Regulatory Science Activity Report

FY2024

PMDA

独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

CONTENTS

1. PMDA Regulatory Science Activity Report

The Pharmaceuticals and Medical Devices Agency (PMDA) is a regulatory authority dedicated to promoting public health and safety through the evaluation and approval of pharmaceuticals and medical devices, implementation of safety measures, and provision of relief services for adverse health effects (Figure 1) (for additional details, visit the PMDA website: https://www.pmda.go.jp/english/index.html).

Figure 1. The Three Roles of PMDA—Safety Triangle

PMDA operations must be anticipated, assessed, and evaluated appropriately and promptly using the most current scientific knowledge. To improve the quality of these operations, the PMDA Regulatory Science Center promotes regulatory science (RS) as the foundational scientific approach. The Fifth Mid-Term Plan of PMDA, which commenced in fiscal year 2024 (FY2024)[1] , aims to further advance RS research and related activities, with a greater focus on active dissemination of RS-related information.
This activity report provides an overview of RS-related activities undertaken by PMDA from this perspective. The FY2024 Activity Report highlights collaborative efforts between PMDA and external organizations, Science Board that facilitate discussions with outside experts, Early Consideration that serve as reference points for promoting to adopt new technologies in drug development, RS research workshops that share and discuss various scientific issues from RS perspective, PMDA-involved research activities and related information dissemination efforts, and examples of safety evaluations using real-world data. It is hoped that this report will serve as a valuable resource for understanding the scope and progress of RS-related activities at PMDA.

1 Pharmaceuticals and Medical Devices Agency 5th Mid-term Plan https://www.pmda.go.jp/files/000267756.pdf

2. Introduction

2.1 PMDA Regulatory Science Center: Overview and History

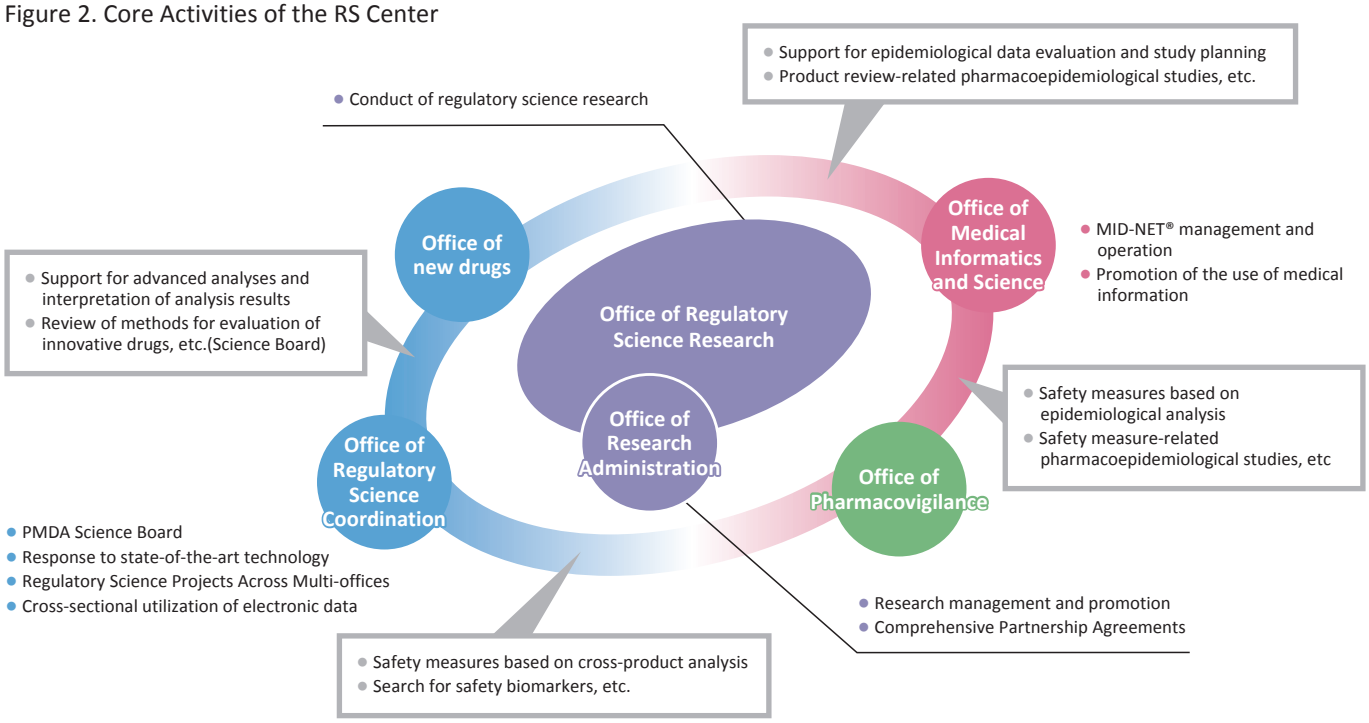
RS is defined as “the science to make precise prediction, evaluation and judgment based on evidence and adapt the achievements of technology to social and human needs in the most optimal way so that the achievements will help people and the society.”[2]

PMDA regards RS as the science aimed at the optimal introduction into society of new products of science, such as discovered substances and new scientific tools and technologies as well as knowledge and information[3] . National policy supports the promotion of RS in translating the outcomes of medical research and development into practical use within society[4] . From this perspective, PMDA has been implementing various initiatives to advance RS.

To further promote RS, PMDA established the RS Center in April 2018. A framework was created to facilitate collaboration with the Review and Safety Departments in RS-related activities with the goal of advancing operational quality. In July 2023, to strengthen the in-house RS research framework, PMDA established the RS Research Department, a new division dedicated to RS research (Figure 2).

Furthermore, the RS Strategic Committee was established in June 2024 as an internal body tasked with addressing RS-related issues across departments and formulating policies to implement RS-related activities more strategically within PMDA.

Figure 2. Core Activities of the RS Center



2 Basic Program for Science and Technology (approved by the Cabinet on August 19, 2011) https://www8.cao.go.jp/cstp/kihonkeikaku/4honbun.pdf

3 Regulatory science as a bridge between science and society. *Clin Pharmacol Ther* 90, 29 (2011).10.1038/clpt.2011.89 https://pubmed.ncbi.nlm.nih.gov/21691273/

4 Law for Promotion of Health and Medical Care Strategy (Law No. 48 of 2014) https://laws.e-gov.go.jp/law/426AC0000000048

2.2 PMDA Fifth Mid-term Plan

Based on the mid-term targets set by the Ministry of Health, Labour and Welfare[5] for the period FY2024–FY2028, PMDA formulated the Fifth Mid-Term Plan (Table 1)[6] . To support the achievement of these targets, PMDA publishes an updated version of the plan annually. Activities of the RS Center focus on "strengthening human resources" "enhancing scientific evidence," "strengthening public communication," and "contributing to the further utilization of medical information." The FY2024 annual plan[7] is presented in Table 2.

Table 1. Pharmaceuticals and Medical Devices Agency Fifth Mid-Term Plan

Improving operational quality through the promotion of RS	
Strengthening human resources	• Develop personnel with an understanding of clinical and related settings through exchanges with external institutions, including those with Comprehensive Partnership Agreements • Develop professionals capable of leading scientific discussions through active engagement in RS activities
Enhancing scientific evidence	• Strengthen organizational research capacity by expanding research efforts • Establish a system for consolidating issues on the review and consultation to facilitate cross-departmental discussion
Strengthening public communications	• Publish findings from RS research and related activities in English-language journals and other academic platforms
Contributing to the further utilization of medical information	• Further improve the accessibility of the Medical Information Database Network(MID-NET®) • Disseminate information on the standardization and quality control of medical information

Table 2. Pharmaceuticals and Medical Devices Agency FY2024 Plan

Improving operational quality through the promotion of RS	
Strengthening human resources	• Proceed with consideration of specific initiatives in re-conclusion of Comprehensive Partnership Agreement • Steadily advance initiatives to secure and expand opportunities to learn about situation of clinical fields through personnel exchange, opinion sharing, and external training with external institutions, including those with Comprehensive Partnership Agreements • Secure opportunities to improve logical thinking skills, including RS-related training, lectures and discussions with expert at academic conferences in Japan and abroad, and consider ways to enable identification and organization of issues in daily work with a greater awareness of RS perspective • To promote research-related work, proceed with consideration of systems about support and appropriate evaluation for research conduction
Enhancing scientific evidence	• Set a high effort rate for research-related work by the Office of RS Research staff and develop research environment, including securing research funds necessary for conducting research, managing their execution, and cooperation with other departments • Proceed with the application for designation as a research institute and the consideration of related regulations as a foundation for stable research activities • Develop related regulations to establish a system to conduct studies more systematically through organizing information at the RS Center, promoting discussions in the Science Board, and enhancing progress management of cross-department studies
Strengthening public communication	• Actively publish the results of RS research-related work in English papers, reports, RS research workshops, and proceed with the improvement of the environment for further strengthening to disseminate information, and on dissemination of information to external stakeholders
Contributing to the further utilization of medical information	• understand user needs of MID-NET® through exchanging opinions with pharmaceutical companies and explore ways to improve usability of MID-NET® • Examine data management methods and system infrastructure necessary to accommodate expansion of data size • Continue to review operational methods to ensure stable operation of MID-NET® • Actively share technological insights and knowledge related to standardization and quality control gained through the development and operation of MID-NET® at explanatory meetings, etc.

