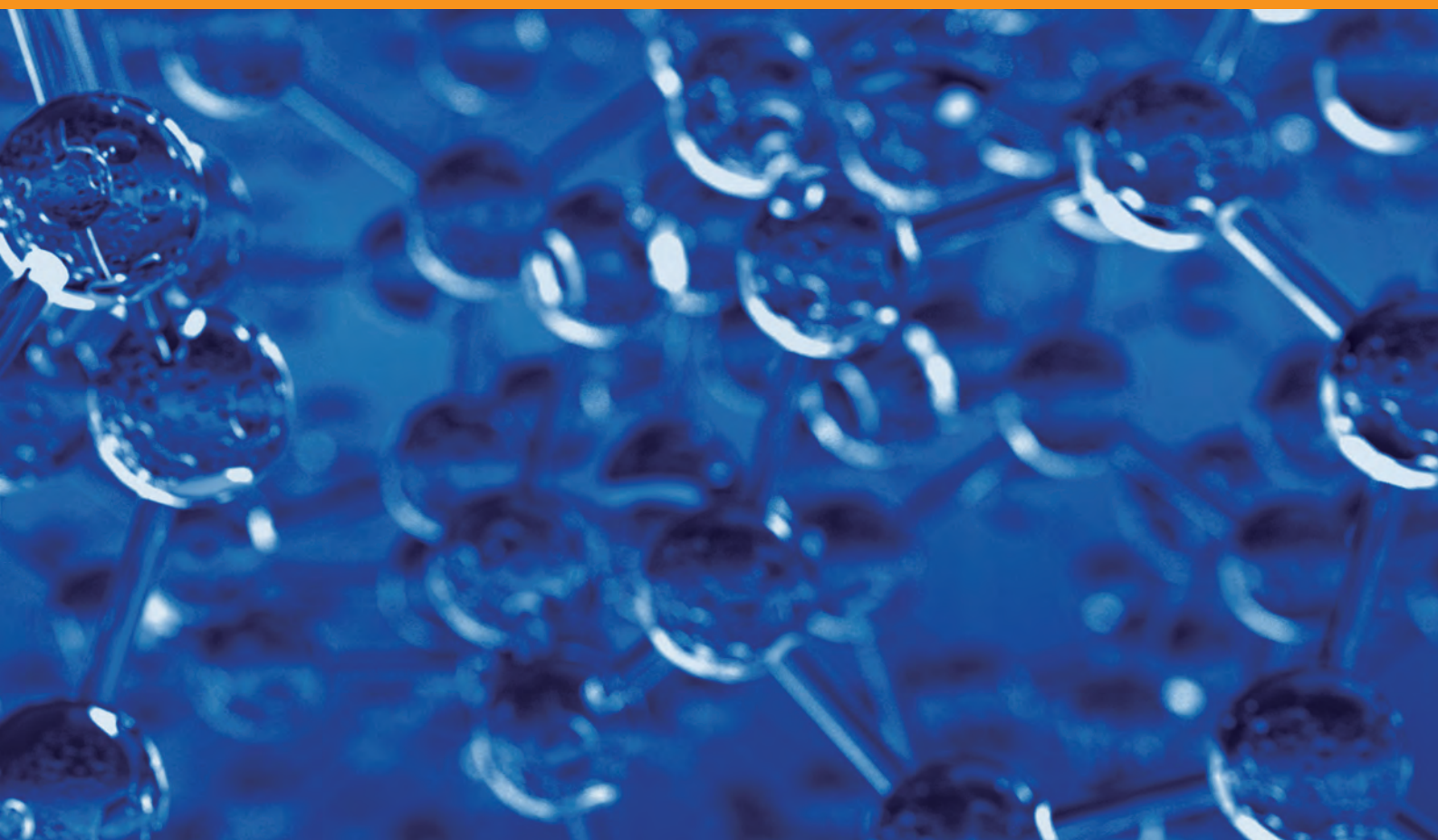
Pharmaceuticals and Medical Devices Agency

Profile of Services



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Our Philosophy

PMDA continues to improve the public health and safety of our nation by reviewing applications for marketing approval of pharmaceuticals and medical devices, conducting safety measures, and providing relief to people who have suffered from adverse drug reactions.

We conduct our mission in accordance with the following principles:

- We pursue the development of medical science while performing our duty with greater transparency based on our mission to protect public health and the lives of our citizens.
- We will be the bridge between the patients and their wishes for faster access to safer and more effective drugs and medical devices.
- We make science-based judgments on quality, safety, and efficacy of medical products by training personnel to have the latest technical knowledge and wisdom in their field of expertise.
- We play an active role within the international community by promoting international harmonization.
- We conduct services in a way that is trusted by the public based on our experiences from the past.

PMDA Code of Conduct

To realize PMDA's mission, we pledge to act in a moral and just way while adhering to the following Code of Conduct grounded in the principles of regulatory science.

1. Compliance
We will act with the highest standards of integrity and in compliance with applicable laws, regulations, and organizational policies.

2. Rigorous Information Management
We will rigorously manage proprietary corporate information and other confidential information such as personal information obtained in the course of our operations.

3. Securing Fairness of Our Operations
We will work to realize an "Honest PMDA" by acting with impartiality, fairness, respect, and civility towards all persons involved in our operations while ensuring a high degree of transparency.

4. Creating Ideal Working Environments
We will strive to create an ideal working environment and to achieve positive interaction between staff members by promoting open, friendly, and constructive communication.

5. Health Management
We will strive to maintain and be mindful of the health and well-being of our colleagues and others we work with.

6. Prevention of Harassments
We will strive to keep our workplace free from harassment or discrimination while respecting the dignity and personality of individual employees.

7. Teamwork
We will collaboratively perform our duties by listening closely to team members at work and understanding each member's position while keeping all involved informed by ensuring timely and appropriate reporting, communication, and consultation.

8. Operational Improvement
We will remain committed to actively improving our operations in order to enhance efficiency and productivity.

9. Proper Management and Use of PMDA Resources
We will ensure the proper management and use of PMDA's resources by avoiding and mitigating conflicts of interest and avoiding actual, potential, and perceived improprieties.

Yasuhiro FUJIWARA, MD, PhD
Chief Executive

PMDA Mission: Contribute to the maintenance and improvement of the public health in Japan

The Pharmaceuticals and Medical Devices Agency (PMDA) plays three key roles—relief services for persons injured by adverse reactions to drugs and regenerative medical products, product reviews, and safety measures. PMDA is engaged in ensuring the quality, efficacy, and safety of medical products—drugs, vaccines, biologics, medical devices, and regenerative medical products, from development to post-market stages, in order to provide citizens and healthcare professionals with rapid access to safer, more effective medical products, and to ensure their safe use.

PMDA is responsible for evaluating, from various perspectives, the latest scientific findings regarding the quality, efficacy, and safety of medical products to assess the advantages and disadvantages of individual products, and for providing medical products to the public in the most optimal way so that people can benefit from them with a sense of security. PMDA staff is committed to performing their duties, keeping in mind that many patients are now waiting for novel therapies, but even so, giving the public access to novel therapies in the best way requires a certain period of time. PMDA is a science-based organization and must deal with emerging and future innovative technologies in a timely manner, while giving top priority to the safety of people.

To this end, PMDA carries out operations promptly and carefully from the scientific point of view by promoting regulatory science, a scientific discipline that enables sound, evidence-based review and evaluation. Further, through enhanced transparency, PMDA strives to accurately communicate its decisions with evidence to all people in Japan, including healthcare professionals and patients.

Relief systems for persons injured by adverse reactions to drugs and regenerative medical products are highly regarded internationally and is the source of Japanese pride, our precious asset. PMDA will carry on with offering support to people who have suffered injuries related to drugs and regenerative medical products.

Today, PMDA is recognized as a regulatory authority standing shoulder-to-shoulder with its counterparts in Europe and the United States. We look forward to playing an active role in discussions on international harmonization of regulations, and will contribute to raising standards at Asian and other regulatory authorities.

PMDA will strive to enhance the quality of operations based on regulatory science and, without being bound by precedents, will proactively address new challenges with a scientific approach, to contribute to the advancement of the public health and safety of all people in Japan.

September 2023

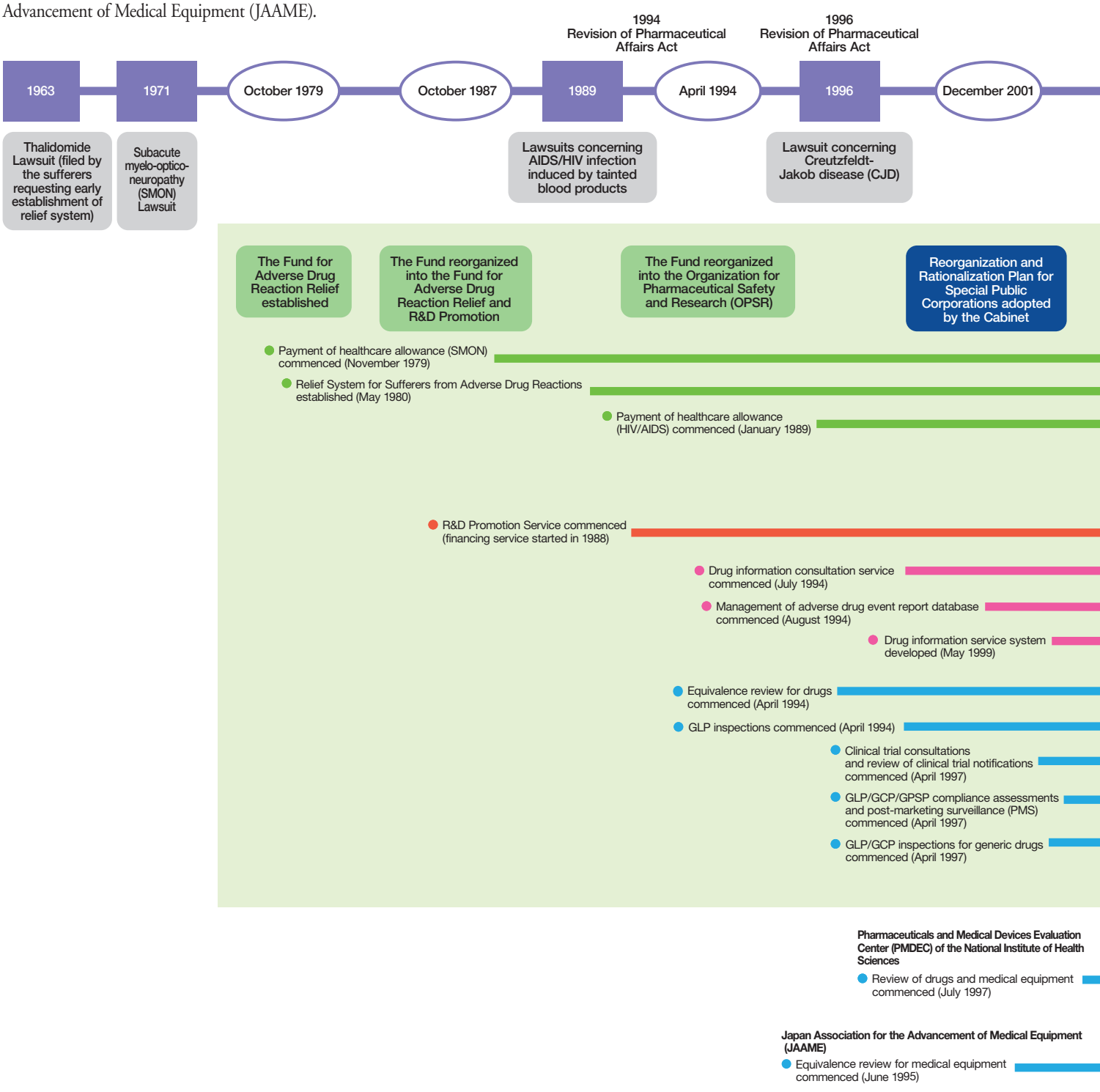
Yasuhiro FUJIWARA, MD, PhD
Chief Executive
Pharmaceuticals and Medical Devices Agency

