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.
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Greetings

Since its establishment in April 2004, the Pharmaceuticals and Medical Devices Agency (PMDA) has focused on the three key areas of relief services for adverse health effects, reviews, and post-marketing safety measures, encompassing the entire life cycle of drugs and medical devices from development through post-marketing surveillance. This so-called “safety triangle” system is unique to Japan. While providing relief services swiftly, PMDA is also striving to resolve the issues of drug lag and device lag and to enhance safety measures by increasing the number of its reviewers and safety staff and by building their expertise.

To further improve public health services and respond to growing demands for more effective and safer drugs and medical devices, we are determined to make utmost efforts to be a leader in advanced medicine. How can we translate innovative academic science into clinical practice, thereby contributing to society? To this end, PMDA is committed to promoting regulatory science and broadening its links and personnel exchanges with academia, healthcare organizations and industry.

The globalization of the pharmaceutical and medical device industries will accelerate the international regulatory harmonization of drugs and medical devices through both reviews and safety measures. PMDA has therefore established the Office of International Programs to engage in international activities.

PMDA will continue to work hard in line with its Philosophy and to serve as one of the world’s leading regulatory agencies.

April 2010

Tatsuya Kondo, M.D., Ph.D.
Chief Executive
Pharmaceuticals and Medical Devices Agency
Outline of the Pharmaceuticals and Medical Devices Agency (PMDA)

Safety Triangle — Comprehensive Risk Management through the Three Functions —

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, which consolidated the services of the Pharmaceuticals and Medical Devices Evaluation Center of the National Institute of Health Sciences (PMDEC), the Organization for Pharmaceutical Safety and Research (OPSR/Kiko), and part of the Japan Association for the Advancement of Medical Equipment (JAAME).

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 ( Reviews ), and by collecting, analyzing and providing post-market safety information ( Safety Measures ).

**Name:** Pharmaceuticals and Medical Devices Agency (PMDA)

**Established:** April 1, 2004

**Legal classification:** Incorporated administrative agency with non-civil servant status
SERVICES

Relief Services for Adverse Health Effects
- Benefits in the form of medical expenses, disability pensions, bereaved family pensions, etc. for people who have suffered health damage such as diseases and disabilities resulting from adverse drug reactions and infections acquired through biological products
- Benefits such as healthcare allowances to subacute myeloptico-neuropathy (SMON) patients, and commissioned benefits services to HIV-positive and AIDS patients
- Financial assistance 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”

Reviews and Related Services
- Regulatory reviews of drug and medical device applications in accordance with the Pharmaceutical Affairs Act
- Guidance and advice relating to clinical trials, etc.
- Inspections conducted to assess compliance with GCP, GLP and other standards in relation to applications for marketing approval, re-examinations and re-evaluations
- Inspections of manufacturing sites, manufacturing processes and quality controls for assessing GMP/QMS compliance
- Re-examinations and re-evaluations in accordance with the Pharmaceutical Affairs Act

Safety Measures
- Collection, analysis and provision of information on the quality, efficacy and safety of drugs and medical devices
- Consultation services for consumers concerning drugs and medical devices
- Guidance and advice for marketing authorization holders to enhance the safety of drugs and medical devices
- Research relating to the development of standards for drugs and medical devices
Number of Executives and Regular Employees

<table>
<thead>
<tr>
<th></th>
<th>April 1, 2005</th>
<th>April 1, 2006</th>
<th>April 1, 2007</th>
<th>April 1, 2008</th>
<th>April 1, 2009</th>
<th>April 1, 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (including executives)¹</td>
<td>291</td>
<td>319</td>
<td>341</td>
<td>426</td>
<td>521</td>
<td>605</td>
</tr>
<tr>
<td>Review Department²</td>
<td>178</td>
<td>197</td>
<td>206</td>
<td>277</td>
<td>350</td>
<td>389</td>
</tr>
<tr>
<td>Safety Department³</td>
<td>43</td>
<td>49</td>
<td>57</td>
<td>65</td>
<td>82</td>
<td>123</td>
</tr>
</tbody>
</table>