5 Pharmaceuticals and Medical Devices Agency 5th Mid-term Target. https://www.pmda.go.jp/files/000267755.pdf
6 Pharmaceuticals and Medical Devices Agency 5th Mid-term Plan. https://www.pmda.go.jp/files/000267756.pdf
7 Pharmaceuticals and Medical Devices Agency Annual Plan FY2014. https://www.pmda.go.jp/files/000267757.pdf

3. Results of RS-related Activities in FY2024

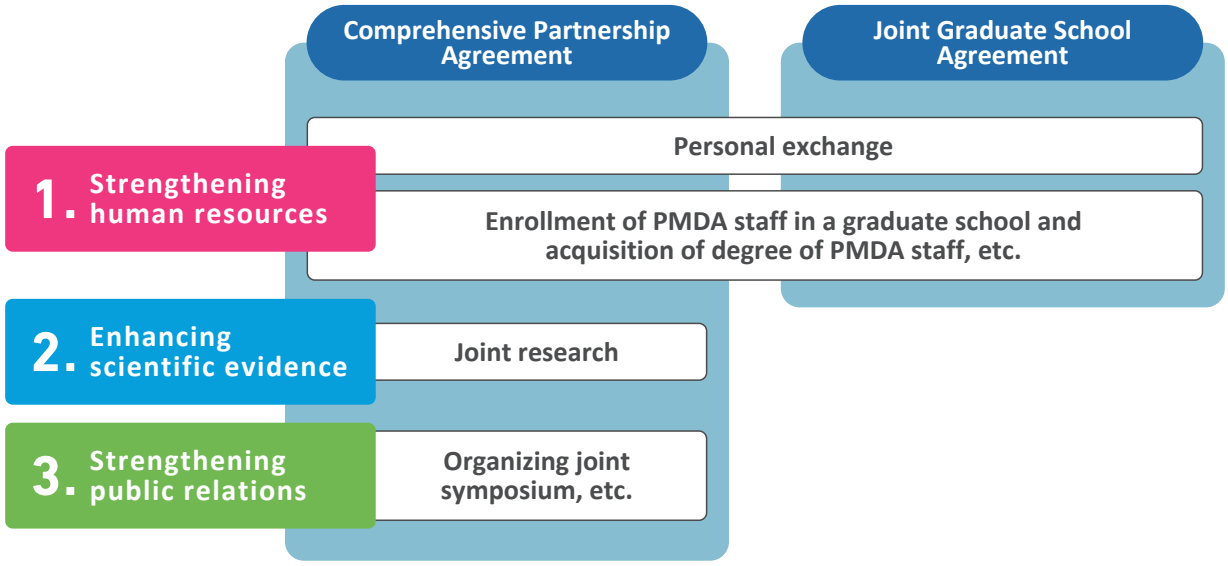
This chapter presents the primary RS-related activities conducted during FY2024.

3.1 Strengthening Human Resources

3.1.1 Activities under Comprehensive Partnership Agreement and Joint Graduate School Agreement for Development of RS Human Resources

PMDA has established a system to work in cooperation and collaboration with external organizations, such as universities / incorporated educational institutions and research & development agency in order to proactively solve the problems revealed in the course of operations and the issues for the practical application of state-of-the-art technologies. This system includes Comprehensive Partnership Agreements that strengthening human resources (e.g., personal exchange, academic degree support), enhancing scientific evidence (e.g., joint research), and strengthening public relations (e.g., organizing joint symposium) as well as Joint Graduate School Agreements that primarily aim to strengthen human resources in RS (Figure 3).

Figure 3. Activities under Comprehensive Partnership Agreement and Joint Graduate School Agreement

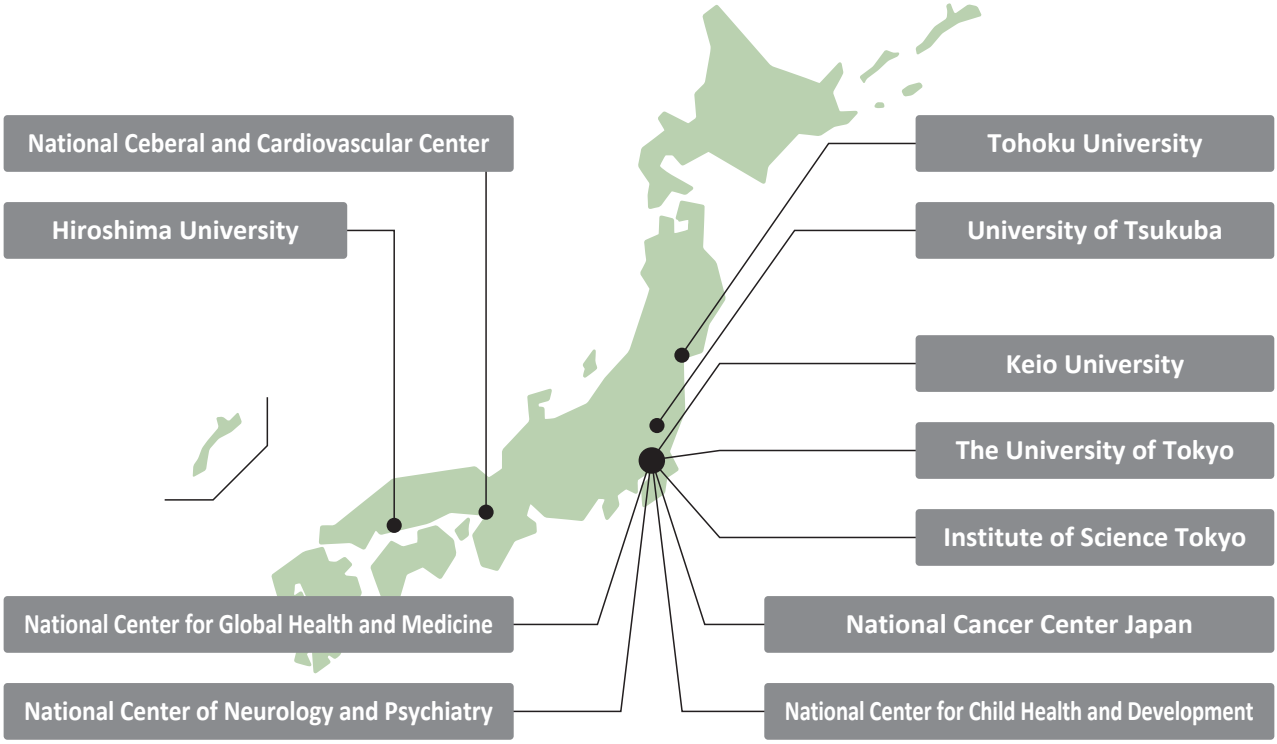


We believe that these activities are beneficial for both PMDA and collaborating organizations from the following viewpoints and contribute to the development of human resources who can lead discussions in the RS field.

- ☑ **Acquisition of knowledge about RS**
- ☑ **Better understanding of the actual situation of medical care or research**
- ☑ **Acquisition of latest scientific technologies and knowledge**

As of March 31, 2025, there are 11 organizations that have concluded the Comprehensive Partnership Agreement. The names of these organizations are as shown in Figure 4.

Figure 4. Comprehensive Partnership Agreement Organizations (as of March 31, 2025)



The major activities of each organization under the Comprehensive Partnership Agreement for FY 2024 are shown in Table 3 below.

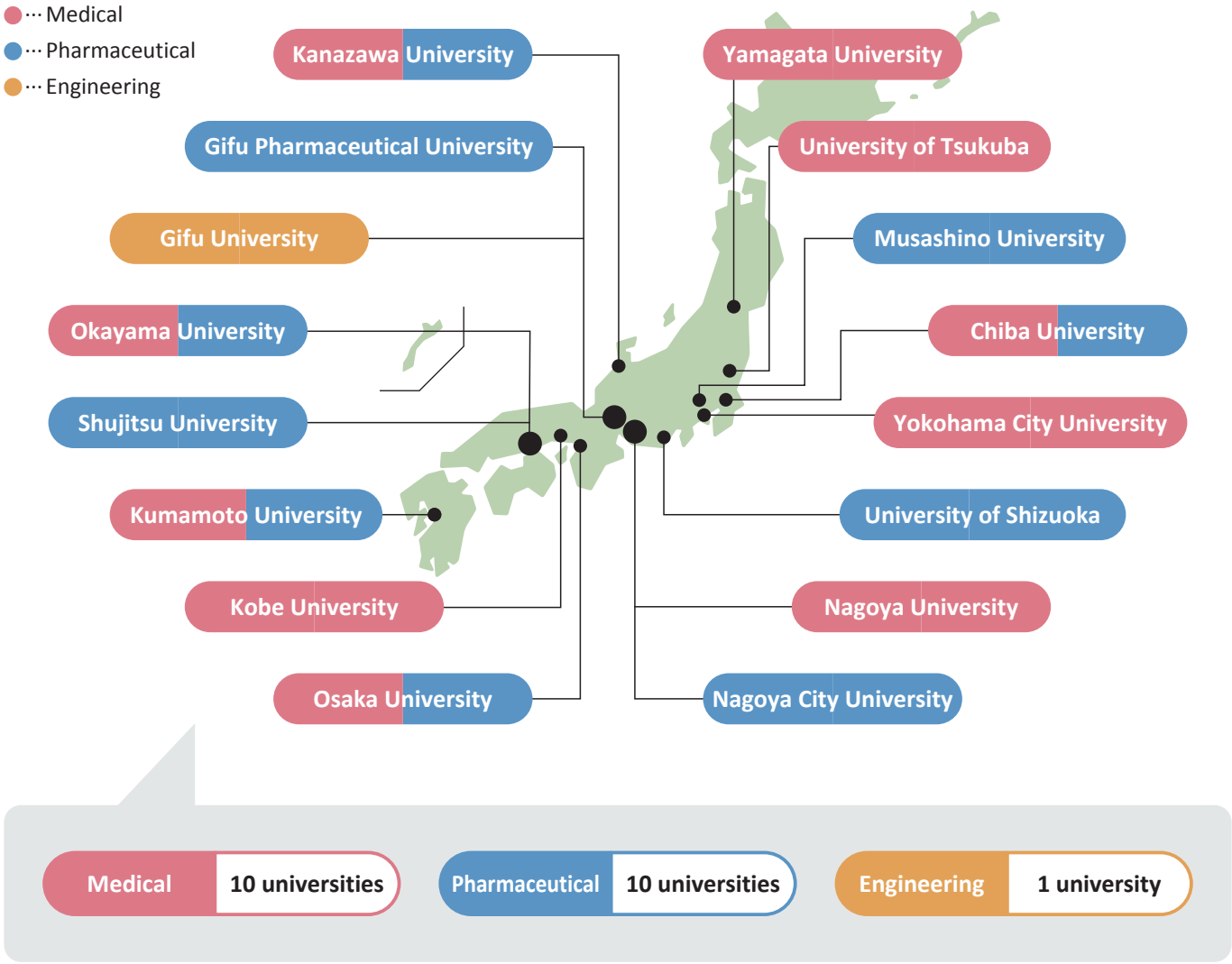
Table 3. Major Activities at the Comprehensive Partnership Agreement Organizations

