Regulatory Science Activity Report

(FY 2023)

Pharmaceuticals and Medical Devices Agency

Pharmaceuticals and Medical Devices Agency

Contents

1. Regulatory Science Activity Report

The Pharmaceuticals and Medical Devices Agency (PMDA) is an administrative agency that primarily provides services in three main areas : Approval Reviews, Post-marketing Safety Measures, and Relief Services for Adverse Health Effects caused by drugs, medical devices, and regenerative medical products (See the PMDA website page for details). In order to improve the quality of these services, the agency is engaged in regulatory science research activities and related initiatives.

The PMDA's Fifth Mid-Term Plan, which began in FY2024, has the goal of further promoting regulatory science research and related activities, including proactive dissemination of regulatory science-related information.

This report summarizes PMDA’s regulatory science-related activities with some details. This is the first report, and will be released every year in the future. Since FY 2024, PMDA has published “Early Considerations”, which serve as reference information to promote the practical application of innovations such as new technologies and the development of innovative drugs. Additionally, PMDA has released YouTube videos in which PMDA staff explained their published papers. The PMDA will continue to work for further enhancing the contents of this report.

We hope that this report is a useful source of information in understanding PMDA's regulatory science-related activities. We would like to ask for your continued understanding and support of PMDA.

December 2024
Pharmaceuticals and Medical Devices Agency
Director of Center for Regulatory Science
Emiko Kondo

2. Introduction

2.1 What is Regulatory Science?

In the fourth Science, Technology, and Innovation Basic Plan[1], the regulatory science (RS) in association with the promotion of life innovation, 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.” In addition, an academic paper[2] published by the PMDA in 2011 defined RS as described below. We consider that this is the science to appropriately deliver science and technology-based outcomes (products, new methods and technologies, knowledge, information, etc.) to society.

> *Regulatory Science 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.*

We believe that PMDA's proactive promotion of regulatory science research on drugs, medical devices, and regenerative medical products—along with the broad dissemination of our points of view as a Japanese regulatory agency—will contribute to the effective execution of PMDA's three key operations (Approval Reviews, Post-marketing Safety Measures, and Relief Services for Adverse Health Effects). Furthermore, it will also enhance public trust in PMDA and Japan's pharmaceutical regulations, promote international harmonization, and enable PMDA to play an active role globally.

2.2 RS Center

PMDA established RS center in April 2018 to further promote RS for improving the quality of Approval Reviews, Post-marketing Safety Measures. PMDA will actively disseminate scientific evidence and issue guidelines, etc. to provide consistent support for innovative drugs, medical devices and regenerative medicine products in Japan, from consultation during development to regulatory review and post-marketing safety measures. In addition, PMDA rearranged its organization in July 2023 to strengthen the PMDA's own RS research system. Currently, the RS Center has 4 divisions: Office of Regulatory Science Coordination, Office of Regulatory Science Research, Office of Research Administration, and Office of Medical Informatics and Science (Figure 1). Each office of the RS Center works in cooperation with relevant divisions of PMDA such as review and safety divisions and external organizations to promote RS and utilize the results for the operations of each division, thereby improving the quality of PMDA's operations.

[1]: Basic Program for Science and Technology (approved by the Cabinet on August 19, 2011)https://www8.cao.go.jp/cstp/kihonkeikaku/4honbun.pdf
[2]: Regulatory science as a bridge between science and society. *Clin Pharmacol Ther* 90, 29 (2011).10.1038/clpt.2011.89 PubMed

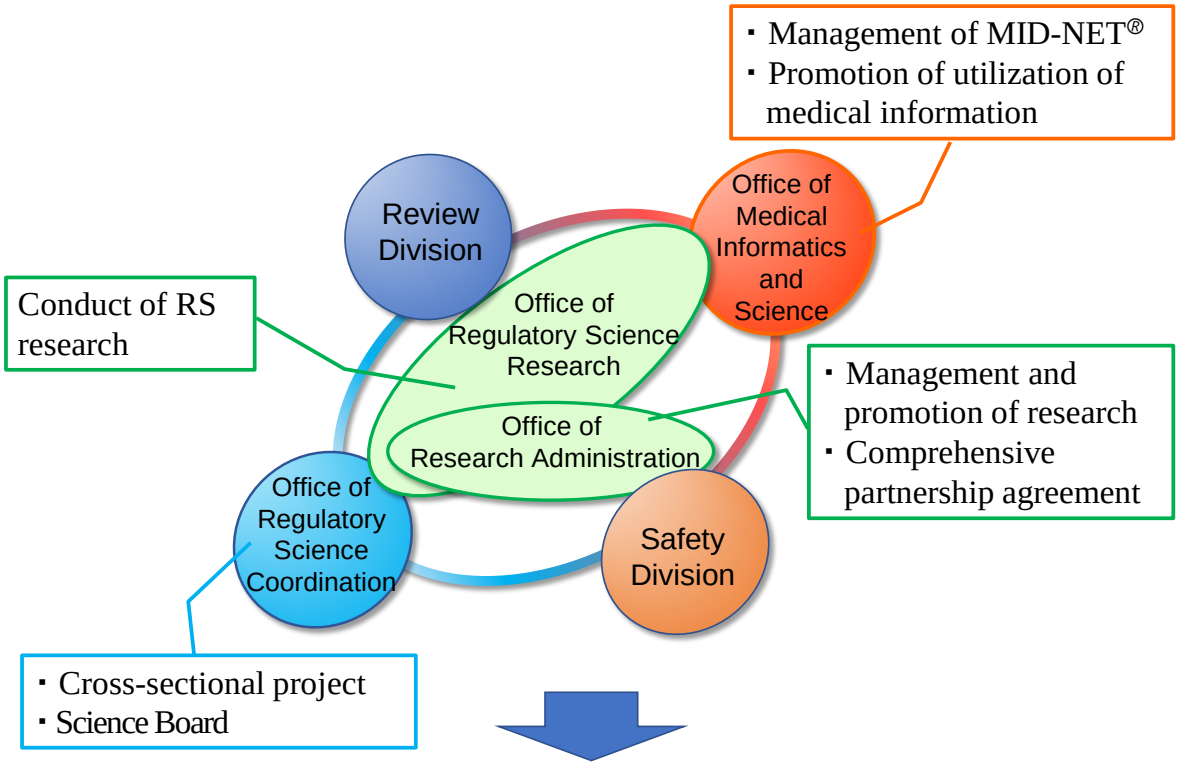


Figure 1 Roles of PMDA RS Center

3. Activity results

In order to achieve the Pharmaceuticals and Medical Devices Agency Mid-term Plans, PMDA has established an annual plan for each fiscal year.