Outline of the Pharmaceuticals and Medical Devices Agency

History of PMDA

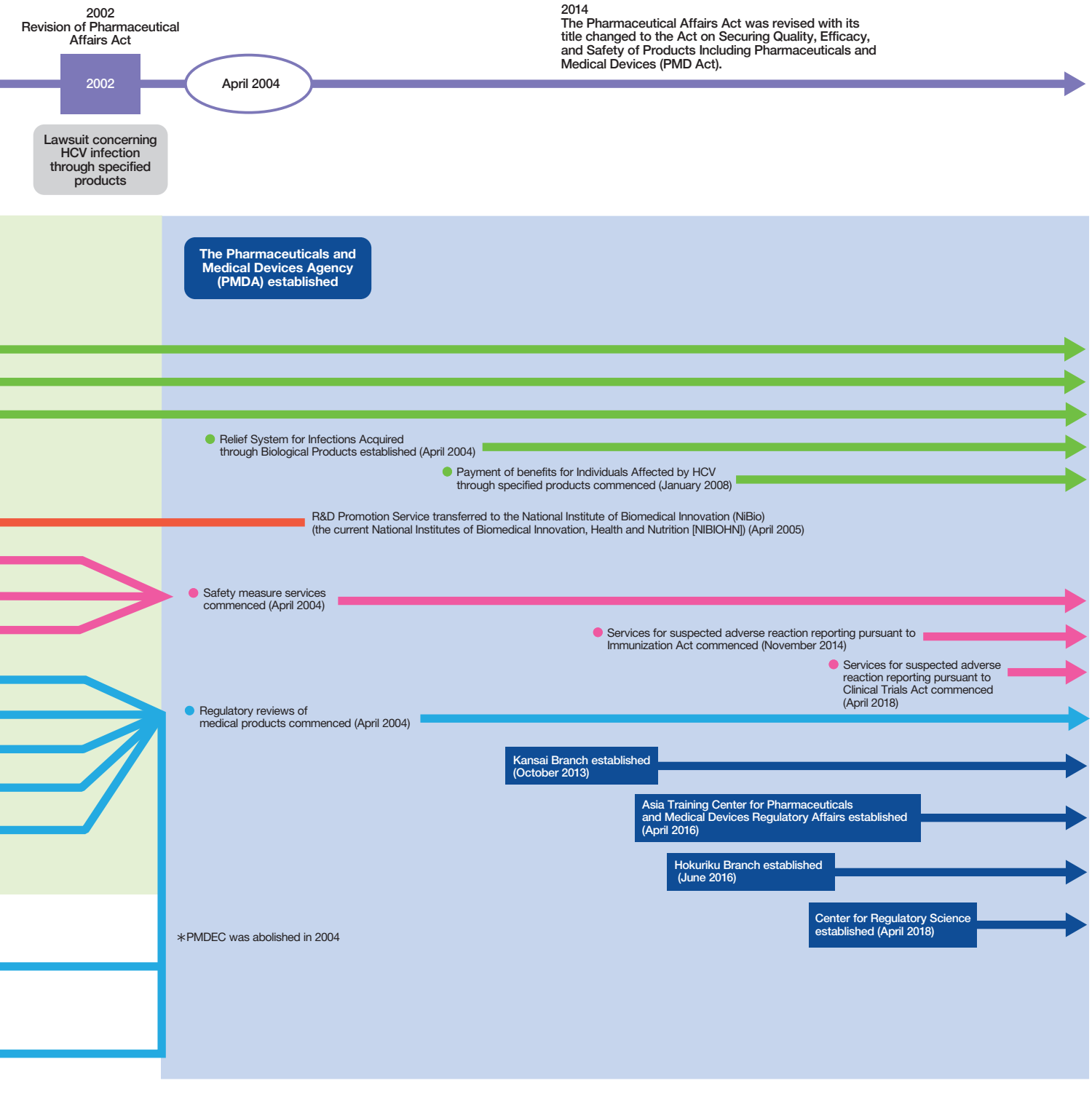
Following the Reorganization and Rationalization Plan for Special Public Corporations, which was approved at a Cabinet meeting in 2001, the Pharmaceuticals and Medical Devices Agency (PMDA) was established and came into service on April 1, 2004, under the Act on the Pharmaceuticals and Medical Devices Agency, with an aim to consolidate the services of the Organization for Pharmaceutical Safety and Research (OPSR), the Pharmaceuticals and Medical Devices Evaluation Center (PMDEC) of the National Institute of Health Sciences, and part of the Japan Association for the Advancement of Medical Equipment (JAAME).

Name: Pharmaceuticals and Medical Devices Agency (PMDA)
Established: April 1, 2004
Legal classification: Agency managed by medium-term objective



Number of Full-time Employees

	April 1, 2019	April 1, 2020	April 1, 2021	April 1, 2022	April 1, 2023
Total (including executives)	936	961	995	1,025	1044
Review Department	561	566	596	610	623
Safety Department	224	237	236	253	260
Relief Department	39	38	40	39	41



Safety Triangle

— Comprehensive Risk Management through the Three Functions —

Services of PMDA

PMDA's mission is to help improve public health in Japan by providing swift relief to people who have suffered health damage caused by adverse drug reactions or infections from biological products (Relief Services for Adverse Health Effects), offering guidance and conducting reviews on the quality, efficacy and safety of drugs and medical devices through a system that integrates the entire process from pre-clinical research to approval (Product Reviews), and by collecting, analyzing and providing post-market safety information (Post-marketing Safety Measures).

Securing Quality, Efficacy and Safety

Three-pillar System Unique to Japan

Post-marketing Safety Measures

- Acceptance of submitted information on precautions
- Collection and organization of safety information from marketing authorization holders (MAHs) or medical institutions
- Scientific research and analysis of collected information
- Consultation services on safety measures for MAHs
- Consultation services for consumers
- Provision of safety information on drugs, medical devices, and regenerative medical products

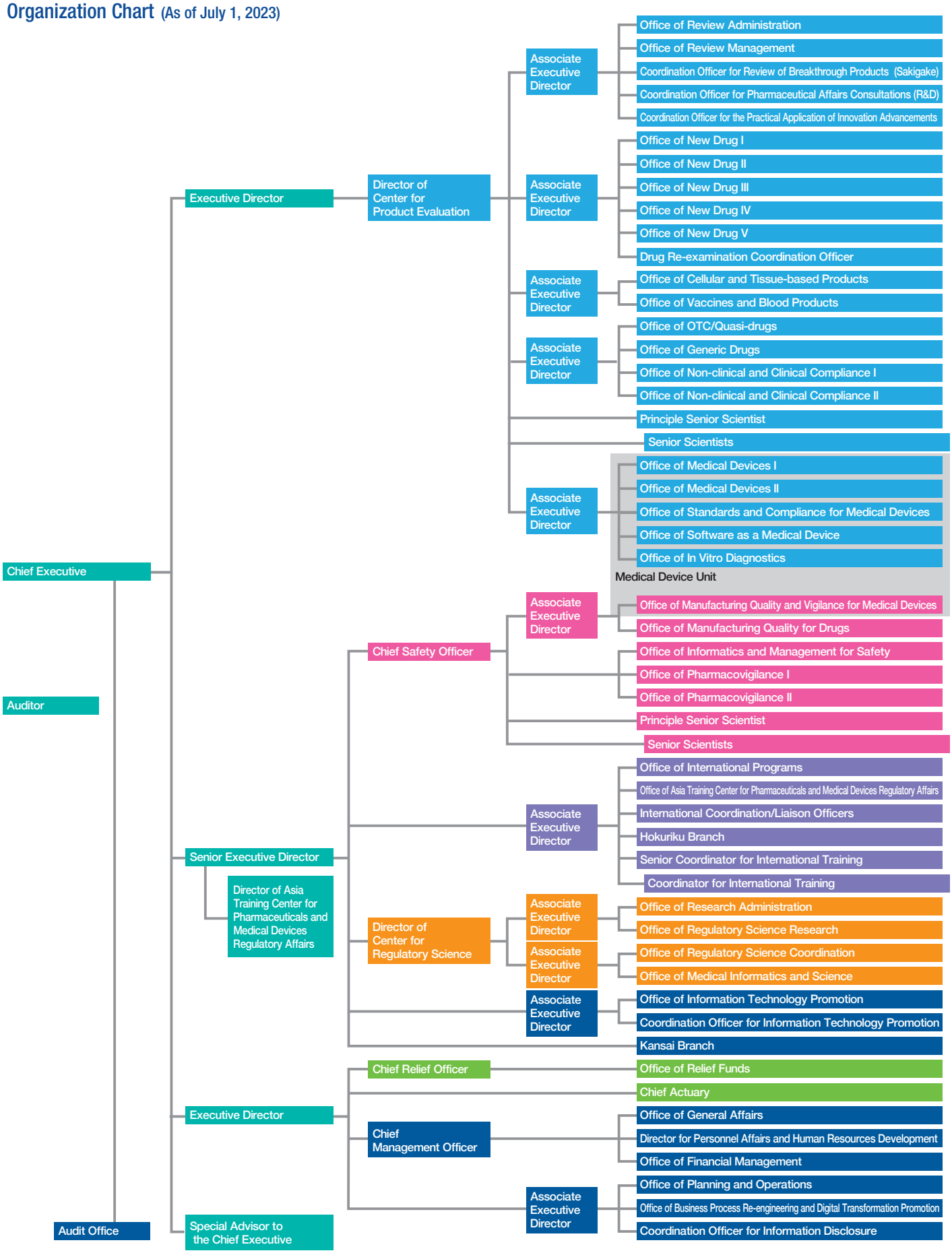
Product Reviews

- Consultations on clinical trials and other issues
- Regulatory review of drugs, medical devices and regenerative medical products
- Re-examinations/re-evaluations
- GLP/GCP/GPSP compliance assessments for regulatory submission documentation
- GMP/QMS/GCTP inspections of manufacturing processes and facilities
- Inspection of registered certification bodies
- Development of standards e.g., Japanese Pharmacopoeia

Relief Services for Adverse Health Effects

- Relief service for adverse drug reactions
- Relief service for infections acquired through biological products
- Health allowances etc., for SMON patients
- Health allowances for HIV-positive and AIDS patients
- Financial assistance under the Act on Special Measures concerning the Payment of Benefits to Relieve Patients with Hepatitis C Infection Caused by Specified Fibrinogen Products and Specified Blood Coagulation Factor IX Products

Organization Chart (As of July 1, 2023)



Relief Services for Adverse Health Effects

PMDA is dedicated to providing swift relief for the people suffering from adverse health effects by conducting active public relations and dissemination of information.

History of Relief Systems

As described in the section titled "Outline of the Pharmaceuticals and Medical Devices Agency (PMDA)," the lawsuits concerning drug-induced suffering such as thalidomide-induced birth defects, subacute myelo-optico-neuropathy (SMON), acquired immunodeficiency syndrome (AIDS) or human immunodeficiency virus (HIV) infection, and Creutzfeldt-Jakob disease (CJD) were filed in Japan. Based on the lessons learned from these drug-induced tragedies, relevant laws were revised to prevent further tragedies from occurring. The occurrence of thalidomide-induced birth defects and Quinoform-induced SMON led to the establishment of the Relief System for Adverse Drug Reactions in 1980. This system aims to assist individuals suffering from health damage caused by adverse drug reactions. In addition, the Relief System for Infections Acquired through Biological Products was established in 2004 because of the spread of HIV infection through tainted blood products and prion disease (CJD) caused by the use of contaminated lyophilized human dura mater.

Five Relief Services for Adverse Health Effects

Drugs have both primary effects (desired therapeutic effects) and secondary effects (adverse effects). The notification issued by the Ministry of Health, Labour and Welfare (MHLW) defines an adverse drug reaction as an unintended adverse event that is possibly related to the drug used. As described in the Review and Related Services and the Post-marketing Safety Measures sections, medical products including drugs are subjected to efficacy and safety evaluation before they are launched on the market. Even if such medical products are properly used with great care, it is almost impossible to completely prevent adverse drug reactions or infections related to biological products.

A product-related adverse event may occur even if the product have been properly used in accordance with the labeled indications, dosage, and precautions for use. Individuals suffering from health damage caused by adverse reactions should be relieved immediately. To respond to social need, the Relief System for Adverse Drug Reactions and the Relief System for Infections Acquired through Biological Products were established as Japan's original systems under which social relief benefits are provided to individuals suffering from health damage, separately from liability for compensation of damage under the Civil Code or public social security systems.

Collaboration between Relief Staff and Safety Staff

PMDA's relief staff and safety staff share information on claims for relief benefits with due consideration given to handling of personal information. The shared information is useful for safety monitoring and reviewed by the safety staff, as in the case of safety information reported from marketing authorization holders (MAHs). Information on repeatedly reported cases is communicated to healthcare professionals by means of issuance of "PMDA Alert for Proper Use of Drugs," in which precautions for use of drugs are plainly explained using graphic illustrations.

Following the enactment of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as the "PMD Act") in 2014, PMDA started to compile cases of adverse reactions related to the claims submitted for relief benefits. Collaboration between the relief and safety departments has been further reinforced to facilitate the task.

Original mascot character "Doctor Q"

About 40 years have passed since the establishment of the Relief System for Adverse Drug Reactions. However, the relief system is unlikely to be known to all users of medical products.

PMDA intensively runs a PR campaign for the relief system between October and December with a focus on the Drugs and Health Week (around October 17 to 23 every year) organized by the MHLW. Video contents and posters are distributed during the campaign period. An original mascot character "Doctor Q" has been featured in the promotional materials since 2011.

In addition, PMDA dispatches its staff members to medical institutions and municipalities for presenting lectures on the relief system and provides e-learning programs on its website to introduce healthcare professionals to the relief system.


Doctor Q

For more information on the Relief System for Adverse Drug Reactions, scan the 2D code shown below.

Relief Services for Adverse Health Effects

Relief Service for Adverse Drug Reactions

Relief System for Adverse Drug Reactions is the public service based on the Act on the Pharmaceuticals and Medical Devices Agency. Under the system, relief benefits are provided to persons with health damage that was caused by adverse reactions to prescription drugs prescribed at hospitals or clinics, over-the-counter (OTC) drugs purchased at pharmacies/drug stores, and regenerative medical products, even if such products were properly used. Such health damages include diseases requiring hospitalization, disabilities significantly limiting daily activities, and fatal cases.

This relief system is applicable to many approved drugs but not to some drugs including those used for the treatment of cancer or other specific diseases.