Contract organizations (In order of the agreement concluded)	Major Activities in FY2024
National Cancer Center Japan Click here for website	• Long-term on-site training for PMDA staff (Pharmaceutical Department and Clinical Trial Management Department)
Hiroshima University Click here for website	• Seminars and RS-focused lectures by PMDA staff at the Graduate School of Medicine and Scientific Research
Keio University Click here for website	• RS-related lectures by PMDA staff at the Faculty of Pharmacy and the Graduate School of Medicine • Specialized pharmacometrics training programs for PMDA staff
University of Tsukuba Click here for website	• RS-related lectures by PMDA staff at the Graduate School of Human Sciences
National Center of Neurology and Psychiatry Click here for website	• Committee tour training for PMDA staff (e.g., clinical trial review board) • Facility tours for PMDA staff (e.g., disease model breeding facilities)
Tohoku University Click here for website	• Joint research initiatives (e.g., optimization of development and reconsideration for the guideline on proper medical device use) • Lectures by PMDA staff at the Faculty of Pharmaceutical Sciences
National Center for Global Health and Medicine Click here for website	• Long-term on-site training for PMDA staff (Pharmaceutical Department) • Study tour training programs of clinical trial management for PMDA staff
National Cerebral and Cardiovascular Center Click here for website	• Medical site tours for PMDA staff (e.g., clinical sites and nonclinical study labs)

Contract organizations (In order of the agreement concluded)	Major Activities in FY2024
National Center for Child Health and Development Click here for website	• Long-term on-site training for PMDA staff (Pharmaceutical Department)
Institute of Science Tokyo(formerly Tokyo Medical and Dental University) Click here for website	• RS-focused lectures by PMDA staff at the Industry–University Collaboration Council
The University of Tokyo Click here for website	• RS-related lectures by PMDA staff at the Graduate School of Interdisciplinary Information

Figure 5 shows universities/incorporated educational institutions with which Joint Graduate School Agreements has been concluded as of March 31, 2025.

Figure 5. Joint Graduate School Agreement Organizations (as of March 31, 2025)



In FY2024, to contribute to the development of human resources in the RS area, PMDA dispatched more than 130 staff members to give more than 210 RS-related lectures at more than 60 universities. Of these, RS-related lectures and related activities were given by 17 PMDA staff members under the Joint Graduate School Agreements and by 23 PMDA staff members under the Comprehensive Partnership Agreements. They served as visiting faculty members at the respective institutions.

3.2 Enhancing Scientific Evidence

To strengthen the scientific evidence base, PMDA conducts discussions through its Science Board and performs cross-sectional reviews. It also works to improve the research capacity of the organization as well as its research environment.

3.2.1 The Science Board and Measures for Advanced Science and Technology

PMDA has established the Science Board composed of external experts with diverse areas of expertise to deliberate on the scientific aspects of reviews involving pharmaceuticals, medical devices, regenerative medical products, and related fields. The Science Board facilitates the appropriate evaluation and commercialization of advanced science and technology and aims to improve the quality of reviews and safety measures.

To address scientific challenges, PMDA implements timely measures in response to emerging technologies by consulting external experts based on the specific context of each theme.

In July 2024, the regulations governing the Science Board were revised to allow for more agile and continuous responses to operational challenges.

Additional information regarding the Science Board and initiatives related to advanced science and technology is available on the website below.

PMDA website The Science Board Measures for advanced science and technology

In 2024, reports were published on the following topics:

Theme

***In vivo* Gene Therapy Products with Target Specificity**

Background and Objectives

Gene therapy can be categorized into two main approaches:

1. *In vivo* gene therapy, wherein a vector carrying the therapeutic gene is administered directly to a patient
2. *Ex vivo* gene therapy, wherein cells are harvested from a patient, genetically modified outside the body, and then reintroduced into the patient

A representative example of *ex vivo* gene therapy is chimeric antigen receptor T-cell (CAR-T) therapy, which is used to treat B-cell malignancies. However, the *ex vivo* approach requires substantial resources, including facilities, goods, and personnel. Consequently, there is increasing interest in transitioning from *ex vivo* to *in vivo* gene therapy approaches. Advancing *in vivo* gene therapy requires careful consideration of target specificity, which is more critical than that in previously developed approaches. Clarifying the key considerations and evaluation challenges in this context would facilitate appropriate development in this field.

* For further details, please refer to the relevant pages of the Science Board[8] .

8 Subcommittee on Cell and Gene Therapy Products Produced in vivo https://www.pmda.go.jp/english/rs-sb-std/sb/subcommittees/0031.html

Discussion Highlights

- Characteristics of vectors used in *in vivo* gene therapy and current development trends
- Key considerations for product development using vectors, particularly before the initiation of clinical trials, and guidance on designing clinical trial protocols

Results

The document titled “Points to Consider in the Development of *in vivo* Gene Therapy Products with Target Specificity - Including *in vivo* CAR-T Development” (July 4, 2024) was published in both Japanese and English.
This report is expected to support the appropriate development of gene therapy products by supplementing existing guidelines and previously issued notifications.

PMDA website Japanese English

3.2.2 RS Projects Across Multi-Offices in PMDA

To address cross-sectional issues on reviews and safety measures, PMDA established working groups (WG) consisting members from multiple departments for each identified issue. This group has been responsible for articulating the underlying concepts and formulating guidelines to support issue resolution.

In FY2024, the existing WG ("the Projects Across Multi-offices") underwent progressive reorganization. This led to the launch of a new initiative, the "RS Projects Across Multi-Offices" in October 2024. The objective of this initiative is to develop a more systematic approach to cross-sectoral issues.

The "RS Projects Across Multiple-Offices" comprises two components: a Cross-Sectional Project Team (PT), which is responsible for drafting notifications and guidelines for each project, and an Opinion Exchange Working Group, which facilitates discussions on cross-cutting issues related to review and safety measures.

The objectives of the activities conducted by PTs and WGs are summarized in Table 4.

PMDA website Japanese English

Table 4. Objectives of Activities Conducted by PTs and WGs in RS Projects Across Multi-Offices

Project Team(PT)	Objective of Activity
Project team for Consideration of Inquiries Concerning Pediatric Drugs Development Program	• This project team considers policy of inquiries concerning pediatric drugs development program in consultation service and approval review of a new drug development for adults.

Working Group(WG)	Objective of Activity
Multi-Regional Clinical Trials WG	• This WG aims to standardize internal opinions and responses within the New Drug Department regarding the handling and necessity of Japanese data, including Multiregional Clinical Trials.
Pediatric Drugs WG	• This WG addresses various projects related to pediatric drug development through cross-sectoral collaboration and by facilitating discussions with both domestic and international stakeholders.
Orphan Drugs WG	• To promote the development of orphan drugs in Japan, this WG disseminates relevant information domestically and internationally and engages in discussions with key stakeholders.
Companion Diagnostics WG	• This WG facilitates discussions on the rational use and development of companion diagnostics.
Patient Centricity WG	• This WG promotes patient engagement initiatives, including cross-sectoral policy discussions on collaboration with patients.

Major notifications issued in FY2024 as a result of cross-functional studies are presented in Table 5. The table summarizes the outcomes of the previous WG under the Projects Across Multi-offices.

Table 5. Major Notifications, etc. Issued through Cross-sectional Studies (FY2024)

WG/PT	Notifications, guidelines, etc.	Overview
Project team for Consideration of Inquiries Concerning Pediatric Drugs Development Program	Initiatives to Promote Pediatric Drug Development, PMDA/CPE Notification No. 1618, PMDA/CRS Notification No. 15 issued by Pharmaceuticals and Medical Devices Agency Director of Center for Product Evaluation Director of Center for Regulatory Science on March 21, 2025 https://www.pmda.go.jp/files/000274940.pdf	During clinical trial consultations, appropriate advice and guidance are provided based on a comprehensive understanding of the drug development plan, including pediatric development. The basic concepts and key considerations for pediatric drug development are clarified.
Companion Diagnostics WG	Partial revision of "Guidance on Drug-Agnostic Companion Diagnostics," Administrative Notice issued by Pharmaceutical Evaluation Division, Medical Device Evaluation Division, Pharmaceutical Safety Division, and Compliance and Narcotics Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare on May 22, 2024 https://www.pmda.go.jp/files/000274873.pdf	Regarding the “Guidance on Companion Diagnostic Drugs, etc.” (Notification No. 0628013 of the PMDA, dated June 28, 2022; hereinafter referred to as the “Guidance”), the Ministry of Health, Labour and Welfare(MHLW)compiled a framework for ensuring compliance with the MHLW Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Drugs (Ordinance No. 169 of 2004) in the development of companion diagnostics that span multiple drug categories and subsequently issued a partial revision of the Guidance.
Real World Data (RWD) WG*	Questions and Answers on Points to Consider for Ensuring Reliability when Using Data of Registry or Medical Information Database in Applications for Approval and Use-Results Evaluation of Medical Devices, Administrative Notice issued by Medical Device Evaluation and Management Division, Pharmaceutical Affairs Bureau, Ministry of Health, Labour and Welfare on May 29, 2024 https://www.pmda.go.jp/files/000271519.pdf	Organizing general considerations for confirming the reliability of registry or medical information databases to be used when an applicant uses data from a registry or medical information databases for applications of approval or use–results evaluation of medical devices.
	Points to Consider When Registry Data are utilized for Partial Change Approval Applications or Revision of Electronic Package Insert for Prescription Drug, PSB/PED Notification No. 1004-4, PSB/PSD Notification No. 1004-1 issued by Director, Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, and Director, Pharmaceutical Safety Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare on October 4, 2024 https://www.pmda.go.jp/files/000274894.pdf	Key Considerations for Using Registry Data in Application for Partial Changes to Ethical Drug Approvals and Revisions of Electronic Package Inserts.
Medical Device International Affairs WG*	Handling of Minor Change Procedures for Partial Modification Related to Cybersecurity Measures in Medical Devices, PSEHB/MDED Notification No. 0423-1 issued by Director of Medical Device Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare on April 23,2024 https://www.pmda.go.jp/files/000268363.pdf	Outlines procedures for notifying or omitting procedural steps in cases of minor changes to cybersecurity in medical devices.

