Greetings from the Chief Executive

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

Since its inception in 2004, the PMDA has steadily improved its outcomes based on regulatory science. Those include significantly diminishing its review time frame for new products. With the emergence of innovative products, an increasing number of cases will have no precedents to refer to, propelling the PMDA to be the first in the world to make regulatory decisions. Quality at the PMDA will be even more important.

The PMDA will promote regulatory science, assess risks and benefits from scientific perspectives while remaining vigilant of timeframes, with the spirit of Safety First. The PMDA will also further transparency, to better convey grounds for its decisions to healthcare professionals, patients, and the public.

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

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

Without being bound by precedents, the PMDA will proactively pursue new initiatives and contribute to the advancement of the public health and safety of all people in Japan.

April 2019

Yasuhiro Fujiwara, MD, PhD
Chief Executive
Pharmaceuticals and Medical Devices Agency
Our Philosophy

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

We conduct our mission in accordance with the following principles:

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

PMDA Code of Conduct

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

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

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

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

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

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

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

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

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

9. Proper Management and Use of PMDA Resources
   We will ensure the proper management and use of PMDA’s resources by avoiding and mitigating conflicts of interest and avoiding actual, potential, and perceived improprieties.
Outline of the Pharmaceuticals and Medical Devices Agency (PMDA)

History of PMDA

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

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

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<td>Thalidomide Lawsuit (filed by the sufferers requesting early establishment of relief system)</td>
<td>Subacute myelo-optico-neuropathy (SMON) Lawsuit</td>
<td>The Fund for Adverse Drug Reaction Relief established</td>
<td>The Fund reorganized into the Fund for Adverse Drug Reaction Relief and R&amp;D Promotion</td>
<td>Lawsuits concerning AIDS/HIV infection induced by tainted blood products</td>
<td>The Fund reorganized into the Organization for Pharmaceutical Safety and Research (OPSR)</td>
<td>Lawsuit concerning Creutzfeldt-Jakob disease (CJD)</td>
<td>Reorganization and Rationalization Plan for Special Public Corporations adopted by the Cabinet</td>
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- See page 30 for the details of lawsuits concerning drug-induced suffering

- Payment of healthcare allowance (SMON) commenced (November 1979)
- Relief System for Sufferers from Adverse Drug Reactions established (May 1980)
- R&D Promotion Service commenced (financing service started in 1988)
- Drug information consultation service commenced (July 1994)
- Management of adverse drug event report database commenced (August 1994)
- Drug information service system developed (May 1999)
- Equivalence review for drugs commenced (April 1994)
- GLP inspections commenced (April 1994)
- Clinical trial consultations and review of clinical trial notifications commenced (April 1997)
- GLP/GCP/GPSP compliance assessments and post-marketing surveillance (PMS) commenced (April 1997)
- GLP/GCP inspections for generic drugs commenced (April 1997)
- Equivalence review for medical equipment commenced (June 1995)
PMDA has become recognized as one of the world leading regulatory agencies because of enhanced regulatory performance, and its staff size has expanded approximately four-fold since its inception. In order to further lead the world as a top regulatory agency, PMDA must build a more solid organizational foundation to achieve its mission over the future, considering its organizational size and increased functions.

With the above understanding, “PMDA Proceeding Project” is currently underway. This project is an initiative to enhance PMDA’s overall organizational foundation.

<table>
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<th>Number of Full-time Employees</th>
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<td>April 1, 2015</td>
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<tr>
<td>Total (including executives)</td>
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<td>Review Department</td>
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<td>Safety Department</td>
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<td>Relief Department</td>
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PMDA’s mission is to help improve public health in Japan by providing swift relief to people who have suffered health damage caused by adverse drug reactions or infections from biological products (Relief Services for Adverse Health Effects), offering guidance and conducting reviews on the quality, efficacy and safety of drugs and medical devices through a system that integrates the entire process from pre-clinical research to approval (Product Reviews), and by collecting, analyzing and providing post-market safety information (Post-marketing Safety Measures).

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

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

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

Safety Triangle

- Securing Quality, Safety and Efficacy
- Reduction in risk
- Three-pillar System Unique to Japan
- Safety Continuous risk mitigation efforts
- Relief Relief measures for health damage caused by adverse drug reactions
- Japanese citizens
Relief Services for Adverse Health Effects

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

Flowchart of Relief System

* A person having a complaint about the decision on his/her eligibility to receive a relief benefit may file a request for a review of the decision with the Minister of Health, Labour and Welfare.
As described in the section titled “Outline of the Pharmaceuticals and Medical Devices Agency (PMDA),” the lawsuits concerning drug-induced suffering such as thalidomide-induced birth defects, subacute myelo-optico-neuropathy (SMON), acquired immunodeficiency syndrome (AIDS) or human immunodeficiency virus (HIV) infection, and Creutzfeldt-Jakob disease (CJD) were filed in Japan. Based on the lessons learned from these drug-induced tragedies, relevant laws were revised to prevent further tragedies from occurring and support systems were established for people affected by the incidents. The Adverse Drug Event Monitoring System originated with thalidomide-induced birth defects. SMON caused by Quinoline led to the establishment of the Relief System for Adverse Drug Reactions which aims to assist individuals who suffered from health damage caused by adverse drug reactions. In addition, the Relief System for Infections Acquired through Biological Products was established because of the spread of HIV infection through tainted blood products and prion disease (CJD) caused by the use of contaminated lyophilized human dura mater.

Drugs have both primary effects (desired therapeutic effects) and secondary effects (adverse effects). Although the latter effects are not always harmful, an unintended adverse event that is possibly related to the drug used is defined as an adverse drug reaction, according to the notification issued from the Ministry of Health, Labour and Welfare (MHLW). As described in the Review and Related Services and the Post-marketing Safety Measures sections, medical products including drugs are subjected to efficacy and safety evaluation before being marketed. Even if such medical products are properly used with great care, it is almost impossible to completely prevent adverse drug reactions or infections from biological products.

A product-related adverse event may occur even if the product was properly used as intended or at the recommended dose. Individuals who suffered from health damage caused by adverse reactions should be relieved immediately. Given such circumstances, the Relief System for Adverse Drug Reactions and Relief System for Infections Acquired through Biological Products were established as Japan’s original systems under which social relief benefits are provided to individuals who suffered from health damage, separately from liability for damage under the Civil Code or social security systems.

In addition, PMDA’s relief and safety departments share the information on claims for relief benefits to effectively use such information for safety measures. The shared information is reviewed in the safety department, together with safety information reported from marketing authorization holders (MAHs). Information on repeatedly reported cases are communicated to healthcare professionals by means of issuance of “PMDA Alert for Proper Use of Drugs,” in which precautions for use of drugs are plainly explained using graphic illustrations.

Following the enforcement of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (hereinafter referred to as the “PMD Act”) in 2014, PMDA started to compile cases of adverse reactions related to the claims submitted for relief benefits. Collaboration between the relief and safety departments has been further reinforced to facilitate the new task.

**Five Relief Services for Adverse Health Effects**

In addition to the services for the Relief System for Adverse Drug Reactions and Relief System for Infections Acquired through Biological Products, PMDA provides the following three relief services for adverse health effects: payment of healthcare allowances and nursing care expenses for SMON patients for whom a settlement has been reached in court (commissioned service), payment of healthcare allowances (including healthcare expense payment as part of investigative research) for patients infected with HIV through the use of tainted blood products (commissioned service), and payment of benefits under the Act on Special Measures concerning the Payment of Benefits to Assist Individuals Affected by Hepatitis C through Specified Fibrinogen Products and Specified Blood Coagulation Factor IX Products Contaminated by Hepatitis C Virus.