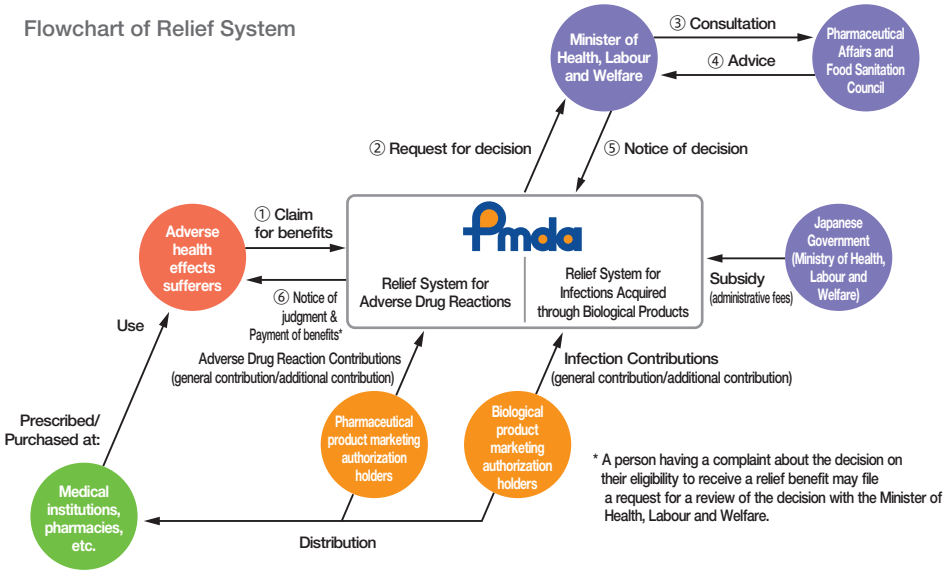
Types of relief benefits and submission of benefit claims

Persons who have suffered from serious health damage caused by adverse reactions or the bereaved families need to submit a claim form for relief benefits directly to PMDA.

Upon receiving a claim for relief benefits, PMDA reviews the claim information and then submits the results to the Minister of Health, Labour and Welfare to request a decision on whether the claim is valid. Once the Minister's decision is notified to PMDA, the acceptance or rejection of the claim is determined based on the decision.

PMDA issues a benefit recipient card to relief benefit recipients (on a request basis) as a part of health and welfare services. The card displays the name of disease(s) and disability(ies) caused by adverse drug reactions and the name of drug(s) considered or suspected to have caused adverse reactions. Benefit recipient card holders can correctly inform healthcare professionals of the card holder's past adverse drug reactions by presenting their card at medical institutions. The information on the benefit recipient card is expected to be useful for future medical treatment given to the card holder. In addition, PMDA conducts consultation services that address mental issues, etc. for relief benefit recipients or their families, and investigative research concerning sufferers from serious and rare adverse health effects caused by drug products.

Flowchart of Relief System



Types and Details of Relief Benefits

Consequences of health damage	Types of relief benefits	Details of relief benefits
Disease requiring hospitalization and medical treatment	Medical expense benefit	Payment to cover actual expenses incurred for treatment of the disease (excluding the portion covered by health insurance).
	Medical allowance	Payment to help cover costs other than medical expenses for treatment of the disease.
Disability, due to which the affected person has significant restrictions in daily activities	Disability pension	Pension payment to compensate for living costs of persons aged 18 or older with a certain degree of disability.
	Pension for disabled child care	Pension payment for parent(s) or legal guardian(s) caring a child(ren) under the age of 18 who has a certain degree of disability.
Death	Pension for bereaved family	The pension is paid to bereaved family members to help rebuild their life if the deceased was the main income earner of the family.
	Lump-sum benefit for bereaved family	Lump-sum benefit is paid to bereaved family members as a consolatory payment if the deceased was not the main income earner of the family.
	Benefit for funeral expenses	Payment for the host of a funeral for the deceased to cover funeral expenses.

Performance of Relief Service for Adverse Drug Reactions

		FY 2018	FY 2019	FY 2020	FY 2021	FY 2022
Number of claims filed		1,419	1,590	1,431	1,379	1,230
Number of claims judged		1,519	1,539	1,594	1,450	1,405
	Approved	1,263	1,285	1,342	1,213	1,152
	Rejected	250	238	244	229	245
	Withdrawn	6	16	8	8	8
Achievement rate*		65.7%	72.3%	55.0%	83.2%	90.2%
Number of claims processed*		998	1,113	877	1,206	1,267
Median processing time (months)		5.4	5.2	5.8	4.6	4.4

* The proportion and number of claims processed within 6 months of filing, calculated based on total claims judged in each fiscal year.

Relief Service for Infections Acquired through Biological Products

The Relief System for Infections Acquired through Biological Products is intended to provide relief benefits to patients who have suffered from health damage such as diseases and disabilities requiring hospitalization that were caused by infection with pathogens through the use of biological products or regenerative medical products manufactured with contaminated ingredients and materials of biological origin, even if such products were properly used. Biological products inculde drug products and medical devices that are manufactured with materials or ingredients derived from human and other living things (except for plants). There are various types of biological products, for example, drug products such as blood transfusion preparations or vaccines and medical devices such as porcine bioprosthetic heart valves or heparin-coated catheters.

The concept of this system is the same as that of the Relief System for Adverse Drug Reactions, but treatment for preventing the onset of a disease in patients infected with its causative pathogenic agent and treatment for patients with secondary infection are also eligible for this relief system.

Performance of Relief Service for Infections

		FY 2018	FY 2019	FY 2020	FY 2021	FY 2022
Number of claims filed		7	0	2	0	1
Number of claims judged		7	2	1	1	0
	Approved	6	2	0	1	0
	Rejected	1	0	1	0	0
	Withdrawn	0	0	0	0	0
Achievement rate*		85.7%	100.0%	100.0%	100.0%	—
Number of claims processed*		6	2	1	1	0
Median processing time (months)		4.6	5.3	5.9	5.2	—

* The proportion and number of claims processed within 6 months of filing, calculated based on total claims judged in each fiscal year.

Healthcare Allowances, etc. for SMON Patients

Since December 1979, PMDA or its predecessor has provided healthcare allowances to SMON patients for whom the judicial settlement was reached, and nursing care expenses to patients with grade III SMON who have very severe or extremely severe symptoms, under commission from drug manufacturers liable for causing SMON in such patients.

Since 1982, PMDA or its predecessor has also provided nursing care expenses to patients with grade III SMON who have severe disabilities (excluding patients with very or extremely severe disabilities), under commission from the Japanese government.

Healthcare Allowances for HIV-positive and AIDS Patients

Under commission from the *Yu-ai* Welfare Foundation, PMDA provides the following three services to patients who have become infected with HIV due to treatment with blood products.

1. Payment of special allowances: Since 1989, PMDA has provided special allowances etc. for AIDS patients for whom a settlement has not been reached in court.
2. Investigative research: Since 1993, PMDA has provided healthcare expenses for HIV-positive patients who have not yet developed AIDS in exchange for reports on their health condition, as well as with the intent to help the prevention of AIDS development.
3. Payment of healthcare allowances: Since 1996, PMDA has provided healthcare allowances for AIDS patients for whom a settlement has been reached in court. The purpose of this service is to improve the welfare of AIDS patients by reducing the cost of monitoring their health.

Patients with secondary and tertiary infections are also eligible for these benefits. Upon receiving a clam for relief benefits, PMDA submits a request for a decision on the claim to the judgment group of the *Yu-ai* Welfare Foundation for healthcare expenses or to the judgment committee of the MHLW for special and healthcare allowances for AIDS patients. Once the decision is notified to PMDA, the acceptance or rejection of the claim is determined based on the decision.

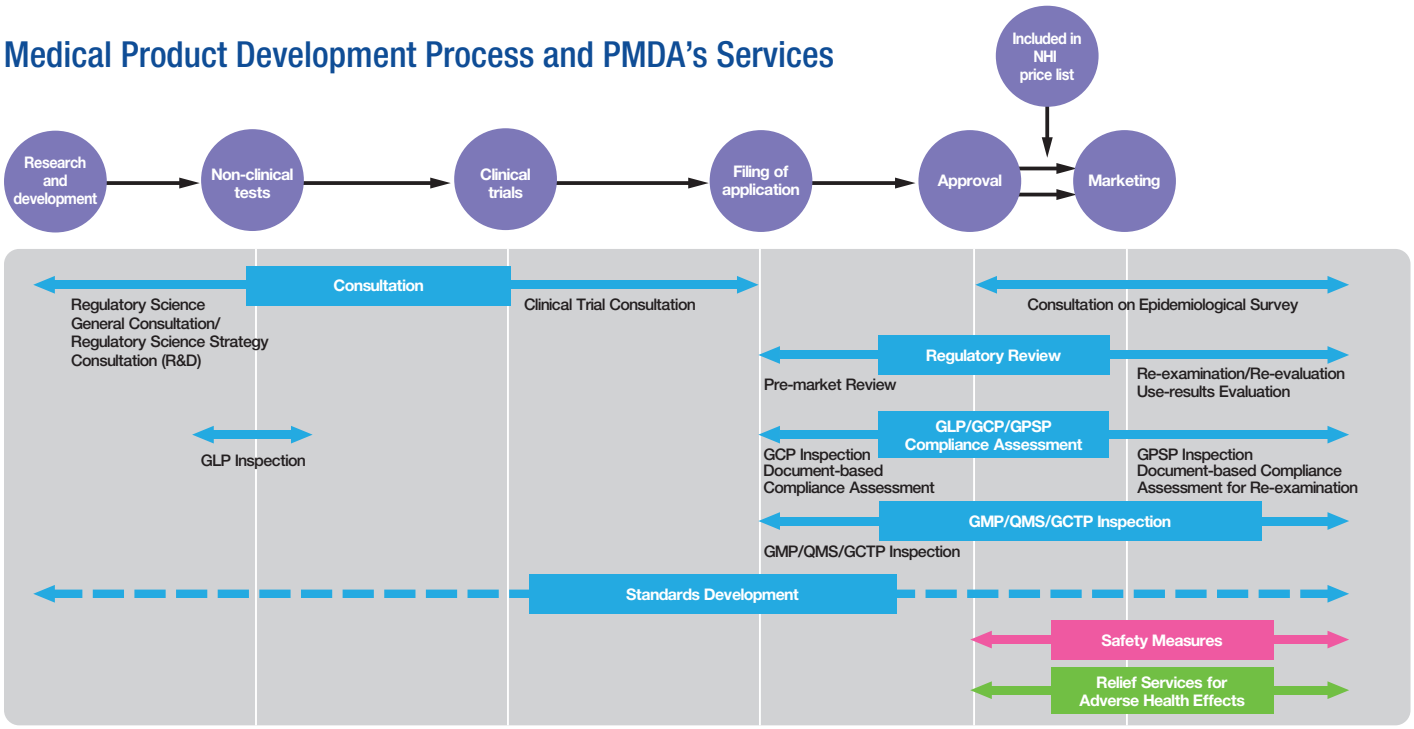
Financial Assistance under the Act on Special Measures concerning the Payment of Benefits to Relieve Patients with Hepatitis C Infection Caused by Specified Fibrinogen Products and Specified Blood Coagulation Factor IX Products

During the period between 1964 and around 1994, several individuals became infected with hepatitis C virus (HCV) through the use of "specified fibrinogen products" or "specified blood coagulation factor IX products" (i.e., HCV-contaminated products) for the treatment of conditions such as massive hemorrhage during pregnancy, childbirth, and surgery, or neonatal hemorrhage. The patients with HCV infection or their bereaved families filed lawsuits for damages against the Japanese government and the pharmaceutical companies responsible. PMDA has provided benefits to those sufferers or their families for whom a settlement has been reached in court, under the Act on Special Measures concerning the Payment of Benefits to Relieve Patients with Hepatitis C Virus Infection Caused by Specified Fibrinogen Products and Specified Blood Coagulation Factor IX Products enacted in January 2008.

Reviews and Related Services

In order to enable patients to have faster access to more effective drugs, medical devices, and regenerative medical products, PMDA is committed to reviewing applications for such products in a prompt and appropriate manner.

Medical Product Development Process and PMDA's Services



During the development process of a new medical product (e.g., drugs, medical devices, and regenerative medical products), the company developing the product needs to conduct various tests and studies to prove the quality, efficacy, and safety of the product. Based on the results of such tests/studies, the company (applicant) submits an application for regulatory approval of the product to the Minister of Health, Labour and Welfare. The product will be approved for commercial use if there are no problems with its quality, efficacy, or safety.

The data submitted to the Minister of Health, Labour and Welfare are reviewed at PMDA in light of the current scientific and technological standards. In addition, PMDA's review includes GLP/GCP/GPSP compliance assessments and GMP/QMS/GCTP inspections. The former service is intended to determine the integrity of clinical trial data from the ethical and scientific aspects by ascertaining whether the clinical trials selected were conducted in accordance with predefined procedures, and the latter service aims to assess the compliance of manufacturing process and manufacturing system for medical products with the requirements of applicable standards. A comprehensive regulatory review consisting of evaluation of efficacy and safety data, assurance of data integrity, and assessment of manufacturing systems, enables people to have access to effective, safe, and quality medical products.

Furthermore, PMDA strives to promote smooth development of medical products by providing consultations in which guidance and advice on the design of studies or criteria for evaluation are given at the pre-submission stage.

Basic Principles for Product Review

Points to consider during the review process include the following: (1) whether the reliability of clinical trials and other studies conducted or the integrity of the data submitted have been ensured; (2) whether the efficacy of the proposed product has been demonstrated by objective evidence such as data from well-controlled clinical trials showing the superiority of the product over placebo; (3) whether the submitted clinical trial data suggest the clinical significance of the product; (4) whether there are any unacceptable risks as compared to the benefits of the product; (5) whether the applicant is capable of consistently supplying reasonably effective and safe products, from the perceptive of quality control; and (6) whether the post-marketing surveillance plan is appropriate.