*WGs involved in the Projects Across Multi-offices, which was progressively dissolved in October 2024

3.2.3 Early Consideration, Guidance, and Guidelines

PMDA promotes responses based on the latest scientific knowledge through the dissemination of Early Consideration and the development of guidelines.

Early Consideration

What is Early Consideration?

Early Consideration refers to the perspective of PMDA on the potential direction of product development, provided as reference information to support the practical application of innovation and the advancement of innovative drug development, even in situations wherein scientific knowledge and supporting data remain insufficiently established.

Positioning and Points to Note

Early Consideration outlines the policy of PMDA at the time of publication regarding the practical application of innovative technologies and the issues to be addressed in the development and evaluation of pharmaceuticals. These policies may change in the future in response to new knowledge, scientific advances, and discussions with industry and academia.

Achievement

In FY2024, PMDA issued 15 Early Considerations, as listed in Table 6, and published them on its website. PMDA intends to continue releasing the corresponding report beyond FY2025.

PMDA website Japanese English

Table 6. Early Considerations (FY2024)

Titles	Overview
Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 5) Quality data required for the approval review of changing a strain in the vaccine for which the manufacturing process is well established, Issued by Office of Vaccines and Blood products, Pharmaceuticals and Medical Devices Agency on May 29, 2024 https://www.pmda.go.jp/files/000272657.pdf	Outlines the quality data required for the approval review (application for partial change in marketing approval) of the SARS-CoV-2 vaccine, for which the manufacturing method has been sufficiently established in Japan
Points to Consider for the Design of Clinical Trials to Assess the Effects of Psychotropic Drugs on Driving Performance, issued by Pharmaceuticals and Medical Devices Agency Office of New Drug lll on August 15, 2024 https://www.pmda.go.jp/files/000271233.pdf	Provides considerations for designing clinical trials to assess the effects of psychotropic drugs on driving performance
Statistical Considerations When Planning Phase I Clinical Trials in Oncology - From the Safety Perspective, issued by Center for Product Evaluation, Pharmaceuticals and Medical Devices Agency on December 4, 2024 https://www.pmda.go.jp/files/000272425.pdf	Provides safety-related considerations for evaluating the operational characteristics of dose-escalation designs based on statistical evaluation of oncology drugs during the 30-day-Clinical Trial Notification Review
Points to consider in the clinical development of drugs for transthyretin amyloid cardiomyopathy, issued by Office of New Drug II, Pharmaceuticals and Medical Devices Agency on December 26, 2024 https://www.pmda.go.jp/files/000273604.pdf	Addresses considerations for clinical trial design for drugs targeting transthyretin amyloid cardiomyopathy, including the need to adapt development strategies to implement changes in clinical practice and to reduce mortality through early therapeutic intervention

Consideration in the development of drugs for pulmonary arterial hypertension, issued by Office of New Drug II, Pharmaceuticals and Medical Devices Agency on January 7, 2025 https://www.pmda.go.jp/files/000273753.pdf	Highlights considerations for planning clinical trials for drugs intended to treat pulmonary arterial hypertension (PAH) in Japan, particularly for patients (including pediatric cases) whose prognosis remains poor despite current therapies, as the development of new PAH therapies is ongoing
Example of Documents on Assessment and Control of DNA Reactive (Mutagenic) Impurities attached to Clinical trial Notification, issued by Center for Product Evaluation, Pharmaceuticals and Medical Devices Agency on January 16, 2025 https://www.pmda.go.jp/files/000274534.pdf	Provides an example method for preparing data to evaluate and manage mutagenic impurities in clinical trial notifications, based on the operational experiments of the ICH M7 guideline, to make investigations more efficient and conduct clinical trials smoothly
Checklist for Common Inquiry Cases to Be Noted When Submitting Approval Applications for New Active Ingredient Containing Pharmaceuticals (Chemical Products), Administrative Notice issued by Center for Product Evaluation, Pharmaceuticals and Medical Devices Agency on January 16, 2025 https://www.pmda.go.jp/files/000274535.pdf	Offers a checklist based on frequently raised inquiries during the quality assessment process for new drug applications, including supplementary explanations and reasons for each point, to help applicants verify dossier contents
Points to Consider for Clinical Efficacy Evaluation of Drugs for Palmoplantar Pustulosis, Administrative Notice issued by Office of New Drug IV, Pharmaceuticals and Medical Devices Agency on January 23, 2025 https://www.pmda.go.jp/files/000273110.pdf	Summarizes the current view of the reviewers on evaluating the efficacy of drugs for treating palmoplantar pustulosis, and the exchange of views with relevant parties including academia and industry at the annual meeting of the Japan Society for Clinical Trials and Research (March 2024)
Concept on “Clinical Evaluation of Drug Interactions Using Endogenous Biomarkers, Administrative Notice issued by Center for Product Evaluation, Pharmaceuticals and Medical Devices Agency on February 14, 2025 https://www.pmda.go.jp/files/000273869.pdf (in Japanese)	Describes the new approach to using endogenous biomarkers for clinical evaluation of drug interactions, consistent with ICH-M12 guidelines
"Points to Consider in Developing Drugs for Pediatric Inflammatory Bowel Disease, Administrative Notice issued by Pharmaceuticals and Medical Devices Agency, Office of New Drug I on March 24, 2025 https://www.pmda.go.jp/files/000274641.pdf	Provides considerations for planning clinical trials of therapeutic drugs for inflammatory bowel disease in children, with the aim of facilitating drug development for this population
Points to consider for externally controlled trials, issued by Center for Product Evaluation, Pharmaceuticals and Medical Devices Agency on March 24, 2025 https://www.pmda.go.jp/files/000275337.pdf	Presents guidance on evaluating the efficacy and safety of drugs using externally controlled trials, including the use of multiple data sources, in marketing approval applications
Points to Consider for Clinical Development of Drugs Intended for Treatment of Antimicrobial-resistant Gram-negative Bacterial Infections, issued by Pharmaceuticals and Medical Devices Agency, Office of New Drug IV on March 24, 2025 https://www.pmda.go.jp/files/000275729.pdf	Details considerations for clinical development of drugs for treatment of antimicrobial-resistant gram-negative bacterial infections, based on insights from recent clinical trial consultations and approval reviews
Points to consider for the discussion with PMDA using the ICH S1B (R1) guideline and in the approval application, issued by Center for Product Evaluation, Pharmaceuticals and Medical Devices Agency, on March 24, 2025 https://www.pmda.go.jp/files/000274671.pdf	Clarifies discussion points with PMDA on exemptions from rat carcinogenicity studies under the ICH S1B(R1) guidelines, and application for approval

Points to Consider for nonclinical safety matters when submitting the initial clinical trial notification, issued by Center for Product Evaluation, Pharmaceuticals and Medical Devices Agency on March 25, 2025 https://www.pmda.go.jp/files/000274660.pdf	Summarizes common inquiries regarding initial clinical trial notifications in recent years, outlining basic concepts for non-clinical safety information, pregnancy avoidance, and inclusion criteria for lactating women
Considerations for Non-Clinical Studies in the Development of Diagnostic Radiopharmaceuticals, issued by Office of New Drug II, Pharmaceuticals and Medical Devices Agency on March 26, 2025 https://www.pmda.go.jp/files/000275204.pdf	Describes an additional explanation of the contents of the "Guideline for Clinical Evaluation of Diagnostic Radiopharmaceuticals" and outlines the current regulatory perspective on non-clinical studies required in the development of diagnostic radiopharmaceuticals, aligned with the newly issued ICH guidelines

Guidance and Guidelines

Table 7 lists the guidance and guidelines (excluding those related to Early Consideration and ICH matters) issued or co-issued by PMDA in FY2024.