Notes:
1. The total number includes 6 executives (including one part-time executive). (Five executives were included as of April 1, 2006.)
2. The Review Department consists of the Director of the Center for Product Evaluation, Associate Executive Directors (excluding the Associate Executive Director responsible for the Office of Regulatory Science Operations), Associate Center Directors, Office of International Programs, International Liaison Officers, Office of Review Administration, Office of Review Management, Offices of New Drug I to V, Offices of Biologics I and II, Office of OTC/Generic Drugs, Offices of Medical Devices I and II, Office of Conformity Audit and senior scientists.
3. The Safety Department consists of the Chief Safety Officer, Offices of Safety I and II and Office of Compliance and Standards.
Services of PMDA

- Relief for Adverse Drug Reaction
- Relief for Infections Acquired through Biological Products
- Health Allowances for SMON Patients
- Health Allowances for HIV-Positive and AIDS Patients
- Relief for Individuals Affected by Hepatitis C through Specified Products

- Consultations
- Drug Reviews
- Medical Device Reviews
- GMP/QMS Inspections
- GLP/GCP/GPSP Inspections

- Information Collection/Organization
- Research and Reviews
- Consultations
- Information Provision
- Standards Development

- Post-marketing Safety Measures

- Review
Relief Services for Adverse Health Effects

PMDA is dedicated to providing swift relief for adverse health effects by actively conducting public relations and providing information, and by expanding its consultation services.
The Organization for Pharmaceutical Safety and Research, the predecessor of PMDA, was established in 1979 as the “Fund for Relief Services for Adverse Drug Reactions,” and started providing such services in May of the following year.

The Organization also provided healthcare allowances to SMON patients under commission from the Japanese government and pharmaceutical companies, as well as to HIV-positive and AIDS patients under commission from the Yu-ai Welfare Foundation.

In April 2004, PMDA began “Relief Services for Infections Acquired through Biological Products” to provide relief benefits to people suffering from adverse health effects such as infections acquired through drug products or medical devices manufactured using ingredients and materials of biological origin.

Also, in January 2008, PMDA started to provide 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.”
Relief Services

Drug products and medical devices are indispensable for human health and welfare, but their efficacy and safety must be ensured before they can be marketed. It is equally important that drugs and medical devices are used properly in order to ensure their efficacy and safety. And yet even if great care is taken in all these respects, it is almost impossible to completely prevent adverse drug reactions or infections from biological products.

Therefore, when drugs used to treat illnesses cause health damage such as infectious diseases or adverse reactions, it is vital to provide relief immediately. The Relief System for Adverse Drug Reactions and the Relief System for Infections Acquired through Biological Products have been established for this purpose.

Relief System for Adverse Drug Reactions

PMDA provides relief benefits relating to health damage such as diseases and disabilities requiring hospitalization that were caused by adverse reactions to drugs prescribed at hospitals or clinics as well as drugs purchased at pharmacies, etc., even if such drugs were properly used.

These relief benefits cover health damage caused by adverse reactions to drugs that were used properly on or after May 1, 1980. However, health damage caused by adverse reactions to certain drugs such as anticancer and immunosuppressant drugs is not eligible for these benefits.

In addition to providing relief benefits, PMDA, as part of its health and welfare services, conducts investigative research on serious and rare cases of adverse health effects caused by drugs.

Cases of Relief Services for Adverse Drug Reactions

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of claims</td>
<td>760</td>
<td>788</td>
<td>908</td>
<td>926</td>
<td>1,052</td>
</tr>
<tr>
<td>Number of judged cases</td>
<td>1,035</td>
<td>845</td>
<td>855</td>
<td>919</td>
<td>990</td>
</tr>
<tr>
<td>Of which: Withdrawn</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Number of cases in progress*</td>
<td>661</td>
<td>624</td>
<td>677</td>
<td>684</td>
<td>746</td>
</tr>
<tr>
<td>Median processing time</td>
<td>11.2 months</td>
<td>6.6 months</td>
<td>6.4 months</td>
<td>6.5 months</td>
<td>6.8 months</td>
</tr>
</tbody>
</table>

* "Number of cases in progress" indicates the value at the end of each fiscal year.