PMDA reviewers assess the overall benefits and risks of a product by conducting the above-mentioned scientific evaluation of the quality, efficacy and safety of the product. The benefit-risk assessment serves for reviewers to determine how to maximize the benefits of the product while controlling its risks. This relies on the principles of regulatory science.

In recent years, simultaneous global development of innovative medical products is becoming a common place. In response to this trend, PMDA makes efforts to accelerate product reviews to keep up with its overseas counterparts, while spending much time in discussions to ensure that the Japanese public have access to safe and reliable medical products.

Priority Review Applications and Conditional Early Approval Systems

Priority review status is granted to orphan drugs indicated for rare diseases including intractable diseases and to SAKIGAKE-designated drugs that are innovative drugs developed ahead of other countries.

Usually, confirmatory clinical trials are essential to confirm the efficacy and safety of an investigational product. In some cases, however, confirmatory clinical trials may be infeasible because of a small number of target patients, or it may take very long time for the clinical trials to be completed even though they are initiated. If an investigational product falls under the cases mentioned above and is indicated for a disease with no effective therapy, it may be eligible for Conditional Early Approval System, under which a conditional approval will be granted to allow early access to a product once the results of clinical trials other than confirmatory clinical trials have demonstrated the efficacy and safety of the product to a certain extent (Conditional Early Approval for Drugs and Conditional Early Approval for Medical Devices and In Vitro Diagnostics).

In addition, some regenerative medical products are eligible for the Conditional and Time-limited Approval System established pursuant to the Act on Securing of Quality, Efficacy, and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act), under which the product may be granted conditional and time-limited approval once its efficacy is predicted and its safety is ensured. Post-marketing safety information on the product is collected and reviewed to make a final decision on the approval of the product.

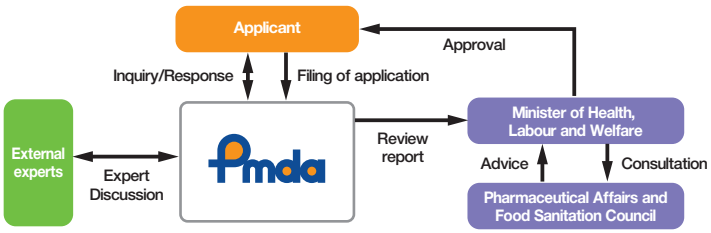
In this way, PMDA performs various approaches to facilitate the early practical use of medical products with high medical need in collaboration with the Ministry of Health, Labour and Welfare (MHLW).

Reviews and Related Services

Drug Reviews

When a marketing application is submitted for a prescription drug with a new active ingredient, composition, dosage and administration, and/or indication that are different from those of previously approved drugs, the drug is classified into the category of "new (prescription) drugs." Datasets submitted with new drug applications include data related to quality and data from non-clinical studies and clinical trials. In the review of a new drug application, a PMDA review team consisting of specialists in various scientific fields including pharmaceutical science, medicine, veterinary medicine, physical science, biostatistics, and epidemiology evaluates the new drug from the aspects of quality, pharmacology, pharmacokinetics, toxicology, clinical implications, biostatistics, and epidemiology. During the review process, the reviewers exchange opinions with external experts (Expert Discussions) to make best use of specialist expertise. The review team prepares reports on the review of the new drug application (review report) to submit them to the Minister of Health, Labour and Welfare.

Regulatory Submission and Approval Process for Medical Products



On the basis of the review reports submitted from PMDA, the Minister of Health, Labour and Welfare makes a decision on the approval of the product after seeking advice from the Pharmaceutical Affairs and Food Sanitation Council (PAFSC) whose committees are composed of external experts in various fields. To secure the transparency of its product review process, PMDA publishes review reports for approved products on its website.

Some new drugs are approved with conditions that vary from product to product. The pharmaceutical company as the marketing authorization holder (MAH) is required to conduct a post-marketing surveillance study (PMS) to collect efficacy and safety data on their product in accordance with the conditions. The MAH submits a re-examination application together with the results of PMS and other data/information collected during the specified re-examination period to PMDA for re-assessment of the efficacy and safety of the approved product.

Drugs reviewed by PMDA

PMDA also reviews the following drugs: generic drugs whose active ingredients are identical* to those of original off-patent brand-name drugs with their re-examination period expired, behind-the-counter (BTC) drugs and over-the-counter (OTC) drugs which can be purchased without a doctor's prescription at pharmacies/drug stores, and quasi drugs including medicated cosmetics.

* *A generic drug contains the same amount of the same active ingredient as that of the original brand-name drug. The indication, dosage and administration, and route of administration of the generic drug should be the same as those of the original drug in principle.*

Review times for new drugs

When PMDA was established, the "drug lag" issue (delayed access to new drugs) had been seen in Japan. PMDA made efforts to speed up its operations by promoting the enhancement of its review system and consultation activities, which resulted in resolution of the drug lag issue by 2011. In recent years, PMDA has achieved the shortest review times for new drugs among regulatory agencies in developed counties such as European countries and the United States.

PMDA endeavors to continually ensure a more predictable review process, aiming to achieve the review time of 12 months for new drugs (9 months for priority review products).

Total Review Time for New Drugs (Priority Review Applications)

	FY 2018	FY 2019	FY 2020	FY 2021	FY 2022
Percentile	80th	80th	80th	80th	80th
Total review time	8.6 months	8.7 months	9.0 months	8.5 months	8.9 months
Number of approved applications	47	40	39	56	61

Total Review Time for New Drugs (Standard Review Applications)

	FY 2018	FY 2019	FY 2020	FY 2021	FY 2022
Percentile	80th	80th	80th	80th	80th
Total review time	11.9 months	11.8 months	11.9 months	11.7 months	11.7 months
Number of approved applications	66	86	84	88	75

Note 1: Values indicate the data for approved applications that were filed in or after April 2004.
Note 2: To calculate review timelines for applications filed during peak periods (March, June, September, and December) in or after 2019, applications filed on or after the 16th day of any of the above months are regarded as filed on the first day of the following month.

ISO9001 Certification (Scope of Certification: New Drug Review)

PMDA's new drug review is certified to the International Organisation for Standardisation (ISO) 9001 Quality Management System. This is an effort to enhance the quality of the review and related services at PMDA.

Medical Device Reviews

Medical devices cover a wide range of products, from adhesive bandages to magnetic resonance imaging (MRI) systems and pacemakers, including even more Software as a Medical Device (SaMD) used for the treatment or diagnosis of diseases. Therefore, medical devices are characterized by a variety of usage patterns and different levels of risk, and their registration procedures vary depending on their risk level (see the classification table). PMDA mainly conducts regulatory reviews for high-risk medical devices.

In the medical device review process, a team consisting of not only reviewers who possess expertise in medical engineering, biological engineering, and biomaterials but also specialists with academic degrees in medicine, dentistry, pharmaceutical science, and other fields reviews the data submitted for a particular product. During the review process, the reviewers exchange opinions with external experts (Expert Discussions) to enable more highly specialized reviews.

Risk-based approach to medical device regulation

Medical devices are classified according to their risk level. While medical devices are divided into three categories under the PMD Act, the international classification system built on the Global Harmonization Task Force (GHTF) guidance has four categories (Class I to IV).

The pre-market regulatory process for medical devices differs depending on the medical device classification. Certification standards have been specified by the Minister of Health, Labour and Welfare for some medical devices that are not subject to PMDA review but are required to be certified by registered certification bodies (third party certification) before being marketed.

Medical Device Classification and Regulation

Risk Level	Low → High			
International Classification	Class I	Class II	Class III	Class IV
Classification under PMD Act	General Medical Devices	Controlled Medical Devices	Specially Controlled Medical Device	
Regulation	Notification to PMDA	Certification by registered certification bodies	Approval by the Minister of MHLW (based on scientific review by PMDA)	
Specific Description	Devices that may pose an extremely low risk to the human body in case of a malfunction Examples: ● In vitro diagnostic devices ● Steel made small devices (including a scalpel, tweezers) ● X-ray film ● Devices for dental technique	Devices that may pose a relatively low risk to the human body in case of a malfunction Examples: ● MRI system ● Electronic endoscope ● Ultrasonic system ● Dental alloy	Devices that may pose a relatively high risk to the human body in case of a malfunction Examples: ● Dialyzer ● Bone prosthesis ● Automated external defibrillator (AED) ● Mechanical ventilator	Devices that are highly invasive and thus may pose a life-threatening risk in case of a malfunction Example: ● Pacemaker ● Artificial cardiac valve ● Artificial breast ● Stent graft

What is Third-party Certification?

Any person who intends to market medical devices or in vitro diagnostics that are designated by the Minister of Health, Labour and Welfare for the purpose of conformity to standards specified by the health minister must obtain certification from a certification body registered by the health minister (registered certification body) for each product to be marketed (third-party certification).

PMDA conducts necessary inspection to assess whether registered certification bodies (including entities that intend to be a registered certification body) meet the requirements for certification bodies before registration or its renewal is granted to them. PMDA is also responsible for periodic on-site inspections of the registered certification bodies.

Registered certification bodies are obligated to submit to the health minister a report to the effect that certification has been granted to, or withdrawn from, a marketing authorization holder. PMDA accepts such reports.

Basic principles for medical device review and review times

Medical devices are categorized as industrial products consisting of a wide variety of elements and the skills of physicians/surgeons who use the devices in clinical settings are also important factors in the risk assessment. Risks are therefore assessed for individual products.

Submission of different datasets is necessary for evaluation of medical devices in different categories. Review timelines vary depending on the device category. PMDA's review teams strive to achieve the target review times for each category. PMDA endeavors to continually ensure a more predictable review process, aiming to achieve the review time of 14 months for new medical devices (10 months for priority review applications).

Total Review Time for New Medical Devices (Priority Review Applications)

	FY 2018	FY 2019	FY 2020	FY 2021	FY 2022
Percentile	80th	80th	80th	80th	80th
Total review time	8.3 months	7.3 months	8.4 months	8.9 months	8.8 months
Number of approved applications	2	3	2	1	2

Total Review Time for New Medical Devices (Standard Review Applications)

	FY 2018	FY 2019	FY 2020	FY 2021	FY 2022
Percentile	80th	80th	80th	80th	80th
Total review time	12.0 months	11.1 months	10.8 months	11.9 months	12.0 months
Number of approved applications	36	27	19	33	19

Note: Values indicate the data for approved applications that were filed in or after April 2004.

Reviews and Related Services

Review of In Vitro Diagnostics

In vitro diagnostics (IVD) are defined as medical devices which are intended to be used for diagnosis of diseases but do not come into direct contact with the human or animal body. IVDs are classified based on their risk into three categories (Class I to III). The procedures for the registration of IVDs are similar to those for medical devices; namely, Class III IVDs requiring approval by the Minister of Health, Labour and Welfare, Class II IVDs subject to either approval by the health minister or certification by registered certification bodies, and Class I IVDs marketed after submission of marketing notification to PMDA.

IVDs include OTC diagnostics such as pregnancy test kits which can be purchased at pharmacies/drug stores, test agents used for examining specimens (blood, urine, feces, and cells) derived from humans for diagnostic purpose at medical institutions, and companion diagnostics for the identification of patients whose outcomes are more likely to demonstrate the efficacy and safety of a particular therapeutic product.

Furthermore, PMDA has taken approaches to address diagnostic tests using state-of-the-art technologies such as gene panel testing, which will lead to the realization of precision medicine allowing analysis and selection of optimal medical treatments for individual patients.

Review of Regenerative Medical Products

Regenerative medical products were newly defined by the PMD Act that was enacted on November 25, 2014. The definitions of regenerative medical products are as follows:

1. Products which are derived from human or animal cells/tissues engineered by methods such as cell culture, and which are those used for the purposes of (a) reconstruction, restoration or formation of structures and functions of the human body, or (b) prevention or treatment of diseases; and
2. Products transfected into human cells/tissues for the purpose of gene therapy.

Although regenerative medical products were previously treated as drugs or medical devices, the enactment of the PMD Act has provided faster access to safer regenerative medicine.

Regulatory framework based on product properties

Regenerative medical products include products derived from engineered living cells/tissues of human or animal origin and products used for gene therapy, and such products have properties different from those of conventional drugs and medical devices. In light of those specific properties, the authorization system and the regulation for safety measures were established for regenerative medical products. For example, the use of living cells/tissues may result in heterogeneity in product quality; therefore, collecting data to support the efficacy of a regenerative medical product is a time-consuming task. In response to these circumstances, the Conditional and Time-limited Approval System has been established under the new legislation so that regenerative medical products can be swiftly granted conditional approval for a limited time period once their efficacy is predicted and their safety is ensured. The sponsor of a regenerative medical product granted conditional and time-limited approval under this system is required to further verify the efficacy and safety of the product on the market and then resubmit an application together with collected data for full approval within the specified time period.

In addition, patients with health problems caused by regenerative medical products are eligible for the Relief System for Adverse Drug Reactions or the Relief System for Infections Acquired through Biological Products because the regenerative medical products are granted conditional approval at the stage where further assessment of the product safety is required.

Regenerative medical products approved in Japan

As of the end of March 2023, nineteen regenerative medical products were approved, and four of them were granted conditional and time-limited approval.

GLP/GCP/GPSP Compliance Assessments

PMDA conducts assessments of compliance with the Good Laboratory Practice (GLP), Good Clinical Practice (GCP), and Good Post-marketing Study Practice (GPSP) (i.e., document-based or on-site inspections and data integrity assessments) in association with applications for marketing approval of new medical products and applications for re-examination, re-evaluation, and use-results evaluation of marketed products, which have been submitted to the Minister of Health, Labour and Welfare, and requests for GLP inspection. During the compliance assessment, PMDA inspectors assess whether necessary tests/studies and clinical trials were conducted in an ethically and scientifically appropriate way and in compliance with GLP, GCP, and GPSP, and whether the submitted data comply with the data integrity standards for regulatory submission.