Table 7. Guidance and Guidelines (FY2024)

Titles	Overview
Questions and Answers (Q&A) on Release Testing of the Imported Regenerative Medical Products, Administrative Notice, issued by Medical Device Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, and Compliance and Narcotics Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare on May 30. 2024 https://www.pmda.go.jp/files/000269306.pdf	Questions and Answers (Q&A) regarding release testing of the imported regenerative medical products
Partial Revision of the “Procedures for Developing Post-marketing Study Plans for Drugs, ” PSB/PED Notification No. 0718-1, PSB/PSD Notification No. 0718-1, issued by Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, and Director of Pharmaceutical Safety Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare on July 18,2024 https://www.pmda.go.jp/files/000274320.pdf	Review of procedures for developing post-marketing study plans for drugs, considering recent changes in the drug discovery environment, international harmonization, and the past achievement in the post-marketing safety measures in Japan
Notes on the Evaluation of Efficacy and Safety Using Information Collected as Electromagnetic Records through Information and Communication Devices in Clinical Trials and Post-Marketing Clinical Trials, PSB/PED Notification No. 0920-1, PSB/MDED Notification No. 0920-1, issued by Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, and Director of Medical Device Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare on September 20, 2024 https://www.pmda.go.jp/files/000270881.pdf (in Japanese)	Key considerations for evaluating efficacy and safety using electromagnetic methods, in light of recent developments in information and communication technologies and the increasing diversification and efficiency of clinical trials utilizing such technology
Points to Consider When Registry Data are utilized for Partial Change Approval Applications or Revision of Electronic Package Insert for Prescription Drugs, PSB/PED Notification No. 1004-4, PSB/PSD Notification No. 1004-1, issued by Director, Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, and Director, Pharmaceutical Safety Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, on October 4,2024 https://www.pmda.go.jp/files/000274894.pdf	Guidance on the use of registry data for partial change approval applications and for revising electronic package inserts for prescription drugs

Operation Methods for Changing the Scope of Conduct Based on Risk in Conformity Surveillance of Pharmaceuticals and Regenerative Medical Products, PMDA/CPE Notification No.1399, issued by Director of Center for Product Evaluation, Pharmaceuticals and Medical Devices Agency on January 31, 2025 https://www.pmda.go.jp/files/000273566.pdf (in Japanese)	Procedures for adjusting the scope of compliance inspections based on product characteristics and application dossier contents to improve inspection effectiveness and efficiency
Addendum to the Guideline on Methods for Evaluating the Effects of Psychotropic Drugs on Motor Vehicle Driving Skills, PSB/PED Notification No. 0131-1, PSB/PSD Notification No. 0131-1, issued by Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, and Director of the Pharmaceutical Safety Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare on January 31, 2025 https://www.pmda.go.jp/files/000275374.pdf (in Japanese)	An appendix outlining the basic principles for determining the extent to which psychotropic drugs affect driving skills, based on non-clinical and clinical study data in accordance with the Guideline for evaluating the effect of psychotropic drugs on the performance to drive a motor vehicle
Q&A on the Basic Approach to Biological Safety Evaluation Required for Applications for Marketing Authorization of Medical Devices, Administrative Notice issued by Director of Medical Device Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare on March 11, 2025 https://www.pmda.go.jp/files/000274368.pdf (in Japanese)	A Q&A document summarizing the basic concepts of biological safety evaluations required in applications for manufacturing and marketing approval of medical devices
“Revision of the Basic Approach to Biological Safety Assessment Necessary for Applications for Approval of Manufacture and Sale of Medical Devices,” PSB/MDED Notification No. 0311-1, issued by Director of Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare on March 11, 2025 https://www.pmda.go.jp/files/000274367.pdf (in Japanese)	Revised guidance on the basic concept of biological safety evaluation, intended to assist marketing authorization holders of medical devices in selecting appropriate biological safety testing methods
Partial Revision of “Quasi-drug Ingredient Standard 2021,” PSB No. 0321-1, issued by Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare on March 21, 2025 https://www.pmda.go.jp/files/000275686.pdf (in Japanese)	Amendments to general tests 48, including the addition of the 2,2’-bipyridyl colorimetric method to the 48 iron test, to ensure consistency with the Japanese Pharmacopoeia and other official standards
Guidance on the Use of Skin Sensitization Evaluation Methods Based on the Defined Approach for Safety Evaluation of Quasi-drugs and Cosmetics, PSB/PED Notification No0328-2, issued by Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare on March 28,2 025 https://www.pmda.go.jp/files/000274766.pdf (in Japanese)	Guidance summarizing the evaluation process and key considerations when using alternative skin sensitization tests for safety evaluation of quasi-drugs and cosmetics
Partial Revision of Q&A Guidelines for Bioequivalence Studies of Generic Products for Topical Use, Administrative Notice issued by Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare on March 31, 2025 https://www.pmda.go.jp/files/000275170.pdf (in Japanese)	Revision of the Q&A on the "Guideline for Bioequivalence Studies of Generic Products for Topical Use" and the "Guideline for Bioequivalence Studies for Additional Dosage Forms of Topical Products"
Partial Revision of “Guidelines for Bioequivalence Studies of TGeneric Products for Topical Use,” PSB/PED Notification No.0331-7, issued by Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare on March 31, 2025 https://www.pmda.go.jp/files/000275168.pdf (in Japanese)	Revision of the "Guideline for Bioequivalence Studies of Generic Products for Topical Use" and the "Guideline for Bioequivalence Studies for Additional Dosage Forms of Topical Products"

3.2.4 Research Based on Public Research Funding

PMDA also contributes to public medical research. PMDA staff contribute to the promotion of research as an expert of RS in the public research groups and work together with external researchers toward problem-solving.
In FY2024, PMDA staff were involved as co-investigators in a total of 14 public research groups. More information of the research projects are shown in Table 8 below. For study details, such as study results reports, see the applicable page below.

* Health Labour Sciences Research Grant : https://mhlw-grants.niph.go.jp/

* Japan Agency for Medical Research and Development (AMED) : https://www.amed.go.jp/seika/

Table 8. Public Research Projects Involving PMDA Executives and Employees (FY2024)

Health Labour Sciences Research Grant

Research Area/Category	Research Title
The Regulatory Science Research Project on Pharmaceuticals and Medical Devices	Research on improving the environment for the promotion of multinational clinical trials in the Asian region
	Research on optimization and development of guidelines for proper use of medical devices
	A study on quality control and standardization of medical information databases in consideration of international harmonization for appropriate drug safety evaluation
	Project to promote human resource development for future acquisition of international standards in Japan (medical devices sector)
Comprehensive Research on the Promotion of Cancer Control	Study to establish a psychosocial support system and a safe long-term specimen storage system in cancer and reproductive medicine for pediatric, adolescent, and young adult patients with cancer, aimed at improving survivorship
Health and Labour Sciences Special Research	Research on measures needed to ensure the cybersecurity of medical devices in medical institutions
	Research on revising risk classification under Act on the Safety of Regenerative Medicine
Research on Policy Science (Research on the Promotion of Policy Science)	Research on the development of methodologies and tools for cost-effectiveness evaluation for the revision of analytical guidelines

AMED Project

Research Area/Category	Research Title
Pharmaceutical Regulatory Coordination and Evaluation Research Program	Standardization and construction of database of non-clinical toxicity study terms toward accelerate and high-accuracy of drug safety evaluation
	Research contributing to development of domestic infrastructure for evaluation methods, etc. to ensure the quality and safety of drugs and promotion of international harmonization
	Research on development of quality, efficacy, and safety evaluation systems for Adeno-associated virus: AAV vector-derived gene therapy products using patient samples in in vivo gene therapy
	Research on development of assessment criteria for effects of psychotropics on driving performance
	Research on life cycle management in pharmaceutical manufacturing and management and evaluation methods using advanced techniques
Development of Basic Technology for Drug Discovery for Next-Generation Treatments and Diagnostics	Research on development of internationally-competitive, next-generation antibody drug manufacturing technology / technical research on physical properties, quality evaluation, and management methods toward practical application of next-generation antibody drugs / technical research on quality evaluation and management methods toward practical application of next-generation antibody drugs

3.2.5 Designation as Research Institution for Grants-in-Aid for Scientific Research

To enhance the quality of its review processes, safety measures and relief services for adverse health effects, PMDA has actively encouraged its staff to pursue RS research and has worked to utilize research findings in its activities. In July 2023, PMDA established the Office of Regulatory Science Research within the RS Center to strengthen the capacity of the organization to conduct RS research.

In FY2024, as for the Office of Regulatory Science Research, PMDA formalized the Effort of the office staff, secured a budget for internal research funding, worked to improve the research environment, and then applied for the designation of the office as a research institution under the Grants-in-Aid for Scientific Research program. In December 2024, the Minister of Education, Culture, Sports, Science and Technology granted this designation. Consequently, PMDA became eligible to conduct research funded by the Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, the Ministry of Health, Labour and Welfare, and AMED Research Grants. To further advance research activities, PMDA is continuing to improve its research environment and organizational structure.

3.3 Strengthening Public Communication

PMDA disseminates information in various ways to promote scientific discussions and an understanding of the RS research conducted by PMDA.

3.3.1 PMDA RS Research Workshop

The RS Center regularly holds PMDA RS Research workshops to disseminate the findings of RS research conducted by PMDA and to facilitate a deeper understanding through discussions with external stakeholders. In FY2024, the 8th and 9th sessions attracted 887 and 1,370 participants, respectively. The 8th session, themed “Considering Loss and Lag Issues in Drug/Devices from the Perspective of RS,” included a question-and-answer segment and open discussions. Participants from industry (including global Contract Research Organization), government, and academia exchanged views on drug and medical device lag and loss, as well as potential solutions. The 9th session, themed “RS Perspectives for the Rapid Introduction of Regenerative Medical Products,” addressed topics including challenges under the Cartagena Law, issues related to standards for biological raw materials, and conditional and time-limited approval for regenerative medical products. Both sessions were held with a view to enhancing the understanding of the scope and significance of RS research within PMDA.

★ Click the RS research workshop poster to display the topic. ★

3.3.2 Dissemination on Social Media

PMDA disseminates information through Facebook, X, and YouTube, covering topics such as pharmaceutical and medical device approval reviews, safety measures, relief for adverse health effects, and other activities. Additional content includes information on various events, publicly available materials, and updates on Early Consideration.

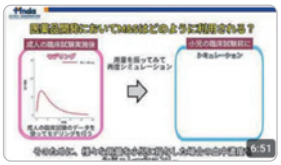
This section presents videos those were published on YouTube in FY2024 (Table9). These include introductory videos of research papers authored by PMDA staff as well as summaries of key review points and concepts from various briefing sessions.

For more information from the PMDA, please access the PMDA's official channel shown on the right to explore the full content.