The plan for FY 2023[3] set targets including "promotion of comprehensive partnership agreements," "preparation of guidelines for proactive collection and evaluation of information on cutting-edge science technology," and "enhancement of research environment and proactive dissemination of research outcomes" for the purpose of improving the quality of operations through promotion of RS. This chapter provides the main activities for FY 2023.

3.1 Activities in 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. Specifically, the comprehensive partnership agreement covers personnel exchange, joint research, dispatching of faculty, supporting the acquisition of degrees, etc. In some cases, the agreement is concluded as a joint graduate school agreement focusing on dispatching of faculty members, supporting the acquisition of degrees, etc., unlike the comprehensive partnership agreement (Figure 2).

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

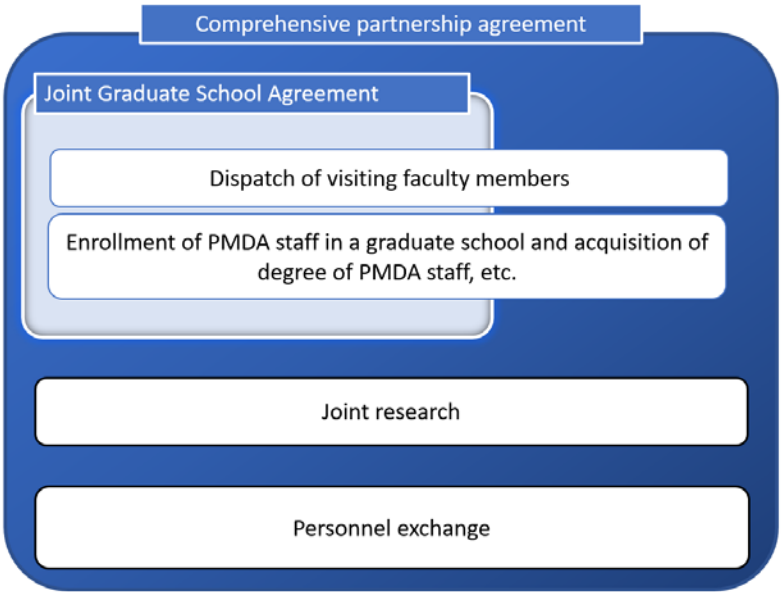


Figure 2 Activities according to Comprehensive Partnership Agreement and Joint Graduate School Agreement

3: PMDA The plan for fiscal year 2023 https://www.pmda.go.jp/files/000251942.pdf

As of April 2024, there are 11 organizations (6 universities/incorporated educational institutions and 5 research and development agencies) that have concluded a comprehensive partnership agreement. The names of these organizations are as shown in Figure 3.

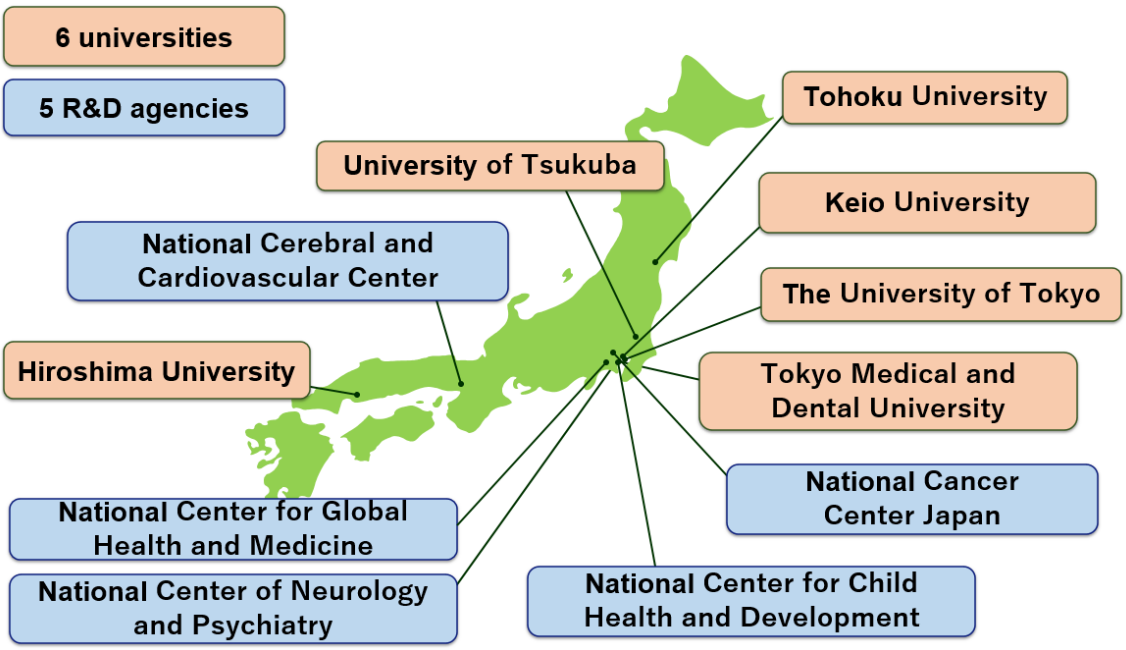


Figure 3 Comprehensive cooperation agreement organizations （As of April 2024）

The major activities of each organization under the comprehensive partnership agreement for FY 2023 are shown in Table 1 below.

Table 1 Main activities at the comprehensive partnership agreement organizations

Contract organizations (In order of the agreement concluded)	Main activities in FY 2023
1. National Cancer Center Japan (Click here to go to the website)	・Giving long-term on-site training (Department of Pharmacy / Clinical Research Support Office) for PMDA staff ・Holding the Master Key Project liaison meetings (opinion exchange meetings) on cancer treatment
2. Hiroshima University (Click here to go to the website)	・Seminars and lectures by PMDA staff on RS at Graduate School of Biomedical and Health Sciences
3. Keio University (Click here to go to the website)	・RS-related lectures by PMDA staff at the Faculty of Pharmacy and Graduate School of Medicine ・Giving trainings specialized in pharmacometrics for PMDA staff
4. University of Tsukuba (Click here to go to the website)	・Lectures on Regulatory Science (RS) by PMDA staff at the Graduate School of Comprehensive Human Sciences ・Lecture on pharmaceuticals and medical devices development management by the university staff open to PMDA staffs