**Original mascot character “Doctor Q”**

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

PMDA intensively conducts a PR campaign for the relief system during the “Drugs and Health Week (around October 17 to 23 every year)” organized by the MHLW. Video contents and posters are distributed during the campaign week. An original mascot character “Doctor Q” has been featured in the promotional materials since 2011.

In addition, PMDA continues to dispatch its staff members to medical institutions and municipalities for presenting lectures on the relief system.
Relief Service for Adverse Drug Reactions

Relief System for Adverse Drug Reactions is the public service based on the Act on the Pharmaceuticals and Medical Devices Agency (Act No. 192 of 2002). Under the system, relief benefits are provided to persons with health damage that was caused by adverse reactions to prescription drugs prescribed at hospitals or clinics, over-the-counter (OTC) drugs purchased at pharmacies/drug stores, and regenerative medical products, even if such products were properly used. Such health damage include diseases requiring hospitalization, disabilities significantly limiting daily activities, and fatal cases.

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

Types of relief benefits

There are seven types of benefits: medical expenses, medical allowances, disability pension, pension for raising handicapped children, bereaved family pension, lump-sum benefits for bereaved families, and funeral expenses.

Medical expenses actually incurred by eligible patients (not including the portion covered by health insurance) for the treatment of their diseases caused by adverse reactions are reimbursable under the relief system. Medical allowances are paid to eligible patients as a fixed amount in consideration of costs except for medical expenses for the treatment of diseases due to adverse reactions.

Disability pension is regularly provided to compensate for living costs of persons aged 18 or older with a certain degree of disability caused by adverse reactions as long as the disability remains. If persons with a certain degree of disability caused by adverse reactions are under the age of 18, pension for raising handicapped children is provided to their parent or legal guardian. Although these benefits are defined as disability pensions, the system is different from the disability basic pension under the National Pension system.

In the case that a person who died from adverse reactions had been the main income earner of a household, bereaved family pension is provided to his or her family for the purpose of rebuilding the life of the family. If a person who died from adverse reactions had not been the main income earner, a lump-sum benefit for bereaved families is provided to his or her family as a consolatory payment. In addition, funeral expenses are paid to the hosts of funerals for those who died from adverse reactions.

How to claim relief benefits

Persons who have suffered from serious health damage caused by adverse reactions or the bereaved families have to submit a claim form for relief benefits directly to PMDA. When claiming the relief benefits, the claimant needs to prove the casual relationship between the symptoms and clinical course he or she experienced and the drug used. To do so, the claimant needs to obtain certificates from physicians who prescribed the drug in question (certificates for prescription/use) or a proof of purchase in the case of the over-the-counter drug purchased from a pharmacy or drugstore, in addition to a medical certificate written by the physician who treated the adverse health effects caused by adverse reactions. The claimant should ask his or her physician to create these certificates and should submit them to PMDA together with the claim form filled out by the claimant.

Upon receiving a claim for relief benefits, PMDA submits a request for a decision on the claim to the Minister of Health, Labour and Welfare (hereinafter referred to as “the Minister”) after investigating the contents of the claim. Once the Minister’s decision is notified to PMDA, the acceptance or rejection of the claim is determined based on the decision.

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

■ Benefit recipient cards (Japanese version only)

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

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

Since December 1979, PMDA or its predecessor has provided healthcare allowances to SMON patients for whom the judicial settlement was reached, and nursing care expenses to patients with grade III SMON who have very severe or extremely severe symptoms, under commission from the Japanese government and the pharmaceutical companies responsible.

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

Classification of Severity of Disability

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<tr>
<th>Severity Grade</th>
<th>Degree of Disability</th>
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<tbody>
<tr>
<td>Grade I</td>
<td>A person who is considered to have significant limitations in daily activities</td>
</tr>
<tr>
<td>Grade II</td>
<td>A person with disabilities falling somewhere between grade I and III</td>
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<tr>
<td>Grade III</td>
<td>A person who falls under any one of the following categories:</td>
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<tr>
<td></td>
<td>1. A blind person or a person with equivalent visual disabilities</td>
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<tr>
<td></td>
<td>2. A person with a walking disability or a person with equivalent walking disabilities</td>
</tr>
<tr>
<td></td>
<td>3. A person with combined symptoms of impaired eyesight and gait disturbance that result in disabilities classified as being equivalent to the category 1 or 2 above</td>
</tr>
<tr>
<td>Extremely severe disability</td>
<td>A person with disabilities of the categories 1 and 2 above</td>
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Healthcare Allowances for HIV-positive and AIDS Patients

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

1. Payment of special allowances: Since 1989, PMDA has provided special allowances etc. for AIDS patients for whom a settlement has not been reached in court.

2. Investigative research: Since 1993, PMDA has provided healthcare expenses for HIV-positive patients who have not yet developed AIDS in exchange for reports on their health condition, as well as with the intent to help the prevention of AIDS development.

3. Payment of healthcare allowances: Since 1996, PMDA has provided healthcare allowances for AIDS patients for whom a settlement has been reached in court. The purpose of this service is to improve the welfare of AIDS patients by reducing the cost of monitoring their health.

Patients with secondary and tertiary infections are also eligible for these benefits.

Upon receiving a claim for relief benefits, PMDA submits a request for a decision on the claim to the judgment group of the Yu-ai Welfare Foundation for healthcare expenses or to the judgment committee of the MHLW for special and healthcare allowances for AIDS patients. Once the decision is notified to PMDA, the acceptance or rejection of the claim is determined based on the decision.

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

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

Flowchart of Claiming for Benefits

Flowchart of Claiming for Additional Benefits (in the case of aggravation of symptoms)
In order to enable patients to have faster access to more effective drugs, medical devices, and regenerative medical products, PMDA is committed to reviewing applications for such products in a prompt and appropriate manner.

**Reviews and Related Services**

**Drug or Medical Device Development Process and PMDA’s Services**

- **Consultation**
  - Regulatory Science General Consultation/Regulatory Science Strategy Consultation (R&D)
  - GLP Inspection

- **Clinical Trial Consultation**
  - Pre-market Review
  - GLP/GCP/GPSP Compliance Assessment
  - GCP Inspection Document-based Compliance Assessment
  - GMP/QMS/GCTP Inspection

- **Standards Development**
  - GMP/QMS/GCTP Inspection

- **Regulatory Review**
  - Re-examination/Re-evaluation Use-results Evaluation
  - Consultation on Epidemiological Survey

- **Post-market**
  - Safety Measures
  - Relief Services for Adverse Health Effects
During the development process of a new medical product (e.g., drugs, medical devices, and regenerative medical products), the company developing the product needs to conduct various tests and studies to prove the quality, efficacy, and safety of the product. Based on the results of such tests/studies, the company (applicant) submits an application for regulatory approval of the product to the Minister of Ministry of Health, Labour and Welfare (hereinafter referred to as “the Minister of MHLW”). The product will be approved for commercial use if there are no problems with its quality, efficacy, and safety.

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

For the purpose of promotion of international regulatory harmonization, PMDA participates in international conferences on the regulation of medical products while actively incorporating the standards of the International Organization for Standardization (ISO) and other standards into its review guidelines for medical devices.