PMDA official Facebook X YouTube

Table 9. List of RS-related YouTube Videos (Click the image to view)

Videos Introducing Research (in Japanese)

	**What is Modeling and Simulation (M&S)?** Describes technologies used in drug development to predict pharmacokinetics, disease progression, and treatment effects and explains the mechanism of M&S, with a focus on pharmacokinetic examples
	**Drug Safety Measures Using MID-NET® Real-World Data: Examples of Renal Function and Drug-induced Hypocalcemia** Presents findings from the PMDA MIHARI Project, including a risk assessment of hypocalcemia in patients with renal dysfunction receiving bisphosphonates for osteoporosis
	**Is Drug Safety Information Universal? Factors Behind Differences Between Japan and the U.S.** Explores the differences in and contributing factors to drug safety information (e.g., package inserts) between Japan and the United States

RS-Related Videos

	**Center for Regulatory Science** Introduces the activities of the RS Center, including advanced technology evaluation and large-scale clinical data analysis
	**Regulatory Approach to Software as a Medical Device in Japan** Outlines the regulatory framework of Japan for software intended for medical purposes (SaMD)

	**Cartagena Act** Explains biodiversity regulations under the Cartagena Law, which are relevant to the development of gene therapy products
	**Pharmacovigilance Activities** Introduces pharmacovigilance as part of the Risk Management Plan to ensure the safety of post-marketing drugs Click here for risk communication.
	**Video explaining MID-NET®** Provides an overview of the post-marketing database survey using MID-NET® (Click here for the Japanese version) Click here for additional explanatory videos on MID-NET®

3.3.3 Introduction of Major Scientific Articles in FY2024

PMDA staff actively publish the findings of RS research, etc. in peer-reviewed scientific journals.

* For scientific papers published by PMDA staff in the past years, list of information is available for each year. Please refer to the applicable page.
English articles : https://www.pmda.go.jp/english/rs-sb-std/rs/0004.html
Japanese articles : https://www.pmda.go.jp/rs-std-jp/research/0006.html

From the next page onward, the lead author or the corresponding author explains the summary and importance of the articles written in English published in 2024 (Please note that the author's personal views are included, and they do not necessarily represent the official views of the PMDA. This commentary newly describes scientific papers, and some scientific papers are cited and modified in the commentary).

Regulatory Review of Robotic-Assisted Percutaneous Coronary Intervention in Japan

Relevant articles PubMed

Shiba T, Aizawa K, Ho M, Ishii K. Regulatory Review of Robotic-Assisted Percutaneous Coronary Intervention in Japan. ***Circ J.*** 2024; 88: 1737-1744. doi: 10.1253/circj.CJ-24-0474.

Office of Medical Devices I, Takeshi Shiba

Background

The CorPath GRX system was approved in 2018, enabling the first use of robotic-assisted percutaneous coronary intervention (PCI) in Japan. At the time of the marketing approval application, clinical data were available only from overseas studies, and no domestic clinical results were available. Therefore, a use–results survey was deemed necessary to confirm safety and efficacy under Japanese clinical conditions. The survey results indicated favorable clinical outcomes in Japan; however, technical conditions differed from those in other countries.
In this research, we compiled and disseminated both pre-marketing and post-marketing reviews of robotic PCI in Japan, with the expectation that sharing the review approach of PMDA would promote understanding and encourage future development.

Outline

The use–results survey showed no major in-hospital cardiovascular events or high procedural success rates. Although many procedures were performed in patients with complex lesions, the outcomes remained favorable, and the learning curve for the procedure did not appear adversely affected. When introducing robotic PCI in Japan, proper usage guidelines for physicians and facilities were developed in collaboration with relevant academic societies. Comprehensive safety measures, including training programs, were implemented and are considered to have contributed to these favorable results.
Intravascular imaging was performed in >90% of PCI procedures, and a shift to planned manual procedures was undertaken when necessary. The utilization rate of intravascular imaging in Japan has been reported to be higher than that in other countries, and this trend is consistent for robotic PCI. To simplify the procedure and reduce the procedural time, future product development, particularly improvements in compatibility with intravascular imaging catheters, is considered desirable. The collection of real-world data, including results from use–results surveys, was found to be useful for evaluating product efficacy and safety in clinical practice and for identifying potential areas for product improvement.

Table 7. Summary of Research Reports on the CorPath 200 and CorPath GRX Systems

	CorPath 200 system (first-generation)		CorPath GRX system (second-generation)					
	Weisz et al. (2013)[4]	Mahmud et al. (2017)[6]	Smitson et al. (2018)[7]	Dou et al. (2019)[8]	Lemos et al. (2022)[9]	Brunner et al. (2022)[10]	Häner et al. (2023)[11]	Japan use-results survey[3]
Country	US	US	US	China	Brazil	Germany	Switzerland	Japan
No. sites	9	1	1	1	1	1	1	8
No. patients	164	108	40	10	83	71	21	239
No. lesions		157	54	11	112	86	25	292
Lesion classificasion(%)								
B2/C	31.7	78.3	77.8	63.6	77.7	88.4	72	65.9
Procedural characteristics								
Intravascular imaging	—	—	—	—	IVUS: 21.7%	IVUS: 12.8%	—	IVUS and OCT: 93.7%
Contrast use(mL)	144.2±70.4	183.4±78.7	171.6±64.6	127.0±40.3	206.4±111.4	145	194±64	97.6±52.2
Fluoroscopy time(min)	11.1±6.2	18.2±10.4	17.4±5.8	18.2±8.0	—	20.4	11.5	23.3±15.5
Radiation exposure	Cumulative dose: 1.5±0.8Gy	DAP: 12,518±15,970 cGy・cm^2	DAP: 7,054±5,572 cGy・cm^2	Air kerma: 1,681±870 mGy	—	DAP: 2,298 cGy・cm^2	DAP: 5,118 cGy・cm^2	DAP: 111.4±271.9 Gy・cm^2
Clinical outcomes								
Technical success(%)	98.8	91.7	90.0	100	85.7	94.2	81	89.1
Clinical success (%)	97.6	99.1	97.5	100	—	—	100	97.5

(Circ J. 2024; 88(11): 1737-1744. doi: 10.1253/circj.CJ-24-0474. Table 7
Creative Commons License : CC BY-NC-ND 4.0)

Impact on RS, expectations

This paper summarizes the pre-marketing and post-marketing reviews of robotic PCI in Japan and examines the review concepts and development issues based on the product life cycle. In addition to PCI, catheter-based robotic systems have been reported for clinical use in other vascular areas, such as cerebral and carotid interventions.

It is anticipated that this paper will support the development of new products and facilitate the introduction of overseas products into the Japanese market.

Regulatory Perspective Based on Survey of Relationship Between Biopharmaceutical Characteristics and Food Effects on Systemic Pharmacokinetics.

Relevant articles PubMed

Honma N, Yamagishi K, Ideno Y, Takaoka R, Ishiguro A. Regulatory Perspective Based on Survey of Relationship Between Biopharmaceutical Characteristics and Food Effects on Systemic Pharmacokinetics. ***Clin Pharmacol Ther.*** 2025; 118: 29-32. doi: 10.1002/cpt.3622.

Office of Pharmacovigilance II, Office of New Drug V, Naoko Honma

Background

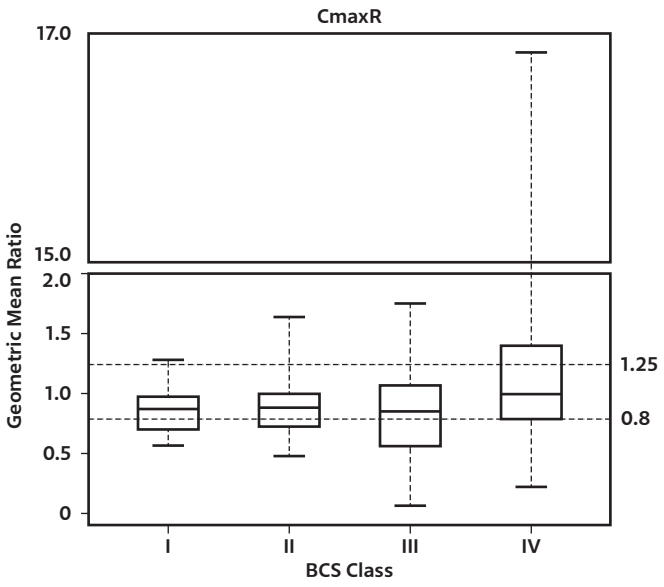
In Japan, the “Clinical Pharmacokinetic Studies of Pharmaceuticals” (Notification No. 796 of the Evaluation and Licensing Division, PMSB, dated June 1, 2001) stipulates that the effect of food should be evaluated in clinical studies using the final formulation. The U.S. FDA guideline (Assessing the Effects of Food on Drugs in INDs and NDAs-Clinical Pharmacology, 2002) states that more than 80% of immediate-release drug products classified as Class I under the Biopharmaceuticals Classification System (BCS)* are not affected by food and that food effect studies may be waived for these drugs. This survey was conducted to examine the relationship between food effects on pharmacokinetics and biopharmaceutical characteristics based on BCS classification. The aim was to clarify the necessity of evaluating the food effects in clinical studies in Japan based on the biopharmaceutical characteristics of the drug.