Payment of Relief Benefits for Adverse Drug Reactions

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of cases</td>
<td>Amount paid</td>
<td>Number of cases</td>
<td>Amount paid</td>
<td>Number of cases</td>
</tr>
<tr>
<td>Medical expenses</td>
<td>717</td>
<td>78,527</td>
<td>572</td>
<td>67,502</td>
<td>603</td>
</tr>
<tr>
<td>Medical allowances</td>
<td>757</td>
<td>70,073</td>
<td>624</td>
<td>60,034</td>
<td>651</td>
</tr>
<tr>
<td>Disability pension</td>
<td>33</td>
<td>653,143</td>
<td>35</td>
<td>692,446</td>
<td>42</td>
</tr>
<tr>
<td>Pension for raising handicapped children</td>
<td>17</td>
<td>40,639</td>
<td>6</td>
<td>30,131</td>
<td>7</td>
</tr>
<tr>
<td>Bereaved family pension</td>
<td>44</td>
<td>502,468</td>
<td>22</td>
<td>493,010</td>
<td>20</td>
</tr>
<tr>
<td>Lump-sum benefits for bereaved family</td>
<td>32</td>
<td>228,708</td>
<td>34</td>
<td>229,446</td>
<td>39</td>
</tr>
<tr>
<td>Funeral expenses</td>
<td>74</td>
<td>14,010</td>
<td>53</td>
<td>10,386</td>
<td>63</td>
</tr>
<tr>
<td>Total</td>
<td>1,674</td>
<td>1,587,567</td>
<td>1,346</td>
<td>1,582,956</td>
<td>1,425</td>
</tr>
</tbody>
</table>

(Unit: Thousands of yen)

Note: The number of cases indicates the cases newly judged as eligible for benefits in each fiscal year. The paid amount includes payments for both new and existing cases.
Since drugs or medical devices using ingredients and materials of biological origin, such as humans and animals, may contain organisms such as viruses that can cause infections, various measures are taken to ensure product safety. However, even safety measures based on the latest scientific knowledge cannot completely eliminate the risk of infections acquired through biological products.

A system for providing relief services for infections acquired through biological products was therefore established in April 2004. In this system, relief benefits are provided to patients who have suffered health damage such as diseases and disabilities requiring hospitalization caused by infections acquired through biological products, even if such products were properly used. Treatment to prevent the onset of disease following infections and cases of patients with secondary infection are also eligible for these relief benefits.

Relief is provided for cases of infections acquired through biological products that were used on or after April 1, 2004.
Relief Services for Adverse Health Effects

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 family and funeral expenses.

Types of Benefits

Payment of Relief Benefits for Infections Acquired through Biological Products

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amount paid (Unit: Thousands of yen)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical expenses</td>
<td>3 475</td>
<td>6 473</td>
<td>3 102</td>
<td>5 204</td>
<td>6 372</td>
</tr>
<tr>
<td>Medical allowances</td>
<td>3 248</td>
<td>6 497</td>
<td>3 352</td>
<td>6 388</td>
<td>8 597</td>
</tr>
<tr>
<td>Disability pension</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Pension for raising handicapped children</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Bereaved family pension</td>
<td>--</td>
<td>1 1,367</td>
<td>--</td>
<td>2,378</td>
<td>--</td>
</tr>
<tr>
<td>Lump-sum benefits for bereaved family</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>1 7,135</td>
<td>--</td>
</tr>
<tr>
<td>Funeral expenses</td>
<td>--</td>
<td>1 199</td>
<td>--</td>
<td>1 199</td>
<td>--</td>
</tr>
<tr>
<td>Total</td>
<td>6 724</td>
<td>14 2,506</td>
<td>6 2,833</td>
<td>13 10,302</td>
<td>14 3,320</td>
</tr>
</tbody>
</table>