Contract organizations (In order of the agreement concluded)	Main activities in FY 2023
5. National Center of Neurology and Psychiatry (Click here to go to the website) 国立研究開発法人 国立精神・神経医療研究センター National Center of Neurology and Psychiatry	・ Giving on-site training on committees (Institutional Review Board of Clinical Studies, etc.) for PMDA staff
6. Tohoku University (Click here to go to the website) TOHOKU UNIVERSITY	・ Collaborative research (Establishment of non-clinical evaluations as an alternative to clinical evaluations related to loading requirements for dental implants, and research on optimization and development of guidelines for the proper use of medical devices) ・ Lecture at Faculty of Pharmaceutical Sciences by PMDA staff
7. National Center for Global Health and Medicine (Click here to go to the website) NCGM	・ Giving long-term on-site training (Pharmaceutical Department/Clinical Trial Management Office) for PMDA staff ・ Giving on-site trainings for PMDA staff on clinical trial management and operation
8. National Cerebral and Cardiovascular Center (Click here to go to the website) 国立研究開発法人 国立循環器病研究センター National Cerebral and Cardiovascular Center cited from National Cerebral and Cardiovascular Center	(Activities suspended due to corona disaster)
9. National Center for Child Health and Development (Click here to go to the website) 国立研究開発法人 国立成育医療研究センター National Center for Child Health and Development	・ Giving long-term on-site training (Department of Pharmaceuticals) for PMDA staff
10. Tokyo Medical and Dental University (Click here to go to the website) 国立大学法人 東京医科歯科大学 TOKYO MEDICAL AND DENTAL UNIVERSITY	・ RS-related lectures by PMDA staff at the industry-academia collaboration council
11. The University of Tokyo (Click here to go to the website) UTokyo	・ RS-related lectures by PMDA staff at the Graduate School of Interdisciplinary Information Studies

Figure 4 shows universities/incorporated educational institutions with which a joint graduate school agreement has been concluded as of April 1, 2024.

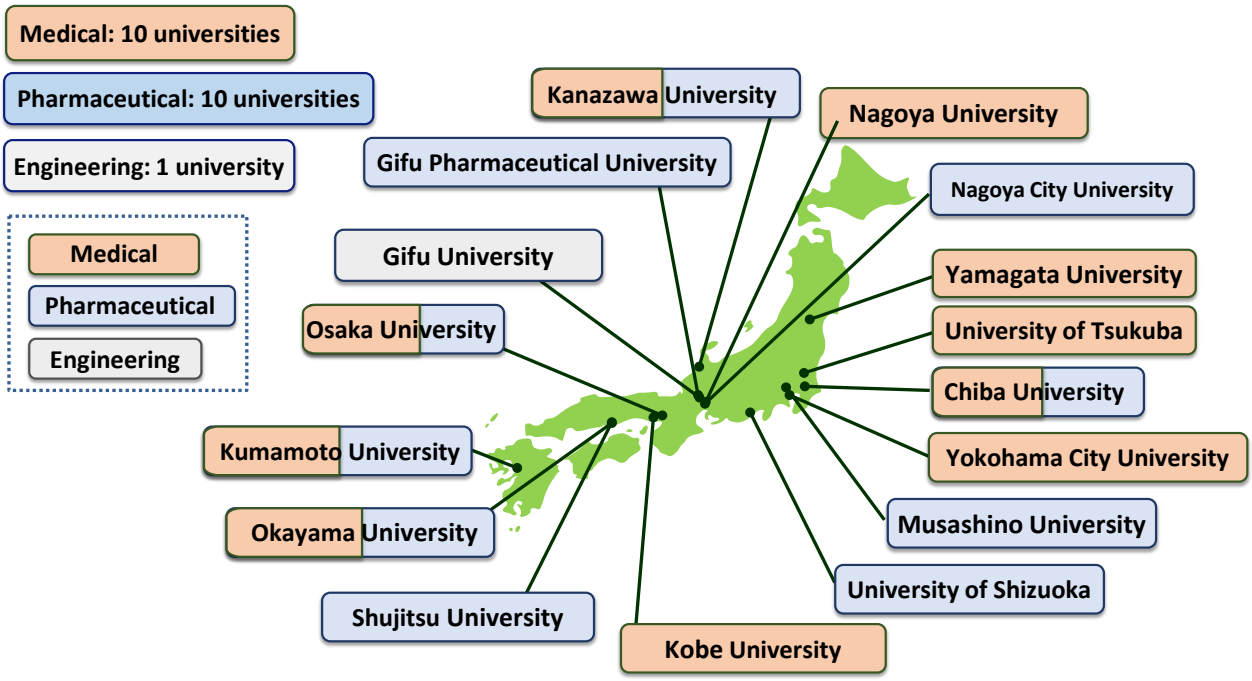


Figure 4 Universities/incorporated educational institutions that concluded the joint graduate school agreement (As of April 1, 2024)

In addition, to contribute to the development of human resources in the RS area, PMDA dispatched more than 110 staffs to give more than 150 RS-related lectures at 48 universities/incorporated educational institutions in FY 2023. Of these, RS-related lecturers, etc. were given by 17 PMDA staffs at universities/incorporated educational institutions with the joint graduate school agreement and by 10 PMDA staffs at universities/incorporated educational institutions with the comprehensive partnership agreement.

3.2 Promotion of scientific approach

The Science Board

The PMDA has established the Science Board consisting of external experts with various expertise as an organization to deliberate matters related to scientific aspects of operations for reviews, safety measures, etc. of drugs, medical devices, and regenerative medical products. [4]
The Science Board aims to improve the quality of reviews, safety measures, etc. by promoting appropriate evaluations and practical applications. In FY 2023, reports were published on the following topics:

Subcommittee on Software as a Medical Device Utilizing AI and Machine Learning

【Background and objective】
As artificial intelligence (AI) technology has advanced, the practical use of Software as a medical device (SaMD), which may change the post-marketing performance with machine learning function, is expected. The subcommittee has clarified the issues related to SaMD with such function in developing and implementing it in society as medical device software.

*For details of the discussion on this topic, please refer to the link of the Science Board. [5]

【Theme】

- Trend analysis of activities for establishing medical-device regulations and medical-device safety standards in Japan and overseas
- Various issues including biases in machine learning, reuse of test data in post-marketing learning, clinical information database, etc.

【Results】
The "Report on AI-based Software as a Medical Device (SaMD)" (August 28, 2023) was prepared and released in both Japanese and English.[6]

It is expected to design the development process properly and perform scientific and rational performance evaluations based on the points to consider presented in this report.

4 The Science Board https://www.pmda.go.jp/english/rs-sb-std/sb/science-committee/0010.html
5 Subcommittee on Software as a Medical Device Utilizing AI and Machine Learning https://www.pmda.go.jp/english/rs-sb-std/sb/subcommittees/0023.html
6 Report on AI-based Software as a Medical Device (August 28, 2023) :
Japanese version (https://www.pmda.go.jp/files/000263891.pdf), English version (https://www.pmda.go.jp/files/000266099.pdf)

RS Projects Across Multi-Offices in PMDA

In order to address cross-sectoral issues in reviews and post-marketing safety measures, PMDA has established working groups (WGs) consisting of multiple divisions to discuss each issue, and has been working for the publication of our perspective and development of guidelines, etc. for the solutions, taking international harmonization into consideration.