In the process of GLP/GCP/GPSP inspection, PMDA inspectors check the accuracy and completeness of study data and analysis results reported in study reports for each product filed, and ascertain whether the source data/documents are properly maintained.

PMDA conducts the following inspections: on-site GCP inspection where inspectors visit clinical trial sites to investigate the integrity of clinical trials (e.g., the conduct of clinical trials and record keeping); document-based compliance assessment that assesses the integrity of the data prepared by applicants for regulatory submission; and GPSP inspection that assesses the integrity of data submitted for re-examination and re-evaluation.

Apart from the above inspections for products filed, PMDA conducts on-site inspection of test facilities carrying out non-clinical safety studies if the inspection is requested. This type of inspection is intended to determine the compliance of the test facilities with GLP.

Clinical Trials and GCP

A clinical trial refers to a research study conducted to assess the efficacy and potential adverse effects of a drug, medical device, or cellular/tissue-based product used in humans and thereby collect clinical data for regulatory submission. In the process of on-site GCP inspection, PMDA inspectors assess compliance with the GCP by verifying whether the rights and safety of trial subjects were protected in the clinical trial selected and how the clinical trial was managed at the trial site. The inspectors also provide direct feedback to physicians, pharmacists, clinical research coordinators, and nurses at the site of inspection, thus contributing to improvement of the clinical trial environment in Japan.

GMP/QMS/GCTP Inspections

When medical products are manufactured, all product batches should be of the same quality as that of the product which is approved. To ensure this, regulatory standards have been specified for the manufacturing site, manufacturing facilities, the quality management system, etc. (Good Manufacturing Practice [GMP], Quality Management System [QMS], Good Gene, Cellular, and Tissue-based Products [GCTP]). PMDA conducts inspections to investigate whether the products are manufactured properly in compliance with the standards.

Scope and method of inspection

PMDA conducts on-site and desk-top GMP inspections of "high-risk" manufacturing sites located in Japan or overseas for products such as new drugs, biological products or biotechnological products, in order to ascertain whether their manufacturing facilities and manufacturing and quality controls comply with standards of the GMP, and whether the manufacturing sites have a system for manufacturing products of adequate quality. PMDA also conducts inspections in association with the accreditation of foreign manufacturers and the grant of manufacturer's license to Japanese manufacturers of biological products or radiopharmaceuticals.

PMDA conducts on-site and desk-top QMS inspections for marketing authorization holders of medical devices or in vitro diagnostics and the relevant registered manufacturing sites, in order to ascertain whether their manufacturing facilities and manufacturing and quality controls comply with the standards of the QMS, and whether the marketing authorization holders ensure that products of adequate quality are manufactured and marketed in accordance with the standards.

PMDA conducts GCTP inspection of manufacturing sites for regenerative medical products in Japan or overseas, in order to determine whether their manufacturing facilities, manufacturing process, and quality management system comply with the GCTP. PMDA also conducts inspections on compliance with the standards for buildings and facilities, for-cause inspections, and inquiries on cell processing facilities, pursuant to the Act on Securing Safety of Regenerative Medicine.

Enhancing regulatory communication for improvement of quality control

A "GMP Roundtable Meeting" held by PMDA serves as an initiative that helps quality control personnel in the pharmaceutical industry have an appropriate understanding of GMP and maintain GMP-compliant operations, thereby securing the quality assurance and high reliability of drugs.

In the meeting, a group of participants consisting of personnel involved in pharmaceutical manufacturing and GMP inspectors from PMDA and the prefectural governments are seated around a table to discuss topics related to the quality control of drugs. The discussion can provide education on quality control and facilitate information sharing and communication between the public and private sectors.

Among objectionable conditions identified during a GMP inspection, some cases need to be disseminated to the pharmaceutical industry as informative findings. PMDA publicly discloses such findings on its website by issuing the Observed Regulatory Attention / Notification of GMP Elements Letter (ORNGE Letter) that will raise awareness in, and give technical guidance to, relevant personnel in the industry. Through the issuance of the ORNGE Letter, PMDA makes efforts to encourage voluntary corrective actions for improvement of quality control at drug manufacturing sites.

GMP Roundtable Meeting
(In Tokyo, Japan, November 2022)

International cooperation activities

PMDA, together with the MHLW and prefectural governments, serves as a member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) which is a non-binding, cooperative arrangement among regulatory authorities in the field of pharmaceutical GMP. The PIC/S presently comprises more than 50 participating authorities from countries/regions such as Europe, the United States, Asia, and Australasia. The PIC/S develops common standards in the field of GMP to harmonize inspection procedures worldwide. The scheme also actively promotes sharing of information on GMP inspections among members and provides training opportunities for GMP inspectors.

PMDA is participating in the Medical Device Single Audit Program (MDSAP) as part of international cooperation activities for medical device quality control. PMDA's staff act as regulatory authority assessors who perform MDSAP auditing organization assessment. The MDSAP is a program that allows a single audit of a medical device manufacturer's quality management system (QMS) which satisfies the requirements of multiple regulatory authorities. MDSAP members are the regulators of Japan (MHLW and PMDA), the United States, Canada, Australia, and Brazil. Under this program, QMS audits are conducted by MDSAP-recognized third-party auditing organizations and resulting audit reports are utilized by the participating regulatory authorities. In the conventional regulatory framework, medical device manufacturers need to cope with each of on-site QMS inspections performed by regulatory authorities of different countries. However, utilization of this program by the participating regulatory authorities reduces the burden of QMS inspections/audits on medical device manufacturers.

In this way, PMDA endeavors to perform high-quality inspections in an effective and rational manner by contributing to international cooperation activities for securing the quality of medical products and by sharing information with overseas regulatory authorities.

Reviews and Related Services

Standards Development

Development of Japanese Pharmacopoeia standards

In order to ensure that drugs manufactured or approved in Japan are in compliance with appropriate quality standards for specifications and analytical procedures, the Japanese Pharmacopoeia (JP) is specified as an official compendium by the Minister of Health, Labour and Welfare based on the advice from the Pharmaceutical Affairs and Food Sanitation Council. The JP consists of contents such as General Notices, General Rules for Crude Drugs, General Rules for Preparations, General Tests, and Monographs.

The JP has a long history and its first edition was published in 1886. It has since then been updated regularly to keep pace with the latest knowledge, the advance of technology, and the globalization of drug development. The current version as of the end of March 2023 is the Supplement I to the 18th edition of the Japanese Pharmacopoeia. PMDA is involved in the development of draft monographs and general tests to be included in the JP and convenes the JP Expert Committees consisting of external experts for the development and review of drafts for the JP. The drafts with the comments from the JP Expert Committees are published on the PMDA website for public comments before the final drafts are reported to the MHLW by PMDA.

Medical devices and in vitro diagnostics (IVDs) are evaluated using a risk-based approach, and approval standards and certification standards for medical devices and IVDs are developed accordingly. PMDA also plays a role in the development of certification standards and guidelines that provide guidance for review of medical devices and IVDs.

International harmonization

To facilitate pharmacopoeial harmonization with other countries/regions, PMDA participates in international conferences on pharmaceutical drugs, such as the International Meetings of World Pharmacopoeias; the meetings of the Pharmacopoeial Discussion Group (PDG) consisting of the European Pharmacopoeia, Japanese Pharmacopoeia, and United States Pharmacopeia; and the WHO International Nonproprietary Names (INN) meetings.

PMDA also actively takes part in the meetings of the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC) committees, and the standards development working group of the International Medical Device Regulatory Form (IMDRF), in order to facilitate the global adoption of standards originating from Japan or those reflecting the concept accepted in Japan and to promote the harmonization of international standards used for regulation of medical devices among different countries/regions.

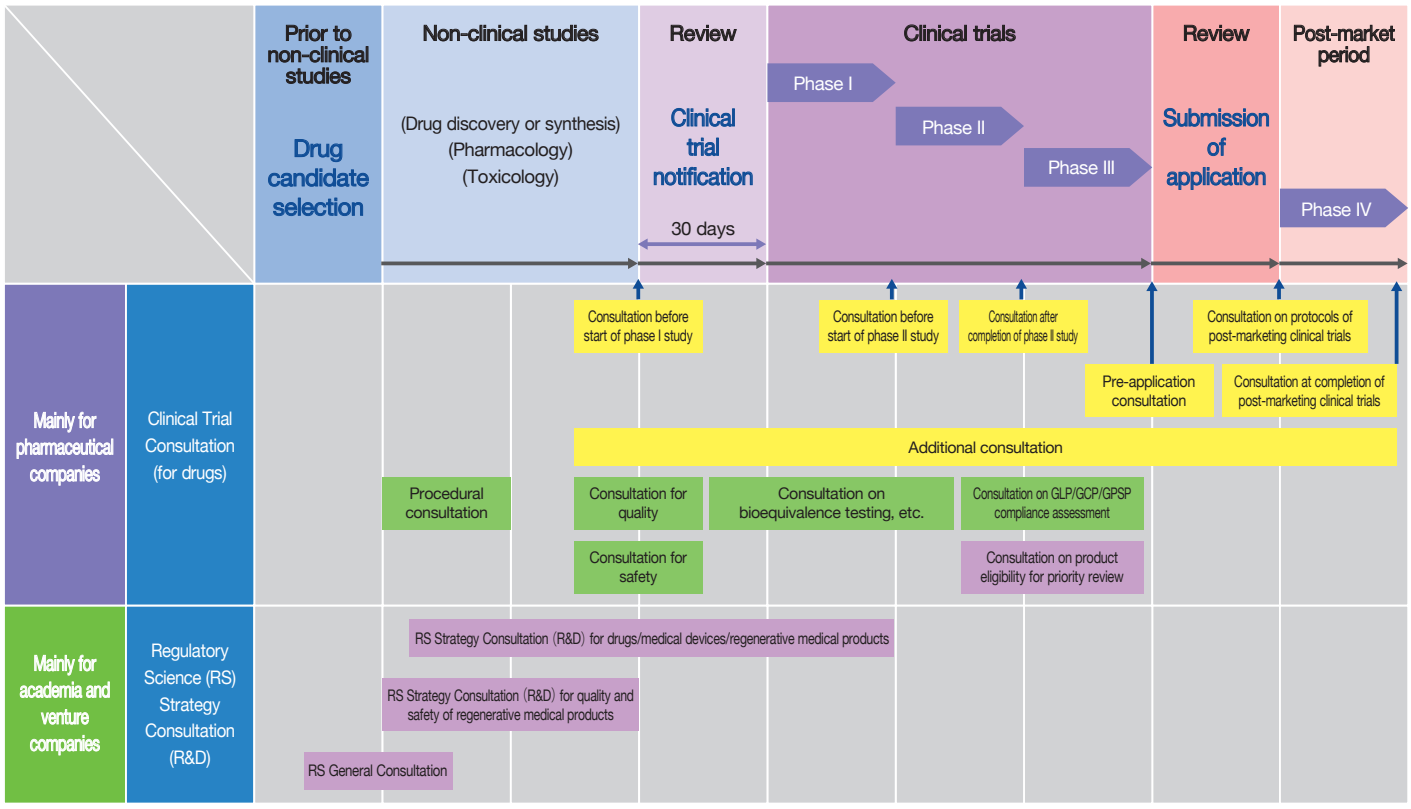
Consultations

PMDA offers consultations to universities, research institutions, and companies that develop medical products to give guidance and advice on development strategy, clinical trial protocols, and data packages for regulatory submissions. A variety of consultations are available for users' convenience, so that companies can request a consultation suitable for their needs at any stage of development of a medical product.

In clinical trial consultations for new drugs, PMDA not only ascertains whether a planned clinical trial complies with the requirements for regulatory submission, taking into consideration the ethical and scientific aspects of and the reliability of the clinical trial as well as the safety of trial subjects, but also gives advice that leads to an improvement in the quality of the clinical trial. PMDA's consultations for new medical devices and regenerative medical products are also provided to give guidance and advice on clinical trials and data packages for regulatory submissions. To promote early access to Software as a Medical Device (SaMD), PMDA has established a dedicated contact point to accept requests for consultations on the qualification of SaMD, medical device regulatory affairs, and health insurance coverage for SaMD, in cooperation with related offices of MHLW.

Furthermore, PMDA offers Regulatory Science Strategy Consultation (R&D) mainly for universities, research institutions, and venture companies to provide advice on the design of studies needed until the proof-of-concept stage and on clinical trial protocol development. Other consultations include simple consultations covering simple advice on confirmation of application category etc. and pre-consultation meetings to identify key issues for consultation meetings.