Cases of Relief Services for Infections Acquired through Biological Products

<table>
<thead>
<tr>
<th>Number of applications</th>
<th>FY 2005</th>
<th>FY 2006</th>
<th>FY 2007</th>
<th>FY 2008</th>
<th>FY 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of judged cases</td>
<td>5</td>
<td>6</td>
<td>9</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Of which: Withdrawn</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Number of cases in progress*</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Median processing time</td>
<td>5.6</td>
<td>3.3</td>
<td>3.0</td>
<td>5.2</td>
<td>5.4</td>
</tr>
</tbody>
</table>

*“Number of cases in progress” indicates the value at the end of each fiscal year.

Documents Required for Claims for Relief Benefits

Claims for relief benefits must be submitted directly to PMDA by the patient who has suffered health damage caused by adverse drug reactions or infections, or by his or her bereaved family.

When claiming relief benefits, it is necessary to prove the pathogenicity and symptoms/progress of the adverse reaction or infection, and the causal relationship between the health damage and the use of the drug. This requires a medical certificate issued by the doctor who treated the adverse reaction or infection as well as a proof of prescription. A claimant for relief benefits should request the doctor to issue the certificates and submit them to PMDA together with the claim form filled out by the claimant.

All necessary forms, including claim forms and medical certificate forms, are available from PMDA, and can be obtained free of charge upon request by the patient suffering from adverse health effects or by his or her family.

The necessary documents can also be downloaded from the PMDA website: http://www.pmda.go.jp
The following cases are not eligible for relief benefits under either the Relief System for Adverse Drug Reactions or the Relief System for Infections Acquired through Biological Products:

1. Cases of adverse health effects resulting from statutory vaccinations (a different public relief system is available for such cases). However, cases of adverse health effects resulting from voluntary vaccinations are eligible for the relief benefits.

2. Cases where it is apparent that the marketing authorization holder is liable for the adverse health effects caused by its drug or biological product.

3. Cases where it was necessary to use the drug or biological product in an amount exceeding the regular dosage for the purpose of saving the patient’s life, even if it was acknowledged beforehand that adverse health effects may occur.

4. Cases of adverse drug reactions, infections acquired through biological products, etc., where the extent of adverse health effects is minor, or where the eligibility period for claiming relief benefits has passed.

5. Cases where the drug or biological product was not used properly.

6. Cases of adverse health effects caused by drugs that are not covered by the relief system (this applies only to the Relief System for Adverse Drug Reactions).

If a claimant is not satisfied with the judgment on eligibility for relief benefits, the claimant may file a request for reconsideration with the Minister of Health, Labour and Welfare within two months after the day on which the claimant is informed of the judgment.

In such a case, the petitioner may give a statement of opinions.
Relief Services for Adverse Health Effects

Healthcare Allowances for SMON Patients

PMDA provides healthcare allowances and nursing care expenses to subacute myelo-optico-neuropathy (SMON) patients for whom a settlement has been reached in court.

Nursing Care Expenses

Since December 1979, PMDA or its predecessor has been providing nursing care expenses to patients with grade III SMON who have very severe or extremely severe symptoms, under commission from drug manufacturers liable for causing SMON in such patients.

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

Healthcare Allowances

Since December 1979, PMDA or its predecessor has been providing healthcare allowances to SMON patients under commission from drug manufacturers liable for causing SMON in such patients.

Healthcare Allowances for HIV-positive and AIDS Patients

PMDA, under commission from the Yu-ai Welfare Foundation, provides the following services to patients who have become infected with HIV through blood products.

Investigative Research

To help prevent the development of AIDS, PMDA provides healthcare expenses to HIV-positive patients who have not yet developed AIDS and who were infected through HIV-tainted blood products, in exchange for reports on their health condition. Patients with secondary and tertiary infections are also eligible for these benefits.