(https://www.pmda.go.jp/english/rs-sb-std/rs/0015.html)

Table 2 below provides the main guidelines, etc. issued in FY 2023 that were supported by each working group.

Table 2 Main Guidelines Issued after Cross-Sectional Discussions (FY 2023)

Related working group	Guidelines, etc. involved	Overview
Pediatric Drugs WG	Planning of the Pediatric Drug Development Program during Development of Drugs for Adults, PSB/PED Notification No. 0112-3 issued by Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare on January 12, 2024 https://www.pmda.go.jp/files/000268525.pdf	The basic concept was clarified on the handling of development plans for pediatric drug, which should be developed during the drug development period for adults
	Partial Revision of "Planning of the Pediatric Drug Development Program during Development of Drugs for Adults", PSB/PED Notification No. 0329-1 issued by Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare on March 29, 2024 https://www.pmda.go.jp/files/000268523.pdf	Clarification of points on specific handling in the development plan for pediatric drugs
	Q & A for "Planning of the Pediatric Drug Development Program during Development of Drugs for Adults", Administrative Notice issued by Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare on March 29, 2024 https://www.pmda.go.jp/files/000268524.pdf	Q & A for making development plans for pediatric drugs, which should be developed during the drug development period for adults
Orphan Drugs WG	Partial Revision of "Designation of Orphan Drugs etc." PSB/PED Notification No. 0116-1 and PSB/MDED Notification No. 0116-1 issued by Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, and Director of Medical Device Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare on January 16, 2024 https://www.pmda.go.jp/files/000268408.pdf	Revision of designation criteria for the number of subjects, medical needs, possibility of development, etc. for designation of orphan drugs, etc.
Multi-Regional Clinical Trials WG	Basic principles for conducting phase 1 studies in Japanese prior to initiating multi-regional clinical trials including Japan for drugs in which early clinical development is preceding outside Japan, PSB/PED Notification No. 1225-2, by Director, Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, on December 25, 2023 https://www.pmda.go.jp/files/000266727.pdf	Clarification of basic principles for conducting phase 1 studies in Japanese prior to initiating multi-regional clinical trials including Japan for drugs in cases where early clinical development is preceding outside Japan
Innovative Manufacturing Technology WG	Guidelines for Continuous Manufacturing of Drug Substances and Drug Products, PSEHB/PED Notification No. 0531-1, by the Director, Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare on May 31, 2023 https://www.pmda.go.jp/files/000249411.pdf	Clarification of points to consider for the development, implementation, operation, and life cycle management of continuous production (cooperation in activities as ICH Q13)
Companion Diagnostics WG	Revision of "Points to consider for application for approval of drugs to be administered based on specific biomarkers that were developed by clinical trials conducted by a sponsor-investigator in patients with rare cancer", PSB/PED Notification No. 0319-1 and PSB/MDED Notification No. 0319-1 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 March 19, 2024 https://www.pmda.go.jp/files/000267507.pdf(in Japanese)	Revision of points on the use of in vitro diagnostics or medical devices approved for other indications in tests for subject enrollment in investigator-initiated clinical trials in patients with rare cancers

Medical Device International Affairs WG	Confirmation of compliance with Article 12, Paragraph 3 of the Essential Principles for Medical Devices, PSEHB/MDED Notification No. 0523-1, by Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare on May 23, 2023 https://www.mhlw.go.jp/content/11120000/001203129.pdf	Clarification of points on confirmation of compliance with Article 12, Paragraph 3 of the Essential Principles for Medical Devices
	Q & A for Application of Article 12, Paragraph 3 in the Criteria for Essential Principles of Medical Devices, PSEHB/MDED Administrative Notice, issued by Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare on July 20, 2023 https://www.pmda.go.jp/files/000263421.pdf(in Japanese)	Q & A for Confirmation of compliance with Article 12, Paragraph 3 of the Essential Principles for Medical Devices
	Basic Principles for Adverse Events Reporting Regarding Cybersecurity of Medical Devices, PSB/PSD Notification No. 0115-2, issued by Director of Pharmaceutical Safety Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare on January 15, 2024 https://www.pmda.go.jp/files/000272598.pdf	Clarification of points on adverse event reports by marketing authorization holders regarding medical device cybersecurity
	Q & A for Medical Device Cybersecurity, Administrative Notice issued by Office of Counsellor for Assistance for Development of Specified Drug and Medical Information Management, Health Policy Bureau, Ministry of Health, Labour and Welfare, Medical Device Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, Pharmaceutical Safety Division, Ministry of Health, Labour and Welfare, and Compliance and Narcotics Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, on January 31, 2024 https://www.pmda.go.jp/files/000269643.pdf(in Japanese)	Q & A for Medical Device Cybersecurity including the application, etc. of Article 12, Paragraph 3 of the Essential Principles for Medical Devices
	Management of Vulnerabilities to Ensure Cybersecurity of Medical Devices, PSB/MDED Notification No. 0328-1, PSB/PSD Notification No. 0328-3, issued by Director of Medical Device 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 March 28, 2024 https://www.pmda.go.jp/files/000272597.pdf	Clarification of points to consider about vulnerability management for cybersecurity of medical devices, etc. for smoothly securing the system under marketing authorization holders of medical devices

Contribution to Public Research Groups

PMDA also contributes to public medical research. PMDA staffs contribute to the promotion of research as an expert of RS in the public research group, and work together with external researchers toward problem-solving

In FY 2023, PMDA staffs were involved as co-investigators in a total of 13 public research groups. More information of the research projects are shown in Table 3 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 3 Contribution to Public Research Groups

Health, Labour and Welfare Sciences Research Grants.	
Research field	Title
Pharmaceutical field	A study on quality control and standardization of medical information databases in consideration of international harmonization for appropriate drug safety evaluation
Medical device field	Research on optimization and development of guidelines for proper use of medical devices
Regenerative medicine and gene therapy field	Research for application and operation of the Act on the Safety of Regenerative Medicine, etc. for transplantation of genetically-modified heterologous organs and securing of public health safety
Multiple fields (Pharmaceutical / medical device field)	Research contributing to revision of analytical guidelines for cost-effectiveness evaluation of drugs / medical devices
Multiple fields (Pharmaceutical field/regenerative medicine / gene therapy field)	Research on environmental improvement toward the promotion of global clinical trials in Asian region
AMED Project	
Research field	Title
Pharmaceutical field	Regulatory science research on lifecycle management of the pharmaceuticals manufactured, controlled and evaluated by advanced approaches.
	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
	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 standardization of non-clinical toxicity terms and establishment of database that contribute to acceleration/increased accuracy of drug safety evaluation
	Research on development of assessment criteria for effects of psychotropics on driving performance
Medical device field	Research on establishment of non-clinical evaluations as an alternative to clinical evaluations related to loading requirements for dental implants.
	Research on application of medical device malfunction glossary to signal detection and development of supporting tools
Regenerative medicine and gene therapy field	Research on development of quality, efficacy, and safety evaluation systems for AAV vector-derived gene therapy products using patient samples in *in vivo* gene therapy

3.3 Dissemination of RS information

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

PMDA RS Workshop

We regularly hold RS workshops as a place for better understanding of RS research undertaken by PMDA through discussions with external experts.