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

**Basic principles for product review**

During the product review process, PMDA reviewers mainly focus on the following six points:

1. Were clinical trials and other studies conducted properly? (i.e., the integrity of the data submitted)
2. Has the efficacy of a product been demonstrated objectively? For example, the data of well-controlled clinical trials have shown that the product has superior efficacy to placebo.
3. Do the data submitted suggest that the results of clinical trials are of clinical significance?
4. Do the demonstrated benefits of a product outweigh its risks?
5. Is the applicant capable of consistently supplying reasonably effective and safe products, from the perspective of quality control?
6. Is the post-marketing vigilance plan proposed by the applicant appropriate?

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

In recent years, clinical development programs for innovative medical products have been simultaneously undertaken in multiple countries/regions. In response to this circumstance, PMDA makes efforts to accelerate its product reviews to keep up with other regulatory authorities in the world, while spending much time in discussions to ensure that safe and reliable medical products are made available to the public.

**Priority Review Products and Conditional Early Approval Systems**

Priority review is conducted for orphan drugs and specific drugs selected by the Ministry of Health, Labour and Welfare (MHLW) based on the seriousness of the target disease and the medical usefulness. Priority review status is also granted to products designated under the SAKIGAKE Designation System which is intended to facilitate the world’s first practical application of innovative medical products.

Usually, confirmatory clinical trials are essential to confirm the efficacy and safety of an investigational product. In some cases, however, confirmatory clinical trials may be infeasible because of a small number of target patients, or it will take very long time for the clinical trials to be completed even though they are initiated. An investigational product which falls under the cases mentioned above and which is indicated for disease with no effective therapy may be eligible for the Conditional Early Approval System, under which conditional approval will be granted once a certain degree of efficacy and safety of the investigational product are confirmed through clinical trials (Conditional Early Approval System for Drugs and Conditional Early Approval System for Innovative Medical Devices). In addition, some regenerative medical products are eligible for the Conditional and Time-limited Authorization System established pursuant to the PMD Act, under which the product will be granted conditional and time-limited approval once its efficacy is predicted and its safety is ensured. Post-marketing safety information on the product is collected and reviewed to make a final decision on the approval of the product.

In this way, PMDA strives to facilitate the early practical use of medical products with high medical need in collaboration with the MHLW.

*What is the SAKIGAKE Designation System?*

The SAKIGAKE Designation System is an expedited program intended to facilitate the development of innovative drugs, medical devices, and regenerative medical products, leading to their early practical application as the first in the world. The pilot scheme of the SAKIGAKE designation has been implemented, starting in 2015.

In this expedited program, innovative products including new drugs that meet certain requirements will be granted priority status for consultations on regulatory submission and for review by PMDA at a relatively early stage of development. In addition, the program ensures that the applicant’s manufacturing system is properly established and that the product is smoothly supplied to clinical settings once it has been approved.

To accelerate the practical application of SAKIGAKE-designated products, a PMDA manager is assigned to be a review partner (also called a “concierge”) who serves as a liaison between the MHLW and responsible offices at PMDA while regularly managing the progress of product review. Priority consultation and priority review statuses are granted to SAKIGAKE-designated products. By promoting the use of this system, PMDA aims to achieve a standard review time of 6 months. As of the end of March 2019, 7 products have already been approved under this system.

A product eligible for the SAKIGAKE designation should be innovative, intended to treat serious diseases, and demonstrated to have remarkable efficacy in the treatment of the target diseases. In addition, the developer of the product should have an intention of early development and regulatory submission in Japan ahead of other countries.
Standard Drug Development Process

Drug Reviews

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

On the basis of the review reports submitted from PMDA, the Minister of MHLW consults the Pharmaceutical Affairs and Food Sanitation Council (PAFSC) about making a decision on whether to approve the product. The PAFSC’s committees are composed of external experts in various fields. The Minister of MHLW grants approval to the product once the PAFSC concludes that the product may be approved based on the results of regulatory review. To secure the transparency of its product review, PMDA publishes review reports for approved products on its website.

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

Drugs reviewed by PMDA

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

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

Review times for new drugs

When PMDA was established, the “drug lag” issue (delayed access to new drugs) had been seen in Japan. PMDA made efforts to speed up its operations by promoting the enhancement of its review system and consultation activities, which resulted in resolution of the drug lag issue by 2011. In recent years, PMDA has achieved the shortest review times for new drugs among regulatory agencies in developed counties such as European countries and the United States. PMDA endeavors to ensure a more predictable review process, aiming to achieve the review time of 12 months for new drugs (9 months for priority review products).

Towards further improvement in review quality

PMDA is currently working on new approaches to advanced evaluation through accumulation and analysis of electronic study data submitted from applicants, thereby enhancing its product reviews and consultations and reducing burden on sponsors or applicants. This approach has been addressed in the Japan Revitalization Strategy (Cabinet decision on June 14, 2013) and the Healthcare and Medical Strategy (Cabinet decision on July 22, 2014).

What is Drug Lag or Device Lag?

Drug lag or device lag refers to the difference in time required for approval of drugs or medical devices between Japan and other countries. The lag was caused by the delay in regulatory submission in Japan (development lag) and the lengthier review process in Japan than in other countries (review lag). Under such circumstances, the MHLW developed the 5-Year Strategy for the Creation of Innovative Pharmaceuticals and Medical Devices in April 2007, in cooperation with the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Economy, Trade and Industry. In line with this strategy, several initiatives were undertaken to promote the development of drugs or medical devices and the conduct of global clinical trials, and the clinical trials network was developed nationwide. These efforts led to the shortened development lag. In addition, the review lag was almost resolved through PMDA’s approaches to strengthening its review system (the number of reviewers was tripled by 2009) and to enhancing the consultation programs.

Drug lag and device lag can be caused by various factors:

- Differences in the regulatory systems and processes between countries
- Lower efficiency in the approval process in Japan
- Differences in the approval criteria between countries

To improve the review process, PMDA has implemented various strategies, such as:

- Accelerating the review process through the Enhanced Review System
- Strengthening the consultation process with external experts
- Enhancing the transparency of the review process

These efforts have resulted in a reduction of the review times for new drugs in Japan, making the approval process more predictable for applicants.

**Non-clinical studies**
- In animals or cell cultures
- To investigate efficacy and safety

**Studies on quality**
- Specifications for drug substances/drug products
- Stability studies for drug substances/drug products

**Clinical trials**

Non-clinical studies
- In animals or cell cultures
- To investigate efficacy and safety

Early phase II trials

- In a small number of patients
- Mainly for efficacy assessment

Late phase II trials

- In a certain number of patients
- Confirm the safety and effective dose and regimen

Phase III trials (therapeutic confirmatory phase)

- In a large number of patients
- Controlled or open-label trials to confirm efficacy and safety

Filing of application

- For product registration
Medical Device Reviews

Medical devices cover a wide range of products, from adhesive bandages and forceps to magnetic resonance imaging (MRI) systems and pacemakers, which are characterized by a variety of usage patterns and different levels of risk. Procedures for the registration of medical devices vary depending on their risk level (see the classification table). PMDA mainly conducts regulatory reviews for high-risk medical devices.