Healthcare Support Services

PMDA provides healthcare allowances to AIDS patients who have been infected with HIV through blood coagulation factor products and for whom a settlement has been reached in court. The purpose of these healthcare allowances 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.
Financial assistance 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”

**Provision of Financial Assistance**

PMDA provides 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.”

**Flowchart of Claiming for Benefits**

1. Filing a case
2. Successful settlement/arbitration or definitive judgment (the facts of drug administration, a causal relationship, and symptoms are recognized)
3. Claim for benefits based on the settlement, judgment, etc.
4. Payment

**Flowchart of Claiming for Additional Benefits**

1. Request for a medical certificate in the case where the symptom worsens
2. Preparation of a medical certificate stating the symptom
3. Claim for additional benefits based on the medical certificate
4. Payment of additional benefits
Reviews and Related Services

PMDA is committed to conducting appropriate reviews of applications for drugs and medical devices.
In addition to reinforcing the review system by increasing the number of expert reviewers and inspectors, PMDA is striving to enable patients and healthcare professionals to have faster access to drugs and medical devices by using a team review system. In the review system, the same review team is responsible for each step of the review process, from clinical trial consultations to product application reviews to ensure that precise guidance and advice are provided and appropriate reviews and inspections are conducted. In particular, to resolve the issue of the “drug lag,” whereby drugs approved in the US and EU have not yet been approved in Japan and cannot be provided to Japanese citizens, by FY 2011, PMDA is making the review process faster and more efficient by increasing the number of review staff, shortening the period from the start of clinical trials to approval of new drug applications, and training human resources.

In FY 2009, PMDA also took various initiatives to reduce the “device lag,” which is the lag in permitting the use of medical devices, by FY 2013 similarly to the measures taken for the “drug lag.”
Reviews and Related Services

PMDA’s reviews and related services include evaluating the quality, efficacy and safety of drugs and medical devices intended for use in clinical practice, as well as over-the-counter (OTC) drugs and quasi-drugs used in everyday life.

As part of the reviews and related services, PMDA conducts the following: consultations including those prior to clinical trials, where guidance and advice on clinical trials in relation to regulatory submission are given; GLP/GCP/GPSP inspections and audits as to whether the submitted application complies with ethical and scientific standards; application reviews to evaluate the quality, efficacy and safety of the product submitted for approval, taking the result of the GLP/GCP/GPSP inspections into account and in the light of current scientific and technological standards; and GMP/QMS inspections to determine whether the applicant is sufficiently capable of manufacturing the product submitted for approval.

In PMDA, the same review team handles the entire review process from the stage before clinical trials until approval is granted, including clinical trial consultations and product application reviews. This approach makes the reviews faster and more reliable.

In accordance with the recommendations of the Council for Science and Technology Policy, PMDA has been improving its review system for new drugs in order to reduce the drug lag by 2.5 years (consisting of 1.5 years for development and 1 year for new drug application review) by FY 2011.

Measures being taken to achieve this goal include: (1) increasing the number of reviewers, (2) improving training, (3) reducing the development period by significantly expanding and improving the consultations, (4) reinforcing and improving the transparency of the progress management of reviews, (5) facilitating global clinical trials, (6) clarifying review standards, (7) developing a guidance document for the introduction of a system of prior assessment consultation and (8) implementing a project management system. Through these efforts, PMDA will improve the reviews and related services.

Meanwhile, the Ministry of Health, Labour and Welfare drew up the Action Program to Accelerate Reviews of Medical Devices in December 2008, and instructed PMDA to reduce the device lag by 19 months (consisting of 12 months for development and 7 months for new medical device application review) by FY 2013. Following this instruction, PMDA has taken measures to speed up and improve reviews, such as (1) increasing the number of medical device reviewers, (2) improving training, (3) introducing a 3-track review system and prior assessment consultation system, (4) clarifying review standards, and (5) ensuring thorough progress management.