In FY2023, we held the 7th RS Workshop. The main contents are shown in Table 4 below. A total of 518 people attended (as registered participants) and through Q&A and panel discussion, active discussions were held on matters that require further scientific consideration, such as consideration based on international harmonization, the importance of cooperation with Asian countries, and estimation of efficacy, and we provided an opportunity to deepen the understanding of the content and significance of RS research in PMDA.

Table 4 < The 7th RS Workshop: https://www.pmda.go.jp/files/000265423.pdf >

Topics	References
Promotion of practical application of modeling and simulation in drug development	Kijima, S., Yoshida, S. & Ochiai, Y. Activity and perspective on quantitative modeling and simulation in Japan: Update from the Pharmaceuticals and Medical Devices Agency. ***CPT Pharmacometrics Syst Pharmacol*** 11, 1552-5 (2022). 10.1002/psp4.12868 PubMed
Clinical study design with the control of overall type I error	Asano J, Sato H, Hirakawa A. Practical basket design for binary outcomes with control of family-wise error rate. ***BMC Med Res Methodol*** 2023 Feb 27;23(1):52. 10.1186/s12874-023-01872-1. PubMed
Approval and review of biosimilar products	Kuribayashi, R., Nakano, A., Hariu, A., Kishioka, Y. & Honda, F. Historical Overview of Regulatory Approvals and PMDA Assessments for Biosimilar Products in Japan During 2009-2022. ***BioDrugs*** 37, 443-51 (2023). 10.1007/s40259-023-00605-6 PubMed
Nonclinical study criteria required during vaccine development	Okumoto, A., Nomura, Y., Maki, K., Ogawa, T., Onodera, H., Shikano, M. & Okabe, N. Addressing practical issues in the smooth implementation of revised guidelines for non-clinical studies of vaccines for infectious disease prevention. ***Regul Toxicol Pharmacol*** 142, 105413 (2023). 10.1016/j.yrtph.2023.105413 PubMed
Review of regenerative medical products designated as SAKIGAKE products	Maruyama, Y., Sakurai, A., Noda, S., Fujiwara, Y., Okura, N., Takagi, T., Asano, J. & Honda, F. Regulatory Issues: PMDA - Review of Sakigake Designation Products: Oncolytic Virus Therapy with Delytact Injection (Teserpaturev) for Malignant Glioma. ***Oncologist*** 28, 664-70 (2023). 10.1093/oncolo/oyad041 PubMed

Social Media Dissemination

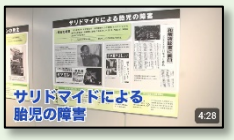
To encourage the general public to understand RS research, we also provide explanations on videos utilizing YouTube, and disseminate related information on Facebook, X (the former Twitter), etc.

Table 5 below shows some of the videos that were uploaded on YouTube in FY 2023 and watched by many people. Here is a selection of RS-related videos. For more information from the PMDA, please access the PMDA's official channel shown on the right to explore the full content.

PMDA official account

YouTube / X (the former Twitter) / Facebook

Table 5 List of RS-related YouTube videos

Contents (*Click on the image* to access the video!)		
Review-related content		(Review) Bioequivalence Studies【in English】
		PMDA's operation in accepting approval applications【in Japanese】
Safety-related content		Explanation about standards related to medical devices【in Japanese】
		~ Explain in 90 seconds ~ Online reporting of adverse reactions, etc. to PMDA: the web site for reporting (for healthcare professionals)【in Japanese】
Relief-related content		Exhibition of drug-related sufferings【in Japanese】
International activity-related content		International Activities【in English】

3.4 Introduction of Major Scientific Articles published in 2023

PMDA staff actively publish the results 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 2023 (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).

Characteristics of Asian Participation in Multi-regional Clinical Trials Reviewed for Drug Approval in Japan: Opportunities for Collaboration Between South-East Asia, East Asia, and Japan

< Relevant articles > PubMed

Aoi, Y., Kato, Y., Asano, K., Otsubo, Y. & Uyama, Y. Characteristics of Asian Participation in Multi-regional Clinical Trials Reviewed for Drug Approval in Japan: Opportunities for Collaboration Between South-East Asia, East Asia, and Japan. ***Ther Innov Reg Sci*** 57, 1298-303 (2023). 10.1007/s43441-023-00566-6

Associate Executive Director (Research Division), Yoshiaki Uyama

< Background >

In the era of global drug development, the cases of new drug application including multi-regional clinical trials (MRCTs) have increased in Japan. For further collaboration in Asia, it is useful to examine the enrollment status of Asian participants in MRCTs evaluated for drug approval in Japan in order to further promote proper development.

< Outline>

In this study, characteristics of MRCTs reviewed for drug approval in Japan were investigated to explore opportunities for collaborations on global drug development in Asia. As a result, more than 90% of reviewed trials were conducted as global MRCTs. In addition to Japan, Asian countries, US, and Europe have participated in various types of MRCTs. When investigating Asian participants as East Asia and South-East Asia separately, approximately 70% of MRCTs with Japan participation also include the participants in East-Asian countries. On the other hand, the MRCTs participated by South-East Asia accounted for less than 30%. When the percentage of patients in MRCTs was examined, the presence of participation in East-Asia or South-East Asia did not affect the proportion of Japanese patients in MRCTs. However, when these East-Asian or South-East Asian countries joined MRCTs simultaneously with Japan, the proportion of Asian patients was approximately 12% for Japan alone while it was increased to approximately 19% with participation of East-Asia and to approximately 32% with participation of both East and South-East Asia. These results suggest that further collaboration in MRCTs between Japan and other Asian countries, especially South-East Asia, may yield more data of Asian populations and lead to a sound scientific basis in considering the proper application of the pooled concept described in the ICH E17 guideline.

< Impact on RS, expectations >

This study suggests that strengthening collaboration between Japan and Asian countries will enable appropriate promotion of drug development and evaluation of efficacy and safety, etc. in consideration of ethnic factors, and may be useful in considering future international collaboration and international harmonization of regulations in Asia.