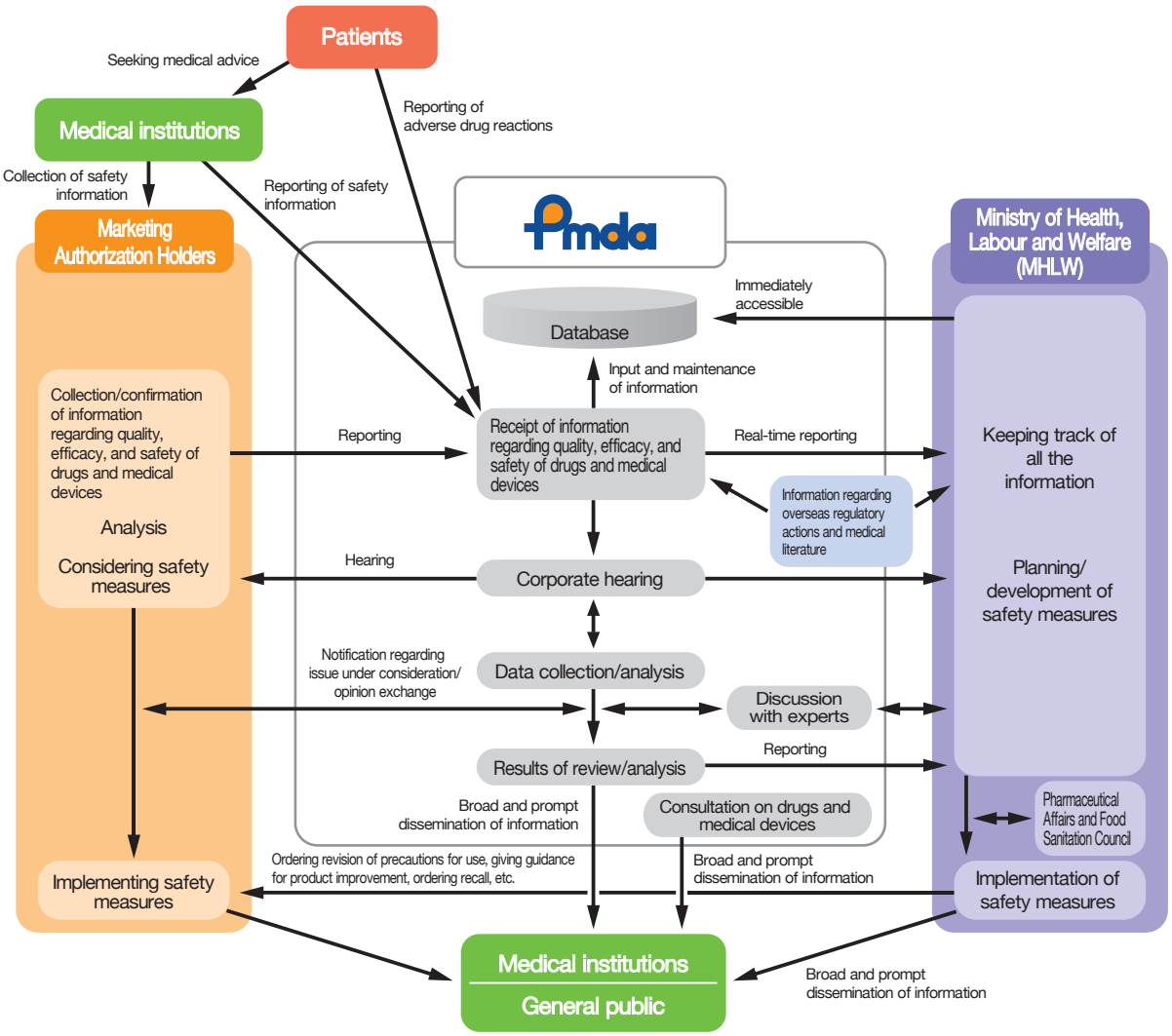
Consultations provided by PMDA



Post-marketing Safety Measures

In cooperation with the Ministry of Health, Labour and Welfare, PMDA is dedicated to improving the safety and reliability of drugs, medical devices, and regenerative medical products.

Flowchart of Safety Measures



Medical products including drugs are essential for protecting our health and lives. Thanks to advancements in science and technology, humans have conquered many difficulties over the years; the medical products created by human ingenuity have allowed us to overcome many diseases.

However, the medical products used for diagnosing or treating diseases may also cause unexpected adverse reactions, so they should be used considering the balance between risk and benefit. It is extremely important that healthcare professionals use medical products properly at all times; safety is achieved through the ceaseless efforts of people who are involved in all stages of the life cycle of these products. And it is this safety that gives users peace of mind.

The safety information reporting system has been enhanced based on the lessons from drug-induced tragedies. PMDA makes efforts to collect risk information through various methods and then communicate new findings to healthcare professionals, thereby ensuring that people have access to safe and reliable medical products.

Post-marketing Safety Measures

Collection, Coordination, and Dissemination of Medical Product Safety Information

Under the PMD Act, healthcare professionals and MAHs are required to submit post-marketing reports on adverse drug reactions, device malfunctions, etc., to the Minister of Health, Labour and Welfare. In addition, MAHs must report to the health minister any measures implemented by overseas regulatory agencies and published research findings regarding their products. Sponsors or sponsor-investigators of clinical trials evaluating investigational drugs or other medical products under clinical development in Japan are also required to submit reports on adverse drug reactions or device malfunctions occurring during clinical trials, measures implemented by overseas regulatory agencies, and relevant published research findings.

PMDA promptly and efficiently compiles the submitted reports into databases that are shared between PMDA and MHLW. In addition, PMDA gathers post-marketing drug safety information through not only mandatory reporting by healthcare professionals and MAHs, but also voluntary reporting by patients or their families. Both reports can be accepted through the online reporting system available on the PMDA website.

Number of Adverse Drug Reaction Reports

From	FY 2018	FY 2019	FY 2020	FY 2021	FY 2022
MAHs (cases in Japan)*	62,110	60,477	51,429	82,308	71,231
MAHs (cases out of Japan)**	490,701	531,394	600,622	989,583	626,015
Healthcare professionals	9,931	9,537	10,985	40,374	11,819
Patients	84	148	126	1,955	419

Number of Medical Device Malfunction Reports

From	FY 2018	FY 2019	FY 2020	FY 2021	FY 2022
MAHs (cases in Japan)*	17,210	21,131	24,474	27,632	27,364
MAHs (cases out of Japan)**	35,334	54,922	104,685	116,860	227,954
Healthcare professionals	487	498	427	354	292

Number of Regenerative Medical Product Malfunction Reports

From	FY 2018	FY 2019	FY 2020	FY 2021	FY 2022
MAHs (cases in Japan)*	163	183	339	375	491
MAHs (cases out of Japan)**	0	962	1,612	2,015	2,572
Healthcare professionals	0	0	6	5	2

Note: The figures in the tables above represent the numbers of post-marketing reports of adverse drug reactions, malfunctions, and infections.
* The figures indicate the total number of adverse drug reactions, malfunctions, and infections reported in Japan.
** The figures indicate the total number of adverse drug reactions, malfunctions, and infections reported out of Japan.

Scientific Research and Analyses

PMDA conducts research and reviews of the collected information through scientific analyses, interviews with companies, and discussions with experts, to determine whether there is any case requiring urgent measures, whether the risk/benefit profile is favorable, and what the optimal safety measures are. All these efforts lead to safety measures for medical products. Furthermore, PMDA widely accepts consultation requests from MAHs to provide precise advice and guidance on safety measures such as the revision of package inserts.

To further these efforts, safety staff works hard to implement effective safety measures in liaison with review and relief staff as well as the MHLW. Meanwhile, applicants are required to submit a risk management plan (RMP) for each of their new drug or follow-on biologic (biosimilar) applications filed in or after April 2013. To facilitate this regulatory framework, risk managers have been appointed who concurrently serve as members of the review department. PMDA thus strives to enhance safety measures by utilizing the submitted RMPs, based on the cooperation between safety staff and drug review staff.

In addition, PMDA endeavors to further enhance the quality of safety vigilance by taking various approaches such as the development of the Medical Information Database Network (MID-NET®) and the use of advanced research methods. The MID-NET® is a distributed database system for electronic medical records. Electronic medical record data extracted from the MID-NET® database and the Japanese National Claims Database are analyzed using pharmacoepidemiological methods (known as the MIHARI Project). Data mining methods (which involve statistical analysis of adverse drug reactions as reported by healthcare professionals or MAHs, thereby detecting signals of adverse drug reactions that may warrant further investigation) are also used for post-marketing drug safety evaluation and other analyses.

Numbers of Reports Submitted to MHLW for Cases Requiring Revision of Package Insert

	FY 2018	FY 2019	FY 2020	FY 2021	FY 2022
Drugs	97	129	207	44	112
Medical devices	2	0	0	0	0
Regenerative medical products	0	0	2	0	0

Note: The figures for drugs indicate the number of active ingredients and those for medical devices indicate the number of term names.

Information Services

A wide range of information on the quality, efficacy, and safety of medical products including drugs is released on the PMDA website in a timely manner, including electronic package inserts for medical products, Risk Management Plans (RMPs) for drugs, recalls, and emergent safety communications (Dear Healthcare Professional Letters). A paper package insert describing the dosage and administration, indication, related adverse reactions, and other information necessary for the proper use of the medical product was contained within the product packaging. However, following the enforcement of the PMD Act, as amended, in August 2021, the use of paper package inserts was abolished, with some exceptions, to introduce electronic package inserts that must be accessible on the PMDA website. The new scheme allows healthcare professionals to constantly have access to the latest labeling information on the PMDA website. Furthermore, all cases of adverse drug reactions and medical device malfunctions reported by healthcare professionals and MAHs are posted on the same website every month.

PMDA also provides the general public with information, such as the "Drug Guide for Patients" which is an easy-to-understand explanation about prescription drugs with warnings, and the "Manuals for Management of Individual Serious Adverse Drug Reactions (for the general public)" which outline individual adverse drug reactions and describe key points for early detection and treatment of initial symptoms in an easy-to-understand manner. In addition, the Agency offers an email information service called "PMDA medi-navi" (available in Japanese only), through which important safety information posted on its website is distributed to those who subscribe to the service.

In addition to online information services through the PMDA website, a telephone consultation service is available for the general public. This service allows people to seek advice on products such as drugs prescribed by doctors, drugs purchased at pharmacies (i.e. OTC or BTC drugs), and home-use medical devices purchased in stores and to obtain safety information on those products.

Emergent safety communications ("Yellow Letter")

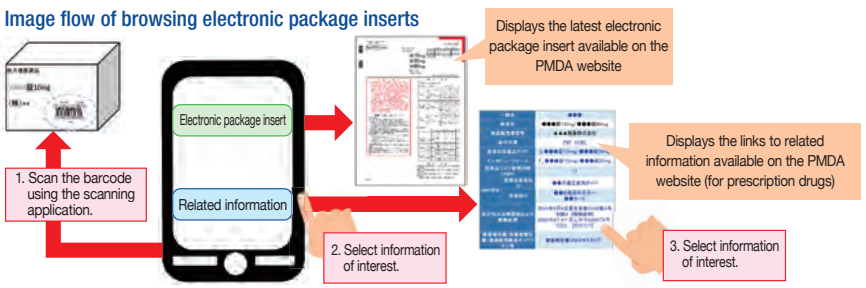
Rapid safety communications ("Blue Letter")

For more safety information on medical products, scan the 2D code shown below.

Electronic Package Inserts

To access the latest "electronic package insert" on the PMDA website, search the database on the website or scan the GS1 barcode on the outer package of a medical product using a smartphone scanning application.

Image flow of browsing electronic package inserts




Electronic package insert

Numbers of Package Insert Information Posted on PMDA Website

	FY 2018	FY 2019	FY 2020	FY 2021	FY 2022
Prescription drugs	14,789	14,740	14,565	14,190	13,865
Medical devices	29,669	31,020	40,229	87,137	93,788
Regenerative medical products	5	9	11	17	18
OTC drugs	11,444	11,303	11,286	11,067	10,875
BTC drugs	15	11	12	14	11
In vitro diagnostics	4,668	4,927	5,080	6,145	6,267

What is a Risk Management Plan?

To ensure the safety of drugs, appropriate measures for the management of risks associated with the drugs should be assessed consistently from the development phase through to the post-marketing phase.

A risk management plan (RMP) is a document containing a summary of risk management for a drug product throughout its life cycle including pre-market development, regulatory review, and post-marketing phases. The RMP consists of the following sections: Safety Specification (important identified risks, important potential risks, and important missing information), Pharmacovigilance Plan (the planned collection and review of information specified in Safety Specification), and Risk Minimization Activities.

RMPs submitted and comprehensible materials and video presentation on introduction to RMP are available on the PMDA website.

What is "PMDA medi-navi"?

The "PMDA medi-navi" (i.e., the pharmaceuticals and medical devices information e-mail service) is an e-mail service that delivers important information on the quality, efficacy, safety, etc., of medical products including drugs to pre-registered e-mail addresses of subscribers, immediately at the time such information is issued. Anyone can subscribe to this service free of charge to obtain important safety information.

The PMDA medi-navi mainly includes:

- Dear Healthcare Professional Letters regarding Emergent/Rapid Safety Communications
- MHLW notifications for instructions on revision of precautions
- Information on product approvals
- Information on Recall (for classes I and II)
- Drug risk information under review

International Activities

While formulating the PMDA International Vision and other policy statements, PMDA has actively promoted international activities such as strengthening partnerships with the US, the EU, and Asian and other countries; participation in and contribution to international harmonization activities such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH); and dissemination of information to the international community in a timely manner. PMDA's efforts have been highly regarded internationally and the agency has been the focus of calls for greater international contribution largely as a result of the substantial reduction in drug and medical device approval times (known as the "elimination of drug and device lags"). Accordingly, PMDA must further contribute to international society.

Under these circumstances, in response to recent changes in the environment surrounding the regulatory agencies and in light of the International Pharmaceutical Regulatory Harmonization Strategy set forth by the Ministry of Health, Labour and Welfare (MHLW) in June 2015, the agency developed the PMDA International Strategic Plan 2015 that specifies international activities the agency should implement by 2023.