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

Risk-based approach to medical device regulation

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

Most of Class III medical devices that may pose a relatively high risk to the human body (specially controlled medical device) and all of Class IV medical devices that are highly invasive and thus pose a life-threatening risk if a malfunction occurs (specially controlled medical device) require approval by the Minister of MHLW before being marketed. Marketing applications for such medical devices are subject to review by PMDA. The procedures for the registration of new medical devices are basically the same as those for new drugs. Certification standards have been specified by the Minister of MHLW for some Class III medical devices. In this case, such medical devices require certification granted by registered certification bodies and do not undergo PMDA’s review before being marketed.

Class II medical devices which may pose a relatively low risk to the human body if a malfunction occurs (specially controlled medical device) and for which certification standards have been specified by the Minister of MHLW require certification granted by registered certification bodies before being marketed. Class II medical devices with no certification standards specified must undergo PMDA’s review and obtain approval by the Minister of MHLW.

To market Class I medical devices that potentially pose an extremely low risk to the human body if a malfunction occurs, their manufacturers should submit marketing notification to PMDA.

Classification and Regulation regarding Medical Devices

Risk Level

<table>
<thead>
<tr>
<th>General Medical Devices</th>
<th>Controlled Medical Devices</th>
<th>Specially Controlled Medical Device</th>
<th>Approval by the Minister of MHLW based on scientific review by PMDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Certification by registered certification bodies</td>
<td>Devices that may pose a relatively low risk to the human body in case of a malfunction</td>
<td>Devices that are highly invasive and thus pose a life-threatening risk in case of a malfunction</td>
</tr>
<tr>
<td>Class II</td>
<td>Notification to PMDA</td>
<td>Devices that may pose a relatively high risk to the human body in case of a malfunction</td>
<td>Examples: Pneumator, Artificial cardiac valve, Artificial breast, Stent graft</td>
</tr>
<tr>
<td>Class III</td>
<td>Devices that are highly invasive and thus pose a life-threatening risk in case of a malfunction</td>
<td>Examples: Pneumator, Artificial cardiac valve, Artificial breast, Stent graft</td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Basic principles for medical device review and review times

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

Submission of different datasets is necessary for medical devices in each category. Review times vary depending on the device category. PMDA’s review teams strive to achieve the target review times for each category.

Review of in vitro diagnostics

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

There are several kinds of IVDs such as OTC diagnostics including pregnancy test kits which can be purchased at pharmacies/drug stores, test agents used for examining specimens (blood, urine, feces, and cells) derived from humans for diagnostic purpose at medical institutions, and companion diagnostics used for identifying patients who are most likely to benefit from a particular therapeutic drug.

Furthermore, PMDA has been proceeding with approaches to diagnostic tests using state-of-the-art technology such as gene panel testing, which will lead to the realization of precision medicine allowing analysis and selection of optimal medical treatments for each patient.
Regenerative medical products were newly defined by the PMD Act that was enforced on November 25, 2014. Those products were handled as drugs or medical devices before the enforcement of the PMD Act which allows for faster access to safer regenerative medicine. The regenerative medicine is the medical technique that reproduces tissues or organs damaged by diseases or injuries. This technology is also expected to be applied to drug development.

**Regulatory framework based on product properties**

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

In addition, patients with health damage caused by regenerative medical products are eligible for the relief system for adverse health effects or the relief system for infections because the regenerative medical products are granted conditional approval at the stage where further verification of the product safety is required.

The marketing authorization holder of the product approved under this authorization system is required to submit a re-application with supporting data collected during the period of conditional approval in order to have the efficacy and safety of the product re-assessed.

**Regenerative medical products approved in Japan**

As of the end of March 2019, seven regenerative medical products were approved, and three of them were granted conditional and time-limited approval.

**What are Regenerative Medical Products?**

Regenerative medical products are defined as:

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

Since these products are all derived from engineered living cells/tissues, the products are characterized by their varied quality and in that their efficacy is difficult to be confirmed in some cases.

The range of the regenerative medical products specified by the Cabinet Order is as follows:

1. Human cellular/tissue-based products (human somatic cell, human somatic stem cells, human embryonic stem cells, and human induced pluripotent stem [iPS] cells) and animal cellular/tissue-based products (animal somatic cell, animal somatic stem cells, animal embryonic stem cells, and animal induced pluripotent stem [iPS] cells)
2. Plasmid vector products, viral vector products, and gene therapy products
GMP/QMS/GCTP Inspections

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

Scope and method of inspection
PMDA conducts on-site and document-based GMP inspections of “high-risk” manufacturing sites for products such as new drugs, biological products or biotechnological products (including foreign manufacturing sites), in order to ascertain whether their manufacturing facilities and manufacturing and quality controls comply with standards of the GMP, and whether the manufacturing sites have a system for manufacturing products of adequate quality. PMDA also conducts inspections in relation to accreditation of foreign manufacturers.

PMDA conducts on-site and document-based QMS inspections for marketing authorization holders of medical devices or in vitro diagnostics and the relevant registered manufacturing sites (of products under review or approved) located in Japan or overseas, in order to ascertain whether their manufacturing facilities and manufacturing and quality controls comply with standards of the QMS, and whether the marketing authorization holders ensure that products of adequate quality are manufactured and marketed in accordance with the standards.

GCTP inspection
PMDA conducts on-site inspection of test facilities carrying out non-clinical safety studies if the inspection is requested. This inspection is intended to determine the compliance of the test facilities with GLP.

GLP/GCP/GPSP Inspection

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

What is a Clinical Trial?

A clinical trial refers to a research study conducted to assess the efficacy and potential adverse effects of a drug, medical device, or cellular/tissue-based product used in humans and thereby collect clinical data for regulatory submission. In the process of on-site GCP inspection, PMDA inspectors verify whether the rights and safety of trial subjects were protected in the clinical trials selected as well as how the clinical trials were managed. The inspectors also provide direct advice to physicians, pharmacists, clinical research coordinators, and nurses at the site of inspection, thus contributing to improvement of the clinical trial environment in Japan.
Any person who intends to market medical devices and in vitro diagnostics that are designated in accordance with standards specified by the Minister of MHLW must obtain the certification by a registered certification body for each product to be marketed (third-party certification). The range of products to be certified by a certification body differs depending on individual certification bodies.

Entities intending to be registered as certification bodies need to submit an application to the Minister of MHLW and to undergo inspection by PMDA, as necessary. PMDA conducts on-site inspection to assess whether such entities meet the standards for certification bodies defined by the International Organization for Standardization (ISO)/ International Electrotechnical Commission (IEC) and standards for certification bodies providing QMS certification services. Furthermore, PMDA conducts on-site inspection before registration as well as for renewal of the registration and periodic inspections.

In addition, registered certification bodies have a formal obligation to report the Minister of MHLW, when certification is granted or cancelled for a marketing authorization holder. PMDA accepts such reports.

**International cooperation activities for medical device quality control**

PMDA is participating in the Medical Device Single Audit Program (MDSAP) as part of international cooperation activities for medical device quality control. PMDA’s staff act as regulatory authority assessors who perform MDSAP auditing organization assessment.

The MDSAP is a program that allows a single audit of a medical device manufacturer’s quality management system (QMS) which satisfies the requirements of multiple regulatory authorities. The regulators participating in the program are those of Japan (MHLW and PMDA), the United States, Canada, Australia, and Brazil. Under this program, QMS audits are conducted by MDSAP-recognized third-party auditing organizations and resulting audit reports are utilized by the participating regulatory authorities. In the conventional regulatory framework, medical device manufacturers need to cope with each of on-site QMS inspections performed by regulatory authorities of different countries. However, utilization of this program by the participating regulatory authorities reduces the burden of QMS inspections/audits on medical device manufacturers.