Characterizing granulocytopenia associated with thiamazole in patients with hyperthyroidism based on real-world data from the MID-NET® in Japan

< Relevant articles > PubMed

Kinoshita, Y., Kajiyama, K., Ishiguro, C., Nonaka, T., Kimura, R., Kikuchi, Y., Horiuchi, N., Iguchi, T. & Uyama, Y. Characterizing granulocytopenia associated with thiamazole in patients with hyperthyroidism based on real-world data from the MID-NET® in Japan. ***Clin Pharmacol Ther*** 113, 924-31 (2023). 10.1002/cpt.2850

Office of Pharmacovigilance I, Yuki Kinoshita

< Background >

Granulocytopenia including agranulocytosis is known as an important adverse event caused by thiamazole, which is used for the treatment of hyperthyroidism. For the purpose of early detection and prevention of more serious granulocytopenia caused by thiamazole, a precaution has been issued to conduct routine blood tests during treatment with thiamazole (once every 2 weeks for the first 2 months of treatment, and on a regular basis thereafter.) for monitoring a decreasing trend in granulocyte count. However, since a certain number of serious cases of granulocytopenia have been reported after administration of thiamazole, the appropriateness of the contents of the precautions was examined.

< Outline>

In patients prescribed thiamazole, the association between the implementation status of the routine tests and the occurrence of granulocytopenia was evaluated utilizing the MID-NET®, a medical information database managed and operated by PMDA. MID-NET® contains the results of various laboratory tests including neutrophil count, which can be used for various investigations. The occurrence of granulocytopenia (neutrophil count ≤ 1,500/μL) in a given period was compared between patients prescribed thiamazole with and without the routine tests to determine whether the routine tests can prevent the occurrence of granulocytopenia. As a result, granulocytopenia was observed to a certain degree even in the patients having the routine tests, and the occurrence did not tend to be lower than that in the patients without the routine tests. There was no finding that routine blood tests necessarily contributed to the early detection of granulocytopenia or the prevention of aggravation (See Table: age and sex adjusted odds ratio). This may be explained by the fact that patients who underwent the routine tests had some risk factors for granulocytopenia compared to those without the routine tests, suggesting that the patients with the routine tests had more substantial need for testing. However, in the patients who experienced granulocytopenia during the period from Day 43 to Day 56 after thiamazole was prescribed (Period 4), neutrophil counts tended to gradually decrease from first prescription date of thiamazole to the occurrence date of granulocytopenia. Therefore, routine tests in some patients may help detect the trend of the occurrence of granulocytopenia early. Although the results of this study did not provide clear findings that routine tests contributed to early detection of granulocytopenia and prevention of its aggravation, it would lead to early detection of granulocytopenia and prevention of its aggravation in some patients. Therefore, we concluded that routine tests have a certain significance as a precaution.

Risk of granulocytopenia in patients treated with thiamazole stratified by the frequency of routine blood test

	Number of patients (%)	Patients with granulocytopenia n	Proportion		Age and sex adjusted odds ratio (95% confidence interval)
Period 1 (first prescription date of thiamazole (t_0) ~ 2nd weeks after t_0)					
Number of target patients	4,371 (100%)	141	3.2	%	
Period 2 (3 – 4th weeks after t_0)					
Number of target patients	4,070 (100%)	62	1.5	%	
Not Conducted †	1,758 (43.2%)	20	1.1	%	1.00 Reference
All Conducted †	2,312 (56.8%)	42	1.8	%	1.63 (0.95 - 2.78)
Period 3 (5 – 6th weeks after t_0)					
Number of target patients	3,887 (100%)	38	1.0	%	
Not Conducted †	1,092 (28.1%)	<18*	<2.0*	%	1.00 Reference
Partly Conducted †	1,607 (41.3%)	<18*	<2.0*	%	2.36 (0.77 - 7.19)
All Conducted †	1,188 (30.6%)	20	1.7	%	4.64 (1.58 - 13.63)
Period 4 (7 – 8th weeks after t_0)					
Number of target patients	3,426 (100%)	30	0.9	%	
Not Conducted †	727 (21.2%)	<10*	<2.0*	%	1.00 Reference
Partly Conducted †	1,962 (57.3%)	20	1.0	%	7.40 (0.99 - 55.22)
All Conducted †	737 (21.5%)	<10*	<2.0*	%	8.97 (1.13 - 71.00)

* When a value was < 10, it was shown as an aggregated value based on the MID-NET® publication rule.

† Patients who had not undergone blood test in all previous periods (“Not Conducted”) and who had undergone blood tests at all previous periods (“All Conducted”) and one of previous periods (“Partly Conducted”).

(Clin Pharmacol Ther. 2023; Table2 in 113: 924-931,

< Impact on RS, expectations >

The utilization of medical information database, such as MID-NET®, allows us to conduct a study reflecting a situation of actual clinical practice (real world). We consider that conducting pharmacoepidemiological studies of this nature will contribute to facilitating the proper use of drugs after the launch and improving the quality of drug safety measures.

Historical Overview of Regulatory Approvals and PMDA Assessments for Biosimilar Products in Japan During 2009-2022

< Relevant articles > Please go to PubMed here.

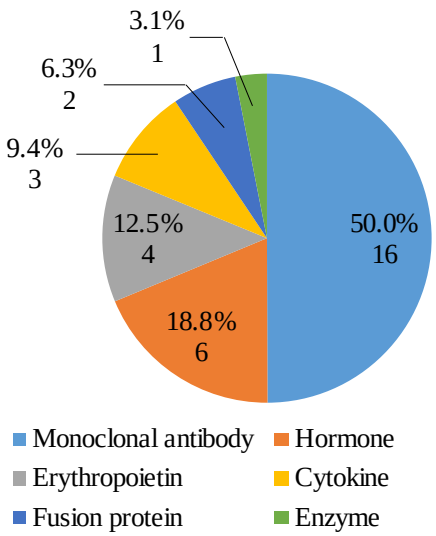
Kuribayashi, R., Nakano, A., Hariu, A., Kishioka, Y. & Honda, F. Historical Overview of Regulatory Approvals and PMDA Assessments for Biosimilar Products in Japan During 2009-2022. ***Bio Drugs*** 37, 443-51 (2023). 10.1007/s40259-023-00605-6

Office of Cellular and Tissue-based Products, Ryosuke Kuribayashi

< Backgrounds >

We would like to disseminate the Japanese regulations to the world. Since no articles touched on the regulations of biosimilar products, we decided to publish basic matters related to the regulations of biosimilar products in international scientific journals as a first step.

< Outline>



This article describes about the data package for quality, nonclinical, and clinical studies required for biosimilar products in Japan based on the "Guideline for Ensuring Quality, Safety, and Efficacy of Biosimilars" (February 4, 2020) and various Q & As, with presenting the backgrounds and awareness of problems at that time. The article also shows the approval trend of biosimilar products by presenting the number of biosimilars approved by December 2022 in Japan and the rate of each type of biological products such as antibodies and hormones. In 2022, of the 32 biosimilar products, 16 (50.0%) were antibody drugs, indicating that many approved biosimilar products were antibody drugs.