As the development, manufacture, and distribution of drugs and other medical products are becoming increasingly globalized, PMDA must increase its efforts to cooperate closely with foreign regulatory authorities, as well as industry and academia. In line with the PMDA International Strategic Plan 2015, PMDA aims to maximize the common health benefits to Japan and the world by building on its experience with international activities, and by making the most of its scientific knowledge, human resources, and electronic information. The three visions and five strategies set out in the strategic plan will serve as the main pillars of PMDA's international activities.

Bilateral Cooperation between PMDA and Foreign Regulatory Authorities (as of the end of December 2021)

PMDA Chief Executive at PIC/S Committee Meeting and Seminar (in Toyama, Japan, November 2019)

A group photograph of participants at the 12th International Summit of Heads of Medicines Regulatory Agencies and the meeting of the International Coalition of Medicines Regulatory Authorities (ICMRA) (in Kyoto, Japan, October 2017)

What is the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use?

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) serves as an international forum where representatives from both the regulatory authorities and pharmaceutical industry discuss the scientific and technical aspects of pharmaceutical regulation to establish guidelines on Quality, Safety, Efficacy, and Multidisciplinary topics. ICH's mission is to "achieve greater harmonization worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner." PMDA, as a member of the Japanese regulatory authority, participates in the ICH Expert Working Group Meeting to involve in the development and revision of the guidelines and facilitate consensus building.

PMDA International Strategic Plan 2015

Three Visions

Vision I: To contribute to the world through regulatory innovation

PMDA will, based on regulatory science, promote public health globally by communicating the outcomes of its first-in-the-world product reviews, safety measures, and relief services

Vision II: To maximize the common health benefits to other countries/regions

PMDA will, in order to realize quicker access to more effective and safer medical products for patients around the globe, communicate more closely with countries around the world to promote regulatory harmonization and collaboration

Vision III: To share the wisdom with other countries/regions

PMDA will, by fully utilizing the accumulated knowledge and experience, contribute to the public health of partner countries/regions through provision of information and training that are essential for building regulatory capacity in those countries

Five Strategies

Strategy 1: Taking the lead, and disseminating the information around the globe

- Establish the "Regulatory Science Center" and other schemes

Strategy 2: Promotion of international regulatory harmonization and global cooperation

- Expediting the global utilization of the Japanese Pharmacopoeia (JP)
- Strengthening the communication with overseas regulatory authorities through mutual personnel exchange

Strategy 3: Increase efficiency of inspections that may lead to future international work-sharing

- Streamline international collaboration in GXP/QMS inspections

Strategy 4: Contribution to international regulatory harmonization activities

- Proactively propose to create guidelines, etc. leading to common health benefit

Strategy 5: Provision of information and training programs that are essential for building regulatory capacity in partner countries

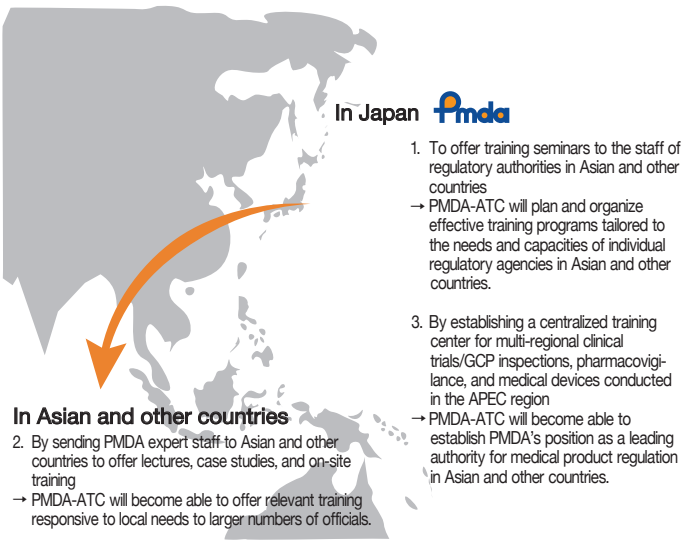
- Launch of "Asian Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs" and other programs

International Activities

Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs

In line with the objectives of the PMDA International Strategic Plan 2015, the Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC) was established in April 2016 as a training center for members of the staff of regulatory authorities in Asian and other countries. The mission of the PMDA-ATC is to promote greater understanding of internationally accepted regulations pertaining to pharmaceuticals and medical devices among regulatory authorities in Asian and other countries. PMDA takes a proactive approach to information sharing and idea exchange with regulators from Asian and other countries regarding its understanding of regulatory science in Japan and accumulated regulatory experience and knowledge. In addition, PMDA-ATC provides training courses including the GMP inspection seminar taking place mainly in the Hokuriku branch office that was established in June 2016. Through offering the training courses, PMDA-ATC promotes higher regulatory standards and the regulatory harmonization in Asian and other countries, thus further strengthening the partnership between PMDA and participating regulatory authorities. In addition to offering in-person training seminars, PMDA-ATC launched webinars in FY 2020 due to the COVID-19 pandemic.

Activities of PMDA-ATC



PMDA-ATC was officially endorsed by the Asia-Pacific Economic Cooperation Conference (APEC) as the APEC LSIF RHSC Training Centers of Excellence for Regulatory Science (CoE) in three fields: multi-regional clinical trials/GCP inspections, pharmacovigilance, and medical devices. Furthermore, the Joint Statement of ASEAN-JAPAN Health Ministers Meeting adopted in 2017 clearly states that the utilization of PMDA-ATC helps improve the regulatory systems of medical products in ASEAN member nations. In this way, PMDA-ATC have been increasingly recognized internationally.

Cooperative Relationships under Grand Design for Asian Pharmaceutical and Medical Device Regulatory Harmonization

Japan aims to realize "Universal Health Coverage (UHC)" as a contribution in the global health sector. In order to realize UHC, it will be essential to disseminate all basic services such as infectious and non-infectious diseases controls, and to respond to the need for prevention, diagnosis and treatment of diseases associated with changes in lifestyle and aging. However, in Asian countries/regions, access to pharmaceuticals and medical devices, including products utilizing innovative technologies, is insufficient, and this is one of the most important issues. International harmonization is considered to play a vital role in resolving this issue. The Basic Principles of the Asia Health and Wellbeing Initiative (hereinafter referred to as the Basic Principles) (approved by the Headquarters for Healthcare Policy of Japan on July 29, 2016, with revision on July 25, 2018) state that Japan will promote harmonization efforts to improve the regulation of pharmaceuticals in Asia. Furthermore, under the Basic Principles, the Grand Design for Asian Pharmaceutical and Medical Device Regulatory Harmonization (on June 20, 2019) and its Implementation Strategy (on July 14, 2020) were formulated by the Headquarters for Healthcare Policy of Japan to present specific initiatives for regulatory harmonization. The policy documents address future initiatives for improvement of the clinical development environment in Asia and the promotion of international regulatory harmonization in which PMDA has been engaged for years.

In response to the government's policy, PMDA reorganized its Office of International Programs in April 2020 to have International Coordination Officers assigned to be responsible for bilateral communication with each of Asian nations. PMDA also endeavors to strengthen its system for further promoting bilateral relationship and regulatory harmonization in Asia by, for example, facilitating human resource development tailored to the individual needs of countries in Asia through training seminars held by the PMDA-ATC.

Collaboration with International Regulators

International collaboration is a key to controlling infectious diseases that can easily spread across the world. PMDA has promptly responded to the public health threat caused by the novel coronavirus disease (COVID-19) in cooperation with the MHLW, overseas regulatory authorities, and other related organizations.

The International Coalition of Medicines Regulatory Authorities (ICMRA), which is an international executive-level coalition of major regulators from every region in the world, provides a global strategic focus for medicines regulators and gives strategic leadership on shared regulatory issues and challenges. ICMRA members discuss international alignment on important topics such as regulatory considerations in the development of COVID-19 treatments and vaccines. PMDA serves as a vice chair of ICMRA and is involved in various ICMRA's activities. In addition, PMDA co-chaired a COVID-19 workshop and moderated the discussion to build a global consensus on evaluation of COVID-19 vaccines.

Furthermore, to enhance and retain the long-established partnerships between PMDA and its overseas regulatory counterparts, PMDA strives to promote international regulatory collaboration by participating in multilateral meetings, such as those of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the International Medical Device Regulators Forum (IMDRF), and the Asian Network Meeting (ANM), and actively holding several bilateral meetings or symposia with international regulators.

Center for Regulatory Science

PMDA's scientific activities must consist of accurate prediction, evaluation, and judgment based on clear evidence, while incorporating the latest scientific findings. To improve its activities, PMDA promotes regulatory science that forms the basis of regulatory decisions.

Regulatory science plays an important role in adapting the achievements of technology to social and human needs in the most optimal way, by making precise prediction, evaluation and judgment based on evidence. The practical application of outcomes of medical research and development activities involves two aspects of regulatory science; the benefits (such as therapeutic effects) and risks (such as adverse reactions) of drugs, etc. as the outcomes of research and development activities are assessed accurately (science) while the best tools that optimize benefits and control the risks are developed to support regulatory decision-making (technology), so that approved products can be used in clinical practice in the most optimal manner.

To further advance regulatory science, PMDA established the Center for Regulatory Science (CRS) in April 2018. Since then, PMDA has made efforts to improve the quality of review and related services and safety measures by creating a collaborative environment where scientific staff members in the CRS work with reviewers from review and safety departments on regulatory science-related activities. A further extension of the aforementioned approach is needed to strengthen the regulatory science research efforts of PMDA. To this end, PMDA newly established the Office of Regulatory Science Research in July 2023, so that its staff members may be actively engaged in regulatory science research.

Center for Regulatory Science

Research Administration

PMDA encourages its scientific staff to pursue regulatory science research so as to increase the quality of review process and safety measures. While supporting the staff members engaged in regulatory science research, PMDA ensures that they are informed of the rules to follow for achieving valuable research outcomes.

In April 2015, PMDA launched the comprehensive partnership program in order to take the initiative in resolving issues identified during the review process and challenges for practical application of state-of-the-art technology, and has since then signed comprehensive partnership agreements with several medical and research institutions that conduct high-quality clinical research. PMDA has made efforts to establish a cooperative and collaborative framework based on personnel exchanges (e.g. staff loaned from partner institutions).

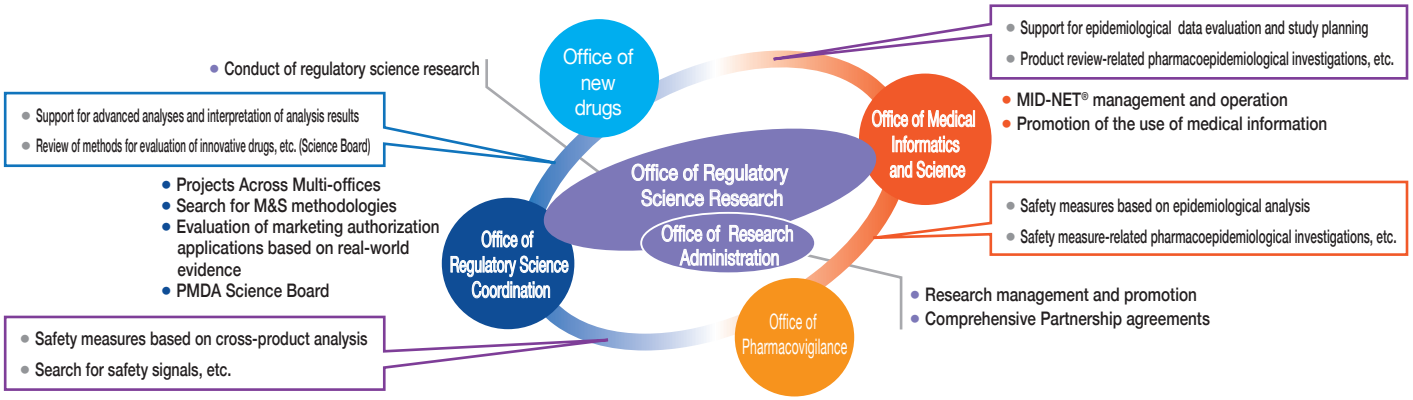
PMDA holds poster and platform presentation sessions highlighting regulatory science research, with the intention of facilitating a better understanding of regulatory science research projects conducted by PMDA's executives and staff and allowing opportunity for author-audience interaction. In the platform presentation session as the main event, PMDA scientists deliver lectures focusing on the activities of the Center for Regulatory Science and the background of their publications. These sessions were favorably accepted by academic researchers, students, and professionals from related industries. The PMDA website also presents the list of, and links to, various papers published by PMDA authors that cover not only regulatory science research but also PMDA's day-to-day activities.

Proactive Publication of Research Outcomes

Year of publication	Number of publications in English	Number of publications in Japanese
2022	27	38
2021	34	37
2020	52	50

Regulatory Science Research

The speed of technological innovation for medical products is increasingly accelerating in recent years. Under these circumstances, PMDA's scientific staff are required to provide appropriate scientific advice to medical product development companies and develop evaluation guidelines after sorting out their own views on innovative technologies, based on regulatory science. In response to these challenges, PMDA established the Office of Regulatory Science Research and assigned its staff members who are actively engaged in regulatory science research. PMDA is aiming at advancing regulatory science research efforts along with appropriately catching up with the latest technologies.



Regulatory Science Coordination

PMDA operates the Projects Across Multi-offices as an approach to addressing topics concerning evaluation and development of medical products including drugs and medical devices. In the cross-sectional projects, staff members from relevant offices across PMDA form working groups by specialized area to discuss individual topics, taking into account international regulatory harmonization. In this way, PMDA leverages the development of standards and guidelines in cooperation with the MHLW.