**Process of Development of Japanese Industrial Standards (JIS) Adopted as Approval and Certification Standards**

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

The JP has a long history and its first edition was published in 1886. It has since then been updated regularly to keep pace with the latest knowledge, the advance of technology, and the globalization of drug development. The current version as of the end of March 2019 is the 17th edition of the Japanese Pharmacopoeia. PMDA is involved in the development of draft monographs and general tests for inclusion in the JP while convening the JP Expert Committees consisting of external experts in order for the drafts to be reviewed. The drafts with the comments from the JP Expert Committees are published on the PMDA website for public comments before the final drafts are reported to the MHLW by PMDA.

Medical devices are evaluated using a risk-based approach and the certification standards and some approval standards for medical devices are developed accordingly. In addition to the JP, certification standards and guidelines which provide guidance for review of medical devices are developed at PMDA (see the figure below).

**Standards Development**

To facilitate harmonization with international standards, PMDA participates in international conferences on drugs, such as the International Meetings of World Pharmacopoetides; the meetings of the Pharmacopoetial Discussion Group (PDG) consisting of the European Pharmacopoeia, Japanese Pharmacopoeia, and United States Pharmacopoeia; and the WHO International Nonproprietary Names (INN) meetings.

PMDA also actively participates in the ISO/IEC meetings and the standards development working group of the International Medical Device Regulatory Form (IMDRF) to enable standards originating from Japan or those reflecting the concept accepted in Japan to be adopted globally and to promote the harmonization of international standards used for regulation of medical devices among different countries.
PMDA offers consultations to give guidance and advice on clinical trials of drugs, etc. as well as on data for regulatory submissions. A variety of consultations are available for users' convenience, so that companies can request a consultation suitable for their needs at any stage of development of a medical product.

In clinical trial consultations for new drugs, PMDA ascertains whether a proposed clinical trial complies with the requirements for regulatory submission, taking into consideration the ethical and scientific aspects and reliability of the clinical trial as well as the safety of trial subjects, and also gives advice that leads to an improvement in the quality of the clinical trial. Starting in FY 2009, PMDA provides prior assessment consultations, in which its reviewers evaluate data on the quality, efficacy, and safety of a product in the pre-submission stage. This consultation process constitutes part of the review of the product once the application is submitted.

PMDA also offers consultations to give guidance and advice on clinical trials and data for regulatory submissions of medical devices and regenerative medical products. In addition, PMDA provides simple consultations covering simple advice such as confirmation of application category, pre-consultation meetings (for drugs) to identify key issues for facilitation of consultation meetings, and general consultations (for medical devices) to provide orientation on overall regulatory system, for example, by presenting notifications.

**Examples of issues addressed**

**For drugs**
- Quality and specification setting
- Nonclinical studies required before the commencement of first-in-human trials
- Protocols of early exploratory clinical trials (phase I and II trials)

**For medical devices**
- Nonclinical studies required before the commencement of clinical studies (trials) in humans
- Conformity to the essential principles
- Specifications on performance and safety
- Preparation of the data package required for regulatory submission

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### Regulatory Science General Consultation and Regulatory Science Strategy Consultation (R&D)

In order to promote the practical application of innovative drugs, medical devices, and regenerative medical products originating in Japan, PMDA offers consultations mainly for universities, research institutions, and venture companies that discovered promising “seed-stage” technologies, starting in July 2011. Such consultations are intended to provide advice on the design of studies needed during the period from the final stage of drug candidate selection to the proof-of-concept trials (or early phase II trials) and clinical trial protocol development. (On April 1, 2017, the Pharmaceutical Affairs Consultation on R&D Strategy was changed to the Regulatory Science General Consultation and the Regulatory Science Strategy Consultation (R&D) to provide enhanced consultation service.)

The Regulatory Science General Consultation is available at the PMDA headquarter in Tokyo, the Kansai Branch in Osaka, and the PMDA Cooperation Center for Consultations on R&D Strategy in Kobe. In the general consultation, PMDA staff give advice on whether subject matter is qualified for the Regulatory Science Strategy Consultation (R&D) and provide orientation on overall regulatory system, for example, by presenting notifications and guidelines. In April 2018, PMDA started to provide the Collaborative Consultation on Practical Application of Innovative Products while sharing information with the Medical Innovation Support Office, Economic Affairs Division, Health Policy Bureau, MHLW.

In addition, the consultation service also provides guidance and advice on the quality and safety of regenerative medical products and on those of gene therapy products which are intended for transgene expression in the human body and used to prevent diseases (e.g., live recombinant vaccines), at an early development stage.
Post-marketing Safety Measures

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

Flowchart of Safety Measures

- **Patients**
  - Seeking medical advice
  - Reporting of adverse drug reactions
  - Notification regarding issue under consideration
  - Consultation on drugs and medical devices
  - Immediate accessible

- **Medical institutions**
  - Collection/confirmation of information regarding quality, efficacy, and safety of drugs and medical devices
  - Analysis
  - Considering safety measures
  - Corporate hearing
  - Data collection/analysis
  - Broad and prompt dissemination of information
  - Results of review/analysis
  - Reporting of adverse drug reactions
  - Requesting revision of package insert

- **Marketing Authorization Holders**
  - Collection/confirmation of information regarding quality, efficacy, and safety of drugs and medical devices
  - Analysis
  - Considering safety measures
  - Implementing safety measures

- **Ministry of Health, Labour and Welfare (MHLW)**
  - Keeping track of all the information
  - Planning/development of safety measures
  - Implementation of safety measures
  - Real-time reporting

- **General public**
  - Medical institutions
  - Medical institutions
  - Pharmaceutical Affairs and Food Sanitation Council
  - Information regarding overseas regulatory actions and medical literature
  - Consultation on drugs and medical devices
  - Results of review/analysis
  - Discussion with experts
  - Reporting
  - Broad and prompt dissemination of information
Medical products including drugs are essential for protecting our health and lives. Thanks to advancements in science and technology, humans have conquered many difficulties over the years; the medical products created by human ingenuity have allowed us to overcome many diseases.

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

The safety information reporting system has been enhanced based on the lessons from drug-induced tragedies. PMDA compiles information on adverse drug reactions, etc. reported from marketing authorization holders (MAHs) and medical institutions, and its safety department implements adequate safety measures, involving its review and relief departments as necessary, in cooperation with the MHLW. In addition, PMDA provides an easy-to-understand summary of medical product safety information on its web site and through e-mail information service.

In order to ensure that people have access to safe and reliable medical products, PMDA makes efforts to collect risk information through various methods and then to communicate new findings to healthcare professionals.

**Acceptance of Labeling Information (Package Inserts) Submitted**

Under the PMD Act, marketing authorization holders (MAHs) of drugs (prescription drugs and BTC drugs), medical devices (Class IV medical devices), or regenerative medical products are required to develop a package insert for each of their products based on the latest findings and to submit it to the Minister of Health, Labour and Welfare. At the same time, the submitted package insert needs to be published on the PMDA website.

PMDA accepts and reviews the package inserts for drugs etc., submitted by MAHs to publish them on its website.

**What is a Marketing Authorization Holder?**

A marketing authorization holder (MAH) is or represents an entity holding a marketing license for medical products manufactured (including commissioning others to manufacture the products, but excluding commissioned manufacturing of the products) or imported by the entity. MAHs are permitted to sell or supply drugs, etc. (except for specified drug substances) and sell, lease, or supply medical devices as permitted under the terms of the relevant product approval.