(Source: BioDrugs. 2023 Jul; 37 (4): 443-451; the position of numbers is partially changed in Figure 4)

< Impact on RS, expectations >

We hope that this paper will facilitate a deep understanding of data required for approval application of biosimilar products in Japan and further promote their development in Japan. In addition, it is expected that the deeper understanding of the regulations in Japan and other countries will enable us to consider challenges in the Japanese regulations and to make more specific discussions in promoting international harmonization of regulations in the future. In the end, we hope to contribute to earlier access of biosimilar products that are cheaper and comparable to the original biological products to patients.

Insights into the clinical development of regenerative medical products through a comparison of three cell-based products recently approved for limbal stem cell deficiency

< Relevant articles > Please go to PubMed here.

Aketa, N., Kasai, M., Noda, S., Asano, J., Kunieda, A., Kawanishi, S., Maruyama, Y. & Honda, F. Insights into the clinical development of regenerative medical products through a comparison of three cell-based products recently approved for limbal stem cell deficiency. ***Ocul Surf*** 29, 220-5 (2023). 10.1016/j.jtos.2023.05.008

Office of Cellular and Tissue-based Products, Shinichi Noda

< Backgrounds >

Between 2020 and 2022, 3 regenerative medical products (Nepic, Ocural, and Sakracy) for limbal stem cell deficiency* were approved one after another in Japan. It was the first time in the world that multiple cell-based medical products were approved for the same ocular disease. Therefore, PMDA decided to disseminate the current status and prospects of clinical development of regenerative medical products internationally from the viewpoint of a regulatory agency by organizing points to consider in review for these products in a cross-sectional manner.

* A disease in which the cornea is covered with conjunctival epithelium or connective tissues due to damage to corneal epithelial stem cells, resulting in reduced visual acuity or adhesion of the ocular surface. The conventional therapy of limbal keratoplasty is known to have problems such as lack of donor cornea and high invasiveness.

< Outline>

All the three products are sheet-like cultured products using the cells collected from the patients themselves. The raw materials of Nepic are derived from the autologous corneal limbus tissues, and the raw materials of Ocural and Sakracy are derived from the autologous oral mucosal tissue. Human amnion membrane is used as the substrate for Sakracy. In addition, for limbal stem cell deficiency*, which is an intractable and rare disease, Nepic and Ocural were developed for the purpose of corneal tissue reconstruction, while Sakracy was developed for the treatment of adhesions associated with limbal epithelial stem cell deficiency*. As a result of the review based on the differences in the above product characteristics and intended use, different indications were set for each product.

Regenerative medical products are often developed for rare diseases, etc. for which treatment methods and appropriate endpoints have not been established, and examples of reference are limited. For this reason, unlike usual drug development, various unknown issues must be resolved through a series of trials and errors from the development phases to the review. It is important to continue scientific discussions between developers and regulatory authorities from the early stage of development in order to promote appropriate development.

Comparison of 3 regenerative medical products in patients with limbal stem cell deficiency

Brand name	Nepic	Ocural	Sakracy
Generic Name	Human (autologous) corneal limbus-derived corneal epithelial cell sheet	Human (autologous) oral mucosa-derived epithelial cell sheet	Human (autologous) oral mucosa-derived epithelial cell sheet using amniotic membrane substrate
Approval Date	March 26, 2020	June 11, 2021	January 20, 2022
Applicant	Japan Tissue Engineering Co., Ltd.		Hirosaki Lifescience Innovation, Inc.
Clinical trial design	Open-label, uncontrolled study		
Primary endpoint	Success rate of corneal epithelial reconstruction		Adhesion score
Approved indications	Limbal stem cell deficiency (Stage II and III in severity) Note that patients in whom the causative disease is an intrinsic factor such as Stevens-Johnson syndrome are excluded.	Limbal stem cell deficiency (Stage II and III in severity)	Alleviating adhesion on the ocular surface in limbal stem cell deficiency (All stages in severity)

(Table 2 of Ocul Surf 29, 220-5 (2023))

< Impact on RS, expectations >

This paper will present the views of regulatory authorities in the review of regenerative medical products and widely disseminate the necessity of close discussions between developers and regulatory authorities from the early stage of development in order to overcome development issues, which may be a help to promote future development of regenerative medical products.

A meta-analysis on the characteristics of placebo effects on urinary function in placebo-controlled clinical trials among Japanese patients

< Relevant articles > Please go to PubMed here.

Hara, T. A meta-analysis on the characteristics of placebo effects on urinary function in placebo-controlled clinical trials among Japanese patients. ***Int J Urol*** 30, 447-54 (2023). 10.1111/iju.15152

Office of Research Administration, Tomohiko Hara

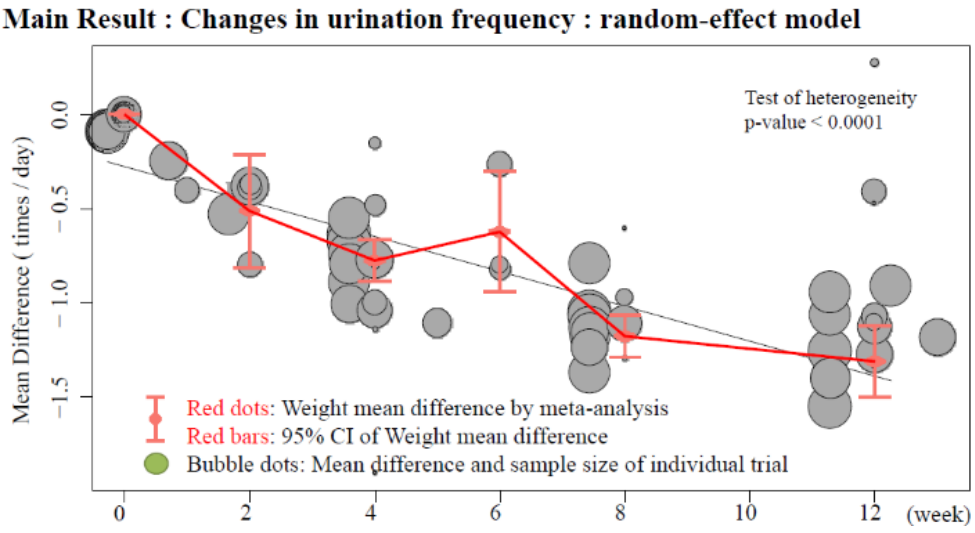
< Backgrounds >

In the process of consultation and review on drugs and medical devices related to urination, the placebo effects in clinical trials with urinary function as the primary endpoint have been reported in Europe and the United States, but not in Japan. The natural history of placebo effects in Japanese clinical trials was considered to be the basic data required for the protocol planning and also useful in evaluating the study results for discussing the protocol, observation period, and effect size in consideration of the placebo effects that are different between Japan and overseas.