Consultations

Upon request, PMDA offers consultations to give guidance and advice on clinical trials for new drugs and medical devices as well as on clinical studies relating to re-examinations and re-evaluations of approved drug products and medical devices.

In clinical trial consultations, PMDA checks whether a proposed clinical trial properly meets 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 guidance and advice on improving the quality of the clinical trial.

In FY 2009, PMDA started a pilot scheme for prior assessment consultations in which data such as on quality, efficacy and safety are evaluated before a new drug application is filed.

In order to promote development and speed up application reviews by providing detailed advice as required at each stage of the product development process, PMDA expanded the categories of clinical trial consultations on medical devices and in vitro diagnostics in FY 2007 so as to provide specific advice for each development stage. For cell- and tissue-based products that are developed using state-of-the-art technology such as pharmacogenomics or regenerative medicine, there is a very strong need for advice on product development and regulatory submission, as there are only a few precedents. PMDA therefore established new categories of consultation services: consultations on submission documentation for cell- and tissue-based products in FY 2007, and consultations on pharmacogenomics/biomarkers in FY 2009.

In addition, simple consultations on generic drugs, OTC drugs and quasi-drugs are available to give guidance and advice in face-to-face meetings with applicants.

For priority review products, PMDA provides consultations on GLP/GCP compliance of study data to be submitted.
Flow of Drugs and Medical Devices: from Development to Marketing

- **Research and development**
- **Non-clinical tests**
- **Clinical trials**
- **Filing of application**
- **Approval**
- **Marketing**

**Clinical trials consultation**
- From clinical trials to new drug application
  - Non-clinical tests
    - Animal test
  - Phase I trials
    - Conducted in healthy volunteers
    - Mainly for safety assessment
  - Phase II trials (First stage)
    - Conducted in small group of patients
    - Initial assessment of efficacy
  - Phase II trials (Late stage)
    - Conducted in patients
    - Determine the dosage with which efficacy and safety will be assessed in the next phase
  - Phase III trials
    - Conducted in larger group of patients
    - Controlled and uncontrolled trials to confirm the efficacy and safety in actual clinical use
  - New drug application

**Review**
- Review of applications for drugs and medical devices
  - MHLW
  - Applicant
  - PMDA
    - Clinical trial consultation/Review (Team review)
  - External experts
    - Expert discussion
  - Post-marketing safety measures
  - Relief for adverse health effects

**MHLW**
- Approval
- Review report
- Application
- Inquiry/response

**PMDA**
- Clinical trial consultation/Review (Team review)

**External experts**
In the regulatory review of drug applications, PMDA reviewers, who have degrees in pharmaceutical science, medicine, veterinary medicine, physical science, biostatistics or other specialties, form a team to evaluate the quality, pharmacology, pharmacokinetics, toxicology, clinical implications, and biostatistics of the particular drug product under review. During the review process, the reviewers exchange opinions with external experts (Expert Discussions) to ensure that reviews are conducted by using advanced expertise.

In particular, for drugs developed with the latest technology such as biotechnology, PMDA reinforces the review system by inviting additional reviewers specialized in particular fields to participate in the review.

To provide healthcare professionals and patients with faster access to improved drugs, PMDA is also speeding up the review process, such as by setting target review times and conducting priority reviews for products designated as such.

While participating in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), which is intended to achieve consistency in regulations related to new drug application data and establish harmonized technical requirements leading to greater mutual acceptance of research and development data between Japan, the US and the EU, PMDA has actively incorporated the guidelines agreed upon in the ICH into its reviews.

A document on the principles of reviews entitled, “Points to Be Considered by the Review Staff Involved in the Evaluation Process of New Drug” was created and explained to the personnel who are responsible for new drug reviews. The principles are published on the PMDA website and help clarify the standards for review.

Drug reviews encompass not only new drugs but also generic drugs that are acknowledged as being equivalent to previously approved drugs, OTC drugs which can be purchased at pharmacies and drug stores without a doctor’s prescription, and