**What is a Package Insert?**

A package insert is an explanatory document included in the packaging of over-the-counter (OTC) drug products purchased at pharmacies/drug stores or prescription drugs purchased by hospitals or pharmacies from a marketing authorization holder (MAH).

The package insert is developed by MAHs for their products in accordance with the regulatory requirements for creating package inserts, which must contain information on the product such as the dosage and administration, indications, and adverse reactions in order to ensure the proper use of the product.

Preparation of a package insert (or labeling) is required for not only drug products but also medical devices and regenerative medical products.

**Consultation Services**

**Consultations for MAHs and other companies**

PMDA provides MAHs and other companies with consultations on a broad range of product safety issues, such as how to revise package inserts, how to promote proper use of products to prevent serious adverse drug reactions, and how to develop and update Risk Management Plans (RMPs) for drugs in the post-marketing stage. In such consultations, PMDA gives specific advice and guidance to MAHs and other companies in order to help promote the safety of medical products, while also raising corporate awareness of safety measures.

**Consultations for general public**

PMDA’s telephone consultation service is also available for the general public. This service allows people to seek advice on products such as drugs prescribed by doctors (prescription drugs), drugs purchased at pharmacies (OTC drugs or BTC drugs), home-use medical devices purchased in stores and to obtain safety information on those products.

In order to ensure that generic drugs are used without any anxiety, PMDA also offers consultation services on the quality, efficacy, and safety of generic drugs and provides the related information.
Post-marketing Safety Measures

**Collection, Coordination, and Dissemination of Medical Product Safety Information**

Under the PMD Act, healthcare professionals and MAHs are required to submit post-marketing reports on adverse drug reactions, device malfunctions, etc., to the Minister of Health, Labour and Welfare. MAHs also must submit reports describing any measures implemented by overseas regulatory agencies and relevant published research findings regarding their products.

Investigational drugs or other medical products under clinical development in Japan are also subject to the requirements regarding adverse drug reaction/device malfunction reporting. Sponsors and sponsor-investigators are required to submit reports on adverse drug reactions or device malfunctions occurring during clinical trials, measures implemented by overseas regulatory agencies, and relevant published research findings.

PMDA also compiles the submitted reports into databases in a prompt and efficient manner, and provides access to these databases to MHLW.

At the end of March 2012, PMDA began receiving voluntary reports from patients and their families on a trial basis to gather information on adverse drug reactions observed in the post-marketing period. The voluntary reporting system was launched officially at the end of March 2019.

**Scientific Research and Analyses**

PMDA conducts research and reviews of the collected information through scientific analyses, interviews with companies, and discussions with experts, to determine whether there is any case requiring urgent measures, whether the risk/benefit profile is favorable, and what the optimal safety measures are. All these efforts lead to safety measures for medical products.

To take effective safety measures, the safety department staff work with the review and relief departments as well as the MHLW, as required. Meanwhile, when application for a new drug or a follow-on biologic (biosimilar) is filed in or after April 2013, the applicant is required to include a Risk Management Plan (RMP) in the application. To facilitate this regulatory framework, risk managers have been appointed who concurrently serve as members of the review department. PMDA thus strives to enhance safety measures by utilizing RMPs based on the cooperation between the safety and drug review departments.

**Aiming for enhanced and advanced safety measures**

PMDA has taken various approaches to enhance and advance safety measures. The Medical Information Database Network (MID-NET®), a system for integrating electronic medical records, has been developed to serve safety evaluation of drugs. Electronic medical record data extracted from the MID-NET® database are analyzed using pharmacoepidemiological methods (known as the MIHARI Project). Data mining methods (which involve statistical analysis of adverse drug reactions as reported by healthcare professionals or MAHs, thereby detecting signals of adverse drug reactions that may warrant further investigation) are also used for analysis.

PMDA strives to improve safety measures through the above approaches.

**What is a Risk Management Plan?**

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

A risk management plan (RMP) is a document comprising summaries of the following elements: Safety Specification (which includes important identified risks, important potential risks, and important missing information), Pharmacovigilance Plan (which includes the planned collection and review of information on Safety Specification), and Risk Minimization Action Plans.

The submitted RMPs have been posted on the PMDA website.
Information Services

A wide range of information on the quality, efficacy, and safety of medical products including drugs is released on the PMDA website in a timely manner, including the package inserts for drugs, etc., Risk Management Plans (RMPs) for drugs, recalls, and emergent safety communications (“Dear Healthcare Professional” Letters). All cases of adverse drug reactions and medical device malfunctions reported by healthcare professionals and MAHs are posted on the same website every month.

PMDA also provides the general public with information, such as the “Drug Guide for Patients,” which is an easy-to-understand explanation about prescription drugs with warnings, and the “Manuals for Management of Individual Serious Adverse Drug Reactions (for the general public),” which outline individual adverse drug reactions, initial symptoms, and key points for early detection and treatment in an easy-to-understand manner.

In addition, the Agency offers an email information service called “PMDA medi-navi” (available in Japanese only), through which important safety information posted on its website is distributed to healthcare professionals who subscribe to the service.

What is “PMDA medi-navi”?
The “PMDA medi-navi” (i.e., the pharmaceuticals and medical devices information e-mail service) is an e-mail service that delivers important information on the quality, efficacy, safety, etc., of medical products including drugs to pre-registered e-mail addresses of subscribers, immediately at the time such information is issued.

Anyone can subscribe to this service free of charge to obtain important safety information.

The PMDA medi-navi mainly includes:

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

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

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

As the development, manufacture, and distribution of drugs and other medical products are becoming increasingly globalized, PMDA must increase its efforts to cooperate closely with foreign regulatory authorities, as well as industry and academia. In line with the PMDA International Strategic Plan 2015, PMDA aims to maximize the common health benefits to Japan and the world by building on its experience, contribute to the public health of partner countries/regions through provision of information and training that are essential for building regulatory capacity in those countries.

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

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

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### Five Strategies

#### Strategy 1: Taking the lead, and disseminating the information around the globe
- Establish the “Regulatory Science Center” and other schemes

#### Strategy 2: Promotion of international regulatory harmonization and global cooperation
- Expediting the global utilization of the Japanese Pharmacopoeia (JP)
- Strengthening the communication with overseas regulatory authorities through mutual personnel exchange

#### Strategy 3: Increase efficiency of inspections that may lead to future international work-sharing
- Streamline international collaboration in GXP/QMS inspections

#### Strategy 4: Contribution to international regulatory harmonization activities
- Proactively propose to create guidelines, etc. leading to common health benefit

#### Strategy 5: Provision of information and training programs that are essential for building regulatory capacity in partner countries
- Launch of “Asian Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs” and other programs

### PMDA International Strategic Plan 2015

#### Three Visions

**Vision I: To contribute to the world through regulatory innovation**

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

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

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

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

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

### A group photograph of participants at the 12th International Summit of Heads of Medicines Regulatory Agencies and the meeting of the International Coalition of Medicines Regulatory Authorities (ICMRA) (in Kyoto, Japan, October 2017)
Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs

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

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

Activities of PMDA-ATC

1. To offer training seminars to the staff of regulatory authorities in Asian and other countries
   PMDA-ATC will plan and organize effective training programs tailored to the needs and capacities of individual regulatory agencies in Asian and other countries.