* BCS classifications are based on solubility and membrane permeability.
Class I: High solubility and high membrane permeability
Class II: Low solubility and high membrane permeability
Class III: High solubility and low membrane permeability
Class IV: Low solubility and low membrane permeability

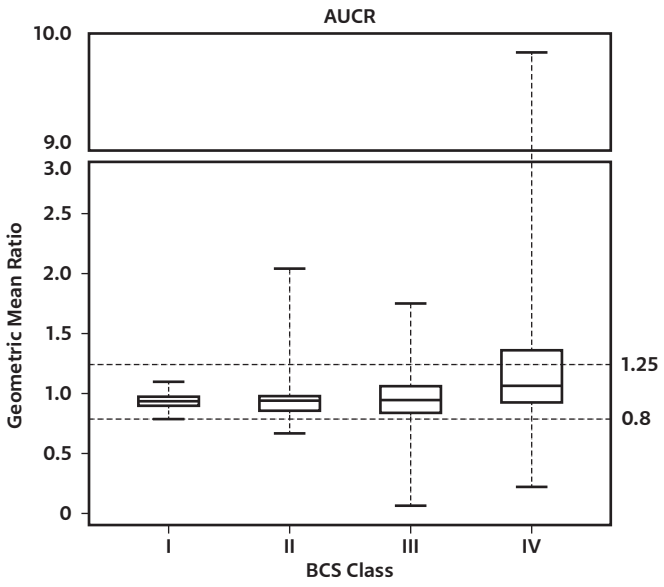
Outline

The ratios of the geometric mean value of pharmacokinetic parameters during a fed state to those during fasted state were analyzed for new drugs approved in Japan since 2004, stratified by BCS classification (Classes I–IV). As shown in the figure below, BCS Class I drugs tended to have a narrower variability and range in both the ratio of maximum blood concentration (CmaxR) and the ratio of the area under the blood concentration–time curve (AUCR) than drugs in other classes. Furthermore, AUCR values for all 15 BCS Class I drugs ranged within 0.8–1.25, suggesting that these drugs were relatively unaffected by food.

a



b



(Clin Pharmacol Ther. 2025 Jul;118(1):29-32. doi: 10.1002/cpt.3622. Figure 1. Cited with permission of the publisher.)

Impact on RS, expectations

This report shows that for drugs with BCS Class I characteristics, alternative approaches—other than conducting clinical studies using the final formulation, as specified in “Clinical Pharmacokinetic Studies of Pharmaceuticals”—may be acceptable for evaluating the food effects. These findings are expected to facilitate scientifically grounded discussions on methodological options and to contribute to a more efficient assessment of food effects.

Risk of artery dissection during systemic exposure to vascular endothelial growth factor pathway inhibitors

Relevant articles PubMed

Okui J, Waki T, Kajiyama K, Sawada S, Watanabe S, Namba Y, Kobayashi A, Kawarasaki S, Amakasu K, Iguchi T, Horiuchi N, Uyama Y. Risk of artery dissection during systemic exposure to vascular endothelial growth factor pathway inhibitors. ***Clin Transl Sci.*** 2024; 17: e70096. doi: 10.1111/cts.70096.

Office of Pharmacovigilance I, Office of Pharmacovigilance II, Takashi Waki

Background

Vascular endothelial growth factor (VEGF) regulates heightened proliferation, migration, degeneration, and permeability of normal blood vessel by binding to VEGF receptors (VEGFRs) on vascular endothelial cells. Pharmacologic inhibition of the VEGF pathway suppresses angiogenesis, an important therapeutic strategy for inhibiting tumor growth and metastasis. However, case reports suggesting an association between the use of VEGF pathway inhibitors (VPIs) and structural abnormalities of the arterial wall, including aortic dissection, have been accumulated. In Japan, in June 2020, “arterial dissection” was added to the “Clinically Significant Adverse Reactions” subsection of the PRECAUTIONS section in the package insert for bevacizumab (genetical recombination) following multiple adverse reaction reports, although data supporting relationships between other VPIs and arterial dissection remain insufficient. Furthermore, the risk of arterial dissection as a class effect of VPIs remained unclear; therefore, a large-scale medical information database study was conducted.

Outline

This cohort-based pharmacoepidemiological study analyzed data from approximately 503,000 patients prescribed any VPIs between 2012 and 2020 using the National Database of Health Insurance Claims (NDB). The primary outcome was the occurrence of arterial dissection. For each of the 12 VPIs listed below, the incidence rate (IR) was estimated, and the incidence rate ratio (IRR) of each VPIs compared with bevacizumab (genetical recombination), as its package insert already listed “arterial dissection” as the adverse reaction, was estimated. As reference, the natural IR of arterial dissection standardized with sex and age of the bevacizumab-prescribed cohort was estimated using the direct method for the general population in Japan.

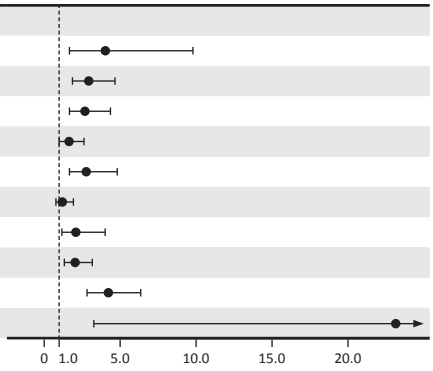
* List of VPIs: axitinib, aflibercept beta (genetical recombination), cabozantinib malate, sunitinib malate, sorafenib tosilate, nintedane ethanesulfonate, pazopanib hydrochloride, vandatenib, bevacizumab (genetical recombination), ramucirumab (genetical recombination), regorafenib hydrate, and lenbatinib mesylate

The IR for bevacizumab was 44.4 per 100,000 person-years. Adjusted IRR point estimates for all other VPIs—except cabozantinibuline malate—were consistently greater than 1.0. All VPIs showed an IR significantly higher than the natural IR of arterial dissection, which was 2.18 per 100,000 person-years (95% confidence interval: 1.86–2.50). These findings were consistent in subgroup analyses and in analyses limited to incident new users . However, cabozantinib malate was unable to evaluate as the number of patients was zero.

Based on the findings and the pharmacological mechanism of VPIs, PMDA concluded that arterial dissection should be considered a common risk for this drug class. On February 2024, the MHLW issued a notification instructing the addition of “arterial dissection” to the “Clinically Significant Adverse Reactions” subsection in the PRECAUTIONS of all VPIs.

Figure: Total Follow-up duration of Patients Prescribed VEGF/VEGFR Inhibitors, and the IR and Adjusted IR of Arterial Dissection Compared with Bevacizumab (Genetical Recombination) During the Follow-up duration

	Number of patients	Total follow-up duration (PY)	Number of outcome cases	IR (/100,000 PY)	IRR [95% CI]	Adjusted IRR * [95% CI]
Bevacizumab	278,722	281,401.43	125	44.4	Reference	Reference
Aflibercept beta	5,657	2,439.76	<10†	-†	-†(1.89 - 11.28)	4.00 (1.63 - 9.80)
Axitinib	13,082	13,010.07	23	176.8	3.98 (2.55 - 6.21)	2.92 (1.84 - 4.64)
Lenvatinib	20,359	13,687.92	19	138.8	3.12 (1.93 - 5.06)	2.62 (1.60 - 4.30)
Nintedanib	20,276	21,324.71	21	98.5	2.22 (1.40 - 3.52)	1.59 (0.98 - 2.56)
Pazopanib	15,141	9,880.31	15	151.8	3.42 (2.00 - 5.84)	2.78 (1.61 - 4.80)
Ramucirumab	73,593	33,322.10	21	63.0	1.42 (0.89 - 2.25)	1.16 (0.73 - 1.86)
Regorafenib	25,691	8,721.58	10	114.7	2.58 (1.36 - 4.92)	2.07 (1.08 - 3.97)
Sorafenib	33,849	20,539.99	23	112.0	2.52 (1.62 - 3.93)	1.99 (1.25 - 3.15)
Sunitinib	16,870	13,370.37	29	216.9	4.88 (3.26 - 7.31)	4.19 (2.78 - 6.33)
Vandetanib	102	125.52	<10†	-†	--†(2.51-128.32)	23.15 (3.22 - 166.40)



CI, confidence interval; IR, incidence rate; IRR, incidence rate ratio; PY, person-year

† Based on NDB publication standards, aggregated values <10 were masked so that they could not be identified.

* Adjusted covariates: Sex, age category (<65 years old or ≥65 years old), the past medical history of diseases and their treatment (hypertension, artery dissection, cardiovascular events, diabetes mellitus, and dyslipidemia).

(Clin Transl Sci. 2024;17:e70096. doi:10.1111/cts.70096 Figure 2. Title is modificated.

Impact on RS, expectations

Pharmacoepidemiological studies reflecting real-world clinical settings can be conducted using medical information databases such as the NDB, enabling safety assessments of drugs across treatment classes such as VPIs, even when individual case reports make it challenging to determine the relationship between a drug and an adverse event. In addition to individual case reports, incorporating data from pharmacoepidemiological studies into safety evaluations enhances the quality of drug safety measures and supports the appropriate post-marketing use of pharmaceuticals.

4. Contributing to the Further Utilization of Medical Information

-Safety Evaluation Using Real- World Data

Examples of safety measures utilizing medical information database study

PMDA conducts pharmaceutical safety assessment under the MIHARI Project, applying pharmacoepidemiological methods to real-world data obtained from sources such as MID-NET® (see page 31 for details), which is managed and operated by PMDA, and the National Database of Health Insurance Claims (NDB), owned by the Ministry of Health, Labour and Welfare.

The MIHARI Project began using medical information database in FY2014 to assess the safety of individual drugs as part of broader efforts to strengthen and enhance the activities of PMDA for pharmaceutical safety. Table 10 presents the results of surveys released in FY2024. Of these, items 2 and 4 resulted in specific safety measures, including revisions of PRECAUTIONS in drug package inserts.