PMDA has also made a move to effectively use electronic clinical study data submitted for marketing applications, thus improving its product review and consultation services.

During the review of individual product applications, PMDA reviewers are allowed to analyze the submitted data on their own and use the analysis results for evaluation of the product submitted and decision-making. Furthermore, accumulated electronic study data will enable reviewers to perform cross-product analysis or advanced analytical techniques such as modeling and simulation (M&S), thereby leading to enhanced evaluation and consultation.

Utilization of Electronic Study Data Submitted

At submission of product application	During regulatory review		Utilization of the accumulated data
Electronic study data submission	**Utilization of electronic study data**	In the future	**Integration of cross-product information**
● Electronic submission of clinical study data by applicants	● Electronic data which can be accessed by reviewers for visualization and analyses ● Easy retrieval of individual case data and exploration of the data ● Implementation of internal analysis utilizing various techniques		● Review and consultation utilizing exhaustive information organized by therapeutic category ● Internal review on specific issues e.g., active use of M&S for: - Reviewing pediatric dosage - Evaluating performance of assessment measures and analytical techniques ● Utilization of the data for guideline development

Science Board

The Science Board to PMDA was established in May 2015. Its objectives are to respond to the progress of medical innovations and to properly address scientific challenges in the field of advanced science and technology. The Science Board consists of external experts in areas such as medicine, dentistry, pharmaceutical science, and engineering. Evaluation methods for innovative drugs, medical devices, and regenerative medical products are discussed at board meetings.

PMDA actively utilizes the Science Board, thereby reinforcing collaboration and communication with scientists from universities and research institutions and healthcare professionals. This enables PMDA to incorporate the latest scientific knowledge into its services, thus leading to the improvement of its reviews and related services including Regulatory Science Strategy Consultations (R&D) as well as safety measures.

Science Board and its Subcommittees

Responsibilities of Science Board	1. Deciding the main topics to be discussed and establishing Subcommittees for the individual topics 2. Selecting the members of the Subcommittees 3. Confirming draft reports and other materials developed by the Subcommittees 4. Disseminating the latest information on the topics (through presentations, etc.)
Responsibilities of Subcommittees	1. Discussing the topics decided by the Science Board and preparing draft reports

The outcome documents of the Sixth Term Science Board meetings (April 2022 to March 2024)

- Points to consider on therapeutic products based on extracellular vesicles (EV) including exosomes

The outcome documents of the Science Board meetings from the first term to the fifth term (May 2012 to March 2022) are also available on the PMDA website.

Medical Informatics and Science

Real-world data (RWD) that are clinical data collected from various medical sources have been highlighted for their use in assessing the safety and other aspects of drugs in the post-marketing clinical setting. Adverse drug reactions (ADRs) reported from medical institutions and pharmaceutical companies have been used to evaluate the safety of drugs. In this case, however, there were some problems; no ADR reporting was initiated unless any adverse event was regarded as a suspected ADR by healthcare professionals, and the incidence of reported ADRs was difficult to calculate. In response to that situation, PMDA strives to utilize RWD, including electronic medical data, in drug evaluation as a source that is different from ADR reports, etc. For example, electronic medical data contained in the MID-NET® and other databases are used for secondary purposes. Such data are analyzed using pharmacoepidemiological techniques to assess the safety of each individual drug. Currently, the results of analyses are utilized for the actual safety measures, such as the revision of precautions for drugs (package inserts).

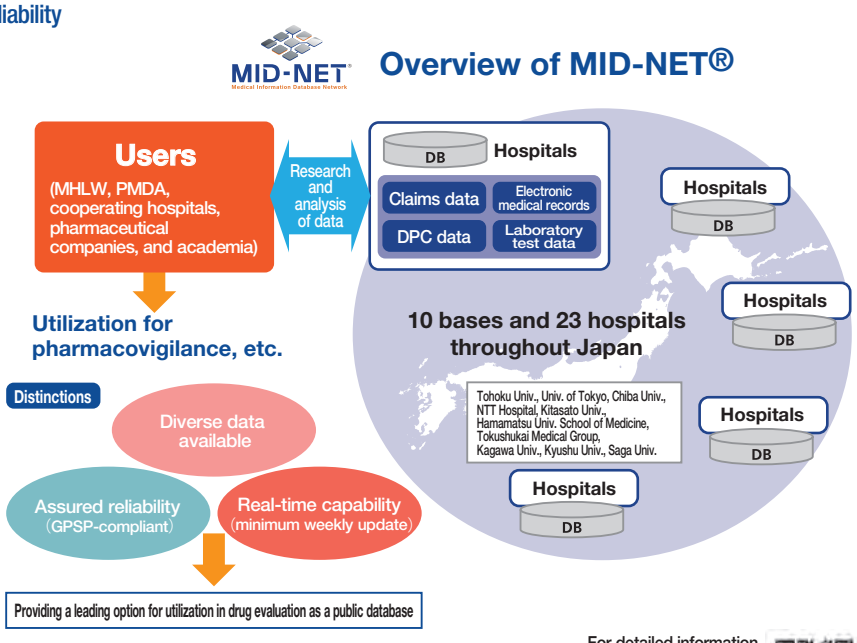
Keys to appropriate drug evaluation using RWD are to achieve the appropriateness of data analysis plans and analytical techniques, understand the distinctions of RWD used, and assure data reliability. PMDA is responsible for the management and operation of the MID-NET® database that is a leading Japanese medical information database. Efforts are made to ensure that the MID-NET® database is in a stable operation while providing assured data reliability. In addition, PMDA considers methods for data quality control and data standardization based on experience with the operation of the MID-NET® database. With the experience and knowledge obtained through tasks related to the MID-NET® operation, PMDA has contributed to the promotion of appropriate utilization of RWD in drug evaluation and other activities.

Through the initiatives mentioned above, PMDA is aiming to support swift implementation of safety measures and improve pharmacovigilance activities, thereby providing increased patient access to more reliable therapeutics drugs.

MID-NET®: A medical information database with assured reliability

The MID-NET® is a medical information database network system developed as a national project in order to analyze data from various data sources. The MID-NET® database contains anonymized electronic medical data such as electronic medical records and claims data retained by cooperating hospitals. The MID-NET® started its full-scale operation in April 2018. The MHLW, PMDA, cooperating hospitals, and other users including pharmaceutical companies and researchers can access the MID-NET® database to make good use of the data for pharmacovigilance. In addition, the qualification of the database users is reviewed by experts for securing the public interest of the system.

Utilization of the MID-NET® enables its users to quantitatively and scientifically evaluate a causal relationship between an adverse event and a particular drug, considering the actual use of the drug in clinical settings. The evaluation results contribute to pharmacovigilance.



- The operation commenced on April 1, 2018
- Please check the following web page for detailed information on MID-NET® such as its distinctions and procedures for use: https://www.pmda.go.jp/safety/mid-net/0001.html

For detailed information on the MID-NET®, scan the 2D code shown on the right.

PMDA's Branches and Exhibition Room for Remembrance of History of Drug-Induced Suffering

Operations at the PMDA Kansai Branch

On October 1, 2013, PMDA established its Kansai Branch in response to requests for the "arrangement of a PMDA-WEST function" which had been proposed by several prefectural and municipal governments including Kyoto Prefecture, Osaka Prefecture, Hyogo Prefecture, Kyoto City, Osaka City, and Kobe City in order to support the promotion of businesses in the Kansai Innovation Comprehensive Global Strategic Special Zone. The proposal was implemented after discussion between the national and local authorities.

The primary operations of PMDA's Kansai Branch include provision of Regulatory Science General Consultations and Regulatory Science Strategy Consultations (R&D) (for pre-consultation meetings), operation of the video conferencing system at the Kansai Branch, and on-site GMP/QMS/GCTP inspections of facilities in the Kansai region.

Video Conferencing at the Kansai Branch Office

The video conferencing system allows a live video connection between the PMDA headquarters in Tokyo and the Kansai branch office. The system enables academic institutions and companies located in the Kansai region to hold consultation meetings without leaving their home region, in order to receive guidance and advice from reviewers participating in the meeting at the Tokyo office. Thus, the Kansai Branch contributes to the efficient use of PMDA's consultation services.

Extensive consultations such as Regulatory Science Strategy Consultations (R&D), clinical trial consultations, and consultations concerning safety measure are available at the Kansai Branch.

A video conference room of the Kansai branch office

Operations at the PMDA Hokuriku Branch

On June 9, 2016, PMDA established its Hokuriku Branch in accordance with the basic policies for relocation of government-related agencies. The Hokuriku Branch is intended to offer GMP inspection seminars organized by the Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs.

A view of the GMP Inspection Seminar

A view of the Quality Control (Herbal Medicine) Seminar

Exhibition Room for Remembrance of History of Drug-induced Suffering

The exhibition room for remembrance of the history of drug-induced suffering was opened within PMDA in March 2020. The exhibition is intended to explain the history of drug-induced suffering and lessons learned therefrom, thereby raising the public awareness of drug-induced suffering. Visitors can read explanatory text panels and watch video testimonies of suffers of drug-induced health damage in the exhibition room. PMDA will welcome not only healthcare and educational professionals but also the general public.

Business days	Monday through Friday (except for national holidays and year-end and New Year's holidays)
Business hours	10 am to 5 pm (excluding 12 pm to 1 pm)
Admission fee	Free
Location	14th Floor, Shin-Kasumigaseki Building, 3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo

Before visiting the Exhibition Room, please check the PMDA website for details. Besides, please confirm the availability of the Exhibition Room on the day you will visit. If a group reservation has been made for the Exhibition Room, other visitors will not be accepted during the time reserved by group visitors.

Contact & Map

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How to Find Us - Location Maps

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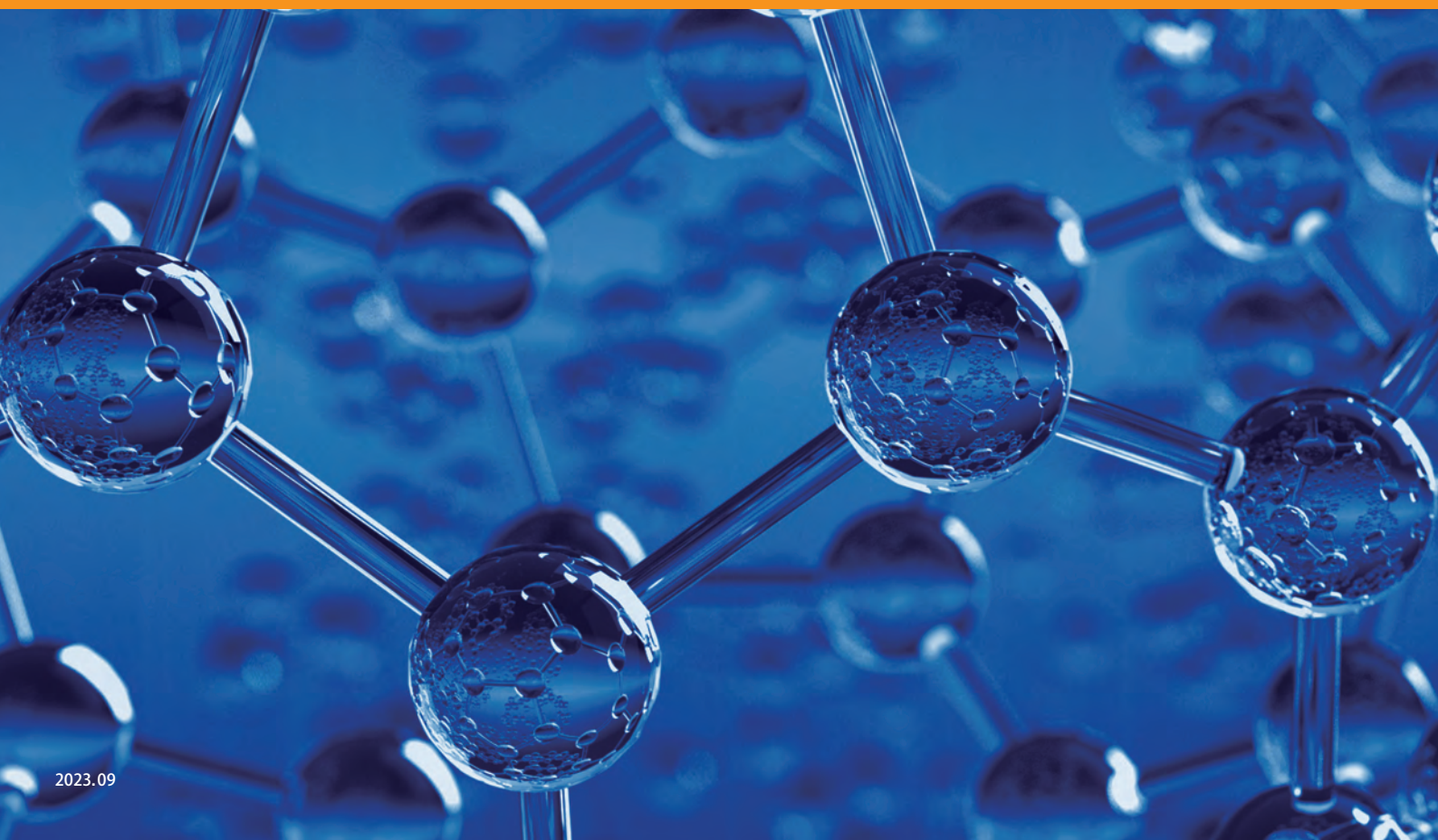

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