2. By sending PMDA expert staff to Asian and other countries to offer lectures, case studies, and on-site training
   PMDA-ATC will become able to offer relevant training responsive to local needs to larger numbers of officials.

3. By establishing a centralized training center for multi-regional clinical trials/GCP inspections and pharmacovigilance conducted in the APEC region
   PMDA-ATC will become able to establish PMDA’s position as a leading authority for medical product regulation in Asian and other countries.
PMDA’s scientific activities must consist of accurate prediction, evaluation, and judgment based on clear evidence, while incorporating the latest scientific findings. To improve its activities, PMDA promotes regulatory science, which forms the basis of regulatory decisions.

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

To further advance regulatory science, PMDA established the Regulatory Science Center (RSC) in April 2018. The RSC consists of the Office of Research Promotion, Office of Advanced Evaluation with Electronic Data, and Office of Medical Informatics and Epidemiology. These offices collaborate with review and safety departments in improving reviews and related services and safety measures.

**Support for and Promotion of Research**

PMDA operates the Projects Across Multi-offices as a framework to develop standards and guidelines that address issues concerning evaluation and development of drugs, medical devices, etc. Under the framework of the Projects Across Multi-offices, working groups consisting of staff members from relevant offices (regardless of review categories) across PMDA discuss individual issues, taking into account international regulatory harmonization. In this way, PMDA leverages the development of guidelines in cooperation with the MHLW.

PMDA has also made efforts to promote regulatory science and foster younger researchers through post-graduate education in several graduate schools with which an agreement on the collaborative graduate school program has been signed. In April 2015, the program was expanded to allow PMDA to conclude an agreement on the comprehensive partnership program with medical and research institutions that conduct high-quality clinical research, in addition to universities. The new program is intended to provide an extensive collaborative framework that exceeds conventional research or education. PMDA strives to foster human resources through active personnel exchanges between partner institutions and the Agency.

**Enhancement of information collection and response to emerging technology products**

PMDA has started activities towards implementation of horizon scanning in order to enhance information collection and to reinforce its response to emerging technology products. Horizon scanning is a systematic process used to identify emerging technologies and trends and to assess their potential impact on the regulatory system. This process will support the establishment of a new regulatory framework suitable for emerging technologies. In the international arena, the International Coalition of Medicines Regulatory Authorities (ICMRA) places a focus on horizon scanning in the innovation project and its members meet to discuss and share the issue. Japan actively contributes to the project of ICMRA. PMDA plans to investigate horizon scanning methodologies based on discussions at the ICMRA meetings. Information collected through horizon scanning for emerging technologies will be screened at the RSC and evaluated at the Science Board and the Projects Across Multi-offices to consider how the information can be used for the establishment of future regulatory framework.

**PMDA Regulatory Science Center**

- Support for epidemiological data evaluation and study planning
- Product review-related pharmacoepidemiological investigations, etc.
- Safety measures based on epidemiological analysis etc.
- Safety measure-related pharmacoepidemiological investigations, etc.
- Epidemiological analysis utilizing medical information such as the NDB and MID-NET
- Management of MID-NET operations
- Office of New Drugs
- Office of Medical Informatics and Epidemiology
- Office of Research Promotion
- Office of Advanced Evaluation with Electronic Data
- Office of Safety
- PMDA Science Board
- Projects Across Multi-offices
- Horizon Scanning
- Comprehensive Partnership Agreements
- Research management and promotion
- Cross-product analysis, creation of disease models, searches for M&S methodologies
- Evaluation of marketing authorization applications based on real-world evidence
- Creation of disease models for data evaluation, etc.
- Support for advanced analyses
Science Board

The Science Board to PMDA was established in May 2015. Its objectives are to respond to the progress of medical innovations and to properly address scientific challenges in the field of advanced science and technology. The Science Board consists of external experts in areas such as medicine, dentistry, pharmaceutical science, and engineering. Evaluation methods for innovative drugs, medical devices, and regenerative medical products are discussed at board meetings. PMDA actively utilizes the Science Board, thereby reinforcing collaboration and communication with scientists from universities and research institutions and healthcare professionals. This enables PMDA to incorporate the latest scientific knowledge into its services, thus leading to the improvement of its reviews and related services including Regulatory Science Strategy Consultations (R&D) as well as safety measures.

PMDA’s Efforts to Facilitate Medical Innovation

Advanced Review and Consultation with Electronic Data

In the current drug development paradigm, electronic clinical study data are analyzed by various methods and the analytical results are used to increase the efficiency of the development process. PMDA strives to improve its product review and consultation services by accumulating electronic study data submitted for marketing applications and then by analyzing them with advanced approaches such as modeling and simulation (M & S). During the review of individual product applications, reviewers are permitted to access the accumulated electronic data and to analyze the data by themselves, which will result in the realization of discussion and decision-making based on the analytical results. In addition, the accumulation of electronic study data allows reviewers to perform cross-product evaluation, thereby accelerating the development of new guidelines and consequently contributing to an increase in the success rate of drug development.

Outcome documents of Science Board meetings

Third term (from April 2016 to March 2018)
- Current state of therapeutic development for rare cancers in Japan, and proposals for improvement
- Issues in and Proposals for Facilitating Drug Discovery by Collaboration between Academia and Industry 2017 - In the Trend of Rapidly Advancing Science
- Regulatory Science on AI-based Medical Devices and Systems

The outcome documents for the first term (from May 2012 to March 2014) and the second term (from April 2014 to March 2016) are also available on the PMDA website.
Every drug is expected to exhibit therapeutic benefits while carrying a risk of adverse effects. To ensure that drugs are used in a way that maximizes benefits and minimizes risks, PMDA researches and analyzes information/data on the quality, efficacy, and safety of drugs, etc. in the post-marketing stage from the viewpoint of pharmacoepidemiology.

PMDA’s main pharmacovigilance initiatives include the Medical Information for Risk Assessment Initiative (known as the MIHARI project) and the development of the Medical Information Database Network (MID-NET\textsuperscript{®}). These initiatives have been set up to monitor and evaluate the safety of drugs by using information sources except for spontaneous adverse drug reaction reporting that serves as a part of safety measures. Both are expected to enhance post-marketing safety measures for drugs.

The MIHARI project launched in 2009 aims to establish a system for monitoring the safety of drugs by using electronic medical data sources such as the MID-NET\textsuperscript{®} database, the Japanese National Claims Database, the health insurance claims database, and the Diagnosis Procedure Combination (DPC) data. In the course of project implementation, several pilot studies were conducted to obtain advanced analysis methods, resulting in the establishment of a system which can proactively monitor adverse drug reactions and identify drugs used. Currently, safety reviewers utilize the system to take actual safety measures by considering issues on individual drugs while exchanging opinions with experts. In addition, the Ministerial Ordinance for GPSP, revised in 2018, allows marketing authorization holders (MAHs) to prepare data for submission of an application for re-examination after conducting post-marketing database surveys using the medical information database.

Under the framework of the MIHARI project, PMDA plans to explore new data sources and new methods extensively so as to continue to utilize electronic medical records properly.

**Proper management and operation of MID-NET\textsuperscript{®}**

The MID-NET\textsuperscript{®} is a medical database network system developed as a national project in order to analyze data from various data sources. The MID-NET\textsuperscript{®} database contains anonymized electronic medical data such as electronic medical records and claims data retained by cooperating medical institutions. The MID-NET\textsuperscript{®} started its full-scale operation in April 2018. Not only PMDA but also other users including pharmaceutical companies and researchers can access the MID-NET\textsuperscript{®} database to make good use of the data for pharmacovigilance. However, the qualification of the database users is reviewed by experts for securing the public interest of the system.