For an overview of the MIHARI Project and details on PMDA's research using medical information database, refer to the following:

- MIHARI Project: https://www.pmda.go.jp/english/safety/surveillance-analysis/0001.html
- Survey conducted by PMDA: https://www.pmda.go.jp/safety/surveillance-analysis/0045.html

Table 10. Pharmacoepidemiological Studies Using Medical Information Database (Results Published in FY2024)

Item No.	Name and Overview of the Study
1	Evaluation of the effect of angiotensin-converting enzyme (ACE) inhibitors on liver function test abnormal using MID-NET ® (August 27, 2024)
	Because the alert status for hepatic dysfunction associated with ACE inhibitors differs among drugs, the frequency of laboratory abnormalities related to hepatic dysfunction after prescribing each ACE inhibitor was compared to evaluate drug-specific risks. Outline of Results: https://www.pmda.go.jp/files/000270045.pdf
2	Evaluation of the risk of kidney function test abnormal in patients with mirogabalin besilate using MID-NET® (August 27, 2024)
	As part of safety signal monitoring* for signal enhancement, the incidence of renal function test abnormalities after prescribing mirogabalin was compared with (1) that after prescribing pregabalin and (2) that after prescribing an extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus (for oral use). Outline of Results: (1) https://www.pmda.go.jp/files/000270052.pdf (2) https://www.pmda.go.jp/files/000270054.pdf Revision of PRECAUTIONS in drug package insert: https://www.pmda.go.jp/files/000270302.pdf
3	Epidemiological study on the benefit–risk balance of generic drugs for prevention of recurrence of noncardiogenic cerebral infarction using MID-NET® (October 4, 2024)
	To support the appropriate use of generic drugs, a safety survey was conducted using MID-NET®, an objectively evaluable medical information database. The study compared (1) the actual prescription of generic drugs such as aspirin, clopidogrel sulfate, and cilostazol with those of originator-products and (2) the recurrence of cerebral infarction and occurrence of hemorrhagic events with these drugs. Outline of Results: https://www.pmda.go.jp/files/000271087.pdf

4	Evaluation of the risk of cardiovascular events due to non-steroidal anti-inflammatory drugs (NSAIDs) using NDB (October 8, 2024)
	Because cardiovascular event alert statuses differ among NSAIDs, the relationship between the time of NSAIDs use, number of days of prescription period, and cardiovascular event occurrence in patients with chronic disease was examined. Outline of Results: https://www.pmda.go.jp/files/000270715.pdf Revision of PRECAUTIONS in drug package insert: https://www.pmda.go.jp/files/000271148.pdf
5	Evaluation of Safety Profiles of COVID-19 Vaccines Based on MID-NET® (October 24, 2024)
	To provide information on the safety of COVID-19 vaccines in clinical practice in Japan, the study (1) evaluated changes in various laboratory values before and after COVID-19 vaccination and (2) applied a self-controlled case series design to assess the occurrence of adverse events following COVID-19 vaccination. Outline of Results: https://www.pmda.go.jp/files/000269817.pdf
6	Evaluation of the risk of other abnormal laboratory tests in patients with voriconazole using MID-NET® (November 13, 2024)
	As part of safety signal monitoring* for signal enhancement, the incidence of elevated potassium levels after prescribing voriconazole was compared with that after prescribing fluconazole or fosfluconazole. Outline of Results: https://www.pmda.go.jp/files/000271818.pdf
7	Evaluation of the risk of cardiovascular events by romosozumab (genetical recombination) using NDB (January 31, 2025)
	In the absence of epidemiological studies in Japanese patients, the frequency of cardiovascular events following romosozumab administration was compared with that after teriparatide (genetical recombination) or teriparatide acetate prescribed for osteoporosis. Outline of Results: https://www.pmda.go.jp/files/000274219.pdf
8	Evaluation of the occurrence of liver function test abnormal in type 2 diabetes mellitus patients prescribed Glucagon-like peptide 1 (GLP-1) receptor agonists using MID-NET® (March 5, 2025)
	Because hepatic dysfunction alert statuses differ among GLP-1 receptor agonists and their combined formulations, the incidence of hepatic dysfunction was compared in patients with type 2 diabetes who were prescribed GLP-1 receptor agonists. Outline of Results: https://www.pmda.go.jp/files/000274105.pdf

* Safety Signal Monitoring is a survey aimed at collecting drug safety information from an early stage. For details, see https://www.pmda.go.jp/safety/surveillance-analysis/0049.html

What is MID-NET®?

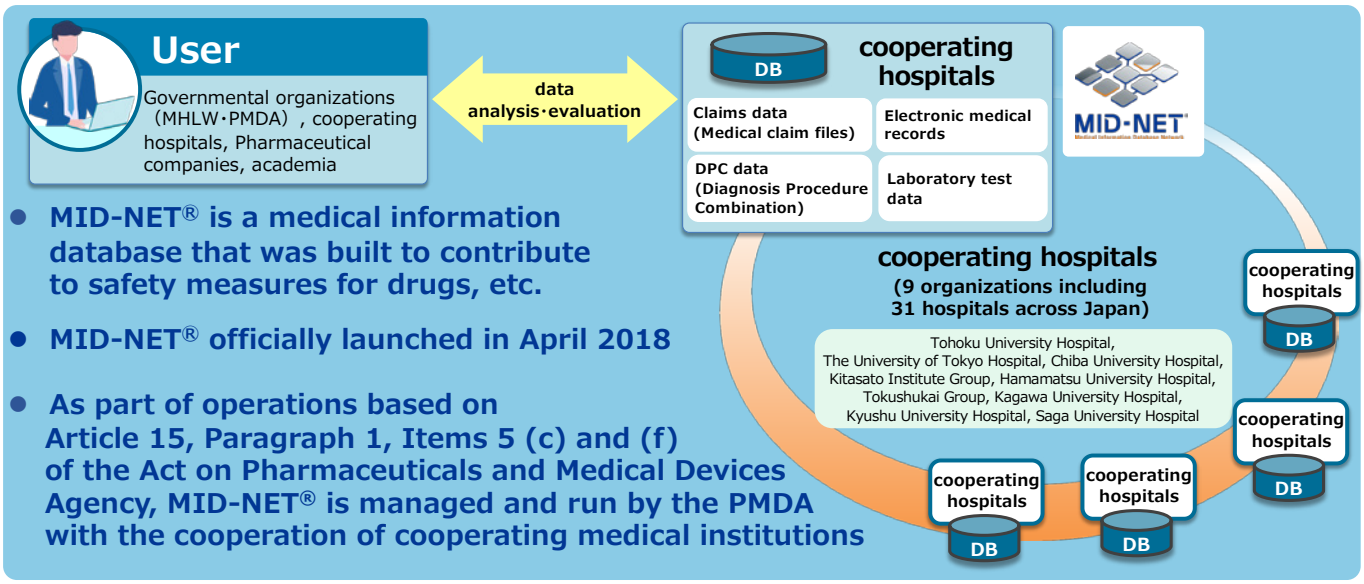
The PMDA Office of Medical Informatics and Science manages and operates MID-NET® under the authority of Article 15, Paragraph 1, Item (5)(c) and (f) of the PMDA Act[9] . This system has been fully operational since April 2018.

MID-NET® is a collective term for a distributed database system and associated networks comprising nine domestic medical institutions, including seven university hospitals and two medical institution groups, totaling 31 medical institutions. The database contains data from electronic medical records, claims, and Diagnosis Procedure Combination records starting in 2019, hereinafter collectively referred to as “HIS.” As of December 2024, the database includes over 8.3 million patients, with an expected annual increase of approximately 400,000 patients. (Figure 6). During data transfer from the HIS to the database, the data formats are standardized according to SS-MIX2 standard for electronic medical records. In addition to measures to protect personal information, key data elements are also standardized.

The Office of Medical Informatics and Science collaborates with participating medical institutions to ensure database reliability and to provide high-quality data that supports its effective utilization. Efforts also focus on assigning standard codes that preserve the original clinical context and verifying the accuracy of data transfer.

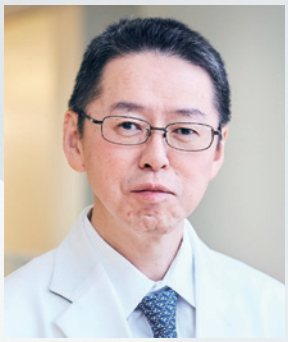
*For more information, refer to MID-NET® brochures and videos at https://www.pmda.go.jp/safety/mid-net/0001.html.

Figure6 Overview of MID-NET®



9 The Act on the Pharmaceuticals and Medical Devices Agency (Law No 192 on December 20, 2002) https://laws.e-gov.go.jp/law/414AC0000000192

5. Message from External Expert



Noboru Yamamoto

Deputy Director of National Cancer Center Hospital,
Director of the Department of Experimental Therapeutics

From the perspective of healthcare professionals, I am surprised and encouraged by the recent transformation of PMDA. Previously, PMDA was perceived as rigid and not user friendly, often regarded as distant from the medical field. However, in recent years, it has significantly changed its stance, evolving to prioritize flexibility and dialog. Although it was once criticized for maintaining a “tough attitude” and requiring the procedures as before, it now exhibits openness by presenting alternatives and engaging in flexible discussions without relying solely on precedents, clearly reflecting a changed approach.

Nevertheless, the actual activities of PMDA remain only partially understood within clinical practice. The “Regulatory Science Activity Report,” which transparently presents the efforts of the PMDA to bridge this gap, is a highly meaningful initiative. This activity report highlights many examples of the flexible and interactive stance of the agency, including collaboration with universities and research institutes, active dissemination of scientific knowledge, use of social media platforms such as X (formerly Twitter), Facebook, YouTube, publication of English-language papers, and the introduction of practical research outcomes. These activities indicate that PMDA is breaking out of its shell and engaging in two-way communication with healthcare professionals and the public.

As a healthcare professional, I strongly resonate with and have high expectations for the transformation and ongoing efforts of PMDA. The development and safe use of pharmaceuticals and medical devices will be further advanced through collaborative efforts between regulators and healthcare providers to share scientific knowledge. I look forward to continuing to support PMDA’s commitment to flexibility and respect for dialog, enabling it to contribute meaningfully to healthcare development and patient benefit.

Editorial Note

We have finally published the second RS activity report. We hope this report is useful for the readers to understand the PMDA' s efforts on regulatory science. We will continue to work for enhancing contents of the future report for meeting your expectations.

If you have any comments, please contact us at

MAIL **rs-research-toiawase(at)pmda.go.jp**

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Disclaimer

This report was prepared by translating into English based on the contents of the Japanese version of the report. If there is any conflict or inconsistency between these two reports, the Japanese report shall prevail.

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Regulatory Science Activity Report

FY2024