< Outline>

Meta-analysis was performed based on the results in the published review reports.

The analysis revealed the placebo effects of urinary frequency, the effective volume, the effect-continued period, etc. in Japanese patients and the measurement items, such as a urine volume which was less likely to be affected by the placebo effects. As seen in the figure, the placebo effects for urinary frequency were found to titrate up for approximately 12 weeks, indicating the between-trial differences are limited. Ethnic-group differences were similar to those reported previously in Western countries.



< Impact on RS, expectations >

Recognizing the natural history of urinary diseases, mean regression, and the placebo effects, and planning and evaluating clinical trials may lead to improved quality of consultation / review services. In addition, PMDA's own conduct of such research may also contribute to improved PMDA's capabilities in reviews. With regard to the natural history of subjects in clinical trials, both placebo and nocebo effects are important viewpoints, and we believe that this research in Japanese patients will contribute to the promotion of RS.

PMDA – Review of Sakigake Designation Products: Oncolytic Virus Therapy with Delytact Injection (Teserpaturev) for Malignant Glioma

< Relevant articles > Please go to PubMed here.

Maruyama, Y., Sakurai, A., Noda, S., Fujiwara, Y., Okura, N., Takagi, T., Asano, J. & Honda, F. Regulatory Issues: PMDA - Review of Sakigake Designation Products: Oncolytic Virus Therapy with Delytact Injection (Teserpaturev) for Malignant Glioma. ***Oncologist*** 28, 664-70 (2023). 10.1093/oncolo/oyad041

Office of Cellular and Tissue-based Products, Yoshiaki Maruyama

< Backgrounds >

In June 2021, the Ministry of Health, Labour and Welfare approved Delytact Injection (generic name: teserpaturev) (hereinafter, “this drug”) as a regenerative medical product for oncolytic virus therapy for the first time in the world. We believe that sharing this review experience internationally will contribute to the appropriate development and evaluation of regenerative medical products.

< Outline>

The active substance of this product is a genetically engineered herpes simplex virus type 1 (strain F) in which the α47 gene and both copies of the γ34.5 gene have been deleted and the infected cell protein 6 (ICP6) gene has been inactivated by the insertion of the lacZ gene from *Escherichia coli*. The direct injection of this product in the tumor of patients with malignant glioma in the following process is expected to prolong the survival of patients with malignant glioma: 1) The mutant virus selectively replicates in tumor cells and destroys the infected cells through the replication process, exerting a cytocidal effect, and 2) the administration leads to induction of tumor-responsive T cells, which activates antitumor immunity. With this product, a non-GCP-compliant Japanese phase I/II study in patients who were refractory to radiotherapy was conducted, and a GCP-compliant Japanese phase II study (Study GD01) was conducted in patients with glioblastoma who had residual or recurrent tumors after radiotherapy with concomitant temozolomide. The tumor response is shown in the table below. Some patients with rapidly-progressing glioblastoma, in whom long-term stable disease is extremely rare, remained stable for a long time in the GD01 study. Therefore, we determined that this drug can be effective to a certain level. However, since the information is limited at present, we consider it appropriate to continuously evaluate and confirm the efficacy of this drug after the approval. The product was approved with 3 approval conditions, including a strict post-marketing evaluation within the period (7 years) after these reviews.

Table Results of additional analysis of tumor response
(Principal investigator's assessment, full analysis set, data cut-off on December 31, 2018)

Best overall response	n (%)
	19
Complete response	0
Partial response	1(5.3)
Stable	18(94.7)
Progression	0
Response (complete response + partial response) (Response rate [95%CI])	1 (5.3[0.1, 26.0])

(Partially modified from Table 24 in the Review Report)

https://www.pmda.go.jp/files/000242808.pdf

< Impact on RS, expectations >

We believe that this article will contribute to the dissemination of regulations for regulatory approvals in Japan by providing the following information to the world:

- The outline of products that have been developed and approved for marketing in Japan ahead of other countries
- Introduction of various systems / regulations applied to this drug ((1) Designation of orphan regenerative medical products, (2) SAKIGAKE Designation review, (3) Cartagena Act, (4) Conditional and time-limited approval)

4. Message from external expert

Deputy Chairperson, PMDA Regulatory Science Research Support Committee
Specially Appointed Professor, University of Tsukuba
Tsukuba Clinical Research and Development Organization
Yoshihiro Arakawa

In the review for approval of drugs and other products, it is essential to continuously gather information on the latest technological trends, and to understand both the possibilities and the potential risks of the products. For potential risks, in particular, it is important not only to consult experts, but also to proactively identify risks based on their own research experience. Currently, PMDA staff are overwhelmed with daily review duties and have limited time for research and self-improvement. However, in order to maintain and improve the quality of reviews, it is strongly expected to promote their research activities.

The candidates for future research are listed below. I hope these could serve as useful suggestions for research.

[Regional characteristics]

PMDA is a regulatory agency that serves as a key role in the ICH's three major regions and is expected to evaluate the efficacy and safety in the region on behalf of East Asia. In particular, now that international clinical trials are becoming the standard, it is crucial to independently analyze the regional characteristics (genetic background, lifestyle, and medical care system) in East Asia and consider these factors in discussions regarding the reliance in East Asia, as well as in ordinary Regulatory Science (RS) consultations.

[Impact of changes in disease structure]

As the focus of research and development shifts from lifestyle-related diseases and cancers to rare diseases and intractable diseases, the profile of required drugs, etc. has been changing. There are many issues to be studied, and it has become necessary to discuss even the medical care system itself. These issues include: methods for identifying target molecules in multifactorial diseases such as neurological diseases; shift from symptomatic therapies to disease-modifying therapies / preemptive medicine before disease onset; shift towards preventive medicine based on genomic information; development of clinically applicable biomarkers and clinical evaluation methods for slowly progressive diseases.

[Changes in modality]

For biological drugs, cell / gene therapies and other new modalities, the development of guidelines based on scientific evidence is required. There still remains a large gap between in vitro and in vivo studies and in the extrapolation from animal models to humans. In this regard, it is essential for reviewers to constantly update their knowledge, including by the interviews with both domestic and overseas experts and the continuous discussions with other regulatory agencies such as FDA.

< Editorial Note >

We have finally published the first 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 rs-research-toiawase△pmda.go.jp ("△" is used here to prevent spam mail; please change "△" to "@").

< Warning >

< 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.

< Photos and illustrations provided >

Pixta, Inc.

< Contact information for this report >

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