Until recently, safety measures for drugs have mainly focused on suspected adverse drug reactions (ADRs) reported from healthcare professionals. Under the circumstances, there were some problems; no ADR reporting was initiated unless any adverse event was regarded as a suspected ADR by healthcare professionals, and the incidence of reported ADRs was difficult to be calculated.

The utilization of the MID-NET\textsuperscript{®} enables the users to more quantitatively and scientifically evaluate a causal relationship between a drug and adverse events.

PMDA aims to support swift implementation of safety measures and to improve pharmacovigilance through the initiatives mentioned above, thereby contributing to the increased access of patients to more reliable therapeutic drugs.
Operations at the PMDA Kansai Branch

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

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

Video Conferencing at the Kansai Branch Office

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

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

Consultations Available through Video Conferencing System Include the Following:

Regulatory Science Strategy Consultation (R&D) (Face-to-Face)
- RS strategy Consultation (R&D) for drugs
- RS strategy Consultation (R&D) for medical devices
- RS strategy Consultation (R&D) for regenerative medical products
- Consultation on quality and efficacy of regenerative medical products
- RS strategy Consultation (R&D) for pharmaceutical development plans, etc.

Consultation
- Clinical trial consultation for new drugs (only for prescription), biological products, etc.
- Consultation on bioequivalence of generic drugs
- Clinical trial consultation for regenerative medical products
- Post-consultations for regenerative medical products (with recording)
- Clinical trial consultation for medical devices and in vitro diagnostics
- Preparatory interview of consultations for medical devices and in vitro diagnostics
- Consultation on GCP/GLP/GPSP
- Consultation on pharmacoepidemiological surveys for drugs
- Consultation on package insert revisions for drugs

Consultation on Safety Measures
- Consultation on safety measures

Operations at the PMDA Hokuriku Branch

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

Video Conferencing at Kansai Branch Office

The video conferencing system provides high-definition images and clear sounds. The simultaneous translation system is available. The zoom function enables users to zoom in to view materials on hand.

Operations at the PMDA Hokuriku Branch

Consultation on Safety Measures
- Consultation on safety measures
The regulatory framework for pharmaceutical products in Japan has evolved in light of the lessons learned from several drug-induced tragedies. PMDA’s Mission Statement declares that “PMDA will conduct its operations in a trustworthy manner with the confidence of the public, and will learn from its past experiences.” This statement encapsulates PMDA’s commitment as a medical product regulatory agency to remembering these tragedies.

**What was the Thalidomide Lawsuit?**

Thalidomide was a drug marketed in the late 1950s and early 1960s in Japan as a hypnotic sedative and as a treatment for gastritis. The drug was first marketed in West Germany. When thalidomide was on the market, it was declared to be safe and non-toxic even in children and pregnant women. However, thousands of babies whose mothers had used thalidomide during the first trimester were born with malformed limbs, deformed ears or hearing loss, or internal organ defects. A link between birth defects and thalidomide was reported by a German pediatrician. Thalidomide was immediately withdrawn from European markets. Meanwhile, withdrawal of thalidomide from the Japanese market occurred as late as 10 months after the German doctor’s report, resulting in a greater incidence of thalidomide-induced birth defects in Japan. The sufferers filed lawsuits for damages against the Japanese government and the pharmaceutical company responsible in 1963, and the suits were resolved by settlement in 1974.

**What was the SMON Lawsuit?**

Subacute myelo-optico-neuropathy (SMON) is a neurological condition caused by Quinoform, a drug that was marketed as a vulnerary in Switzerland around 1900 and was used as an antiflatulant in Japan. In the 1960s, symptoms such as generalised numbness, pain, and visual impairment were observed in individuals who had taken antiflatulents containing Quinoform. The symptoms were initially suspected to be caused by an infectious pathogen, and this led to delayed identification of the true cause of the condition, resulting in an increased number of people becoming adversely affected by the drug. Ultimately, over 10,000 individuals were reported to have been harmed by the use of Quinoform. Although the risks associated with Quinoform use had been reported globally by the 1960s, the sale of drug products containing Quinoform was continued by pharmaceutical companies which claimed that their products were safe. Doctors prescribed these products to their patients in reliance on these claims. Further, no adequate safety evaluation had been performed by the regulatory authority present at the time. These circumstances led to the unprecedented incidence of SMON. The sufferers filed lawsuits for damages against the Japanese government and the pharmaceutical companies responsible in 1971, and the suits were resolved by settlement in 1979.

Following the settlement of the lawsuits concerning thalidomide and SMON, the former Ministry of Health and Welfare submitted a bill, the Adverse Drug Reaction Relief Fund Act, to the Diet in 1979. The aforementioned Act became law on September 7, 1979. The Fund for Adverse Drug Reaction Relief (the predecessor to PMDA’s Relief Division) was established on October 15, 1979.

**What was the Lawsuit concerning AIDS or HIV Infection Caused by Tainted Blood Products?**

Many patients with hemophilia (or bleeding disorder) became infected with human immunodeficiency virus (HIV) mainly between 1982 and 1985 due to the use of unheated blood products (blood components or products that had not been pasteurized or sterilized) that were contaminated with HIV. These HIV-tainted blood products were mainly used for hemostasis or to manage hemorrhaging in hemophilia patients. Despite having been aware of the risk of such products, the pharmaceutical company manufacturing these products continued their sale, and the Japanese government failed to take effective measures to prevent the spread of HIV. These circumstances resulted in the spread of HIV infection in Japan. The sufferers filed lawsuits for damages against the Japanese government and the pharmaceutical company responsible in 1989, and the suits were resolved by settlement in 1996.

**What was the Lawsuit concerning Creutzfeldt-Jakob Disease?**

Lyophilized human dura mater was used mainly as a dural substitute in brain surgery until around 1997, when the importation of lyophilized human dura mater was approved. In response to reports of Creutzfeldt-Jakob disease (CJD) after implantation of lyophilized human dura mater grafts, the former Ministry of Health and Welfare issued an emergent safety communication concerning discontinuation of the use of lyophilized human dura mater grafts. The sufferers filed lawsuits in 1996 for damages against the Japanese government and the responsible manufacturer alleging that some lyophilized human dura mater grafts had been contaminated with a pathogen. The suits were resolved by settlement in 2002.

**What was the Lawsuit concerning Hepatitis C Virus Infection Caused by Specified Blood Products?**

Many individuals contracted hepatitis C virus (HCV) due to the use of blood products contaminated with HCV as hemostatic agents primarily for patients undergoing surgery and during childbirth. A number of these patients subsequently developed chronic hepatitis C or hepatocellular carcinoma. While much of the blame for the production of these contaminated blood products was placed on the pharmaceutical company that manufactured the products, the Japanese government was also accused of failing to take suitable actions to prevent the occurrence and spread of HCV infection induced by use of the contaminated products. The sufferers filed lawsuits for damages against the Japanese government and the pharmaceutical company responsible in 2002. The Act on Special Measures concerning the Payment of Benefits to Relieve Patients with Hepatitis C Virus Infection caused through Specified Fibrinogen Products and Specified Coagulation Factor XI Products was enacted in 2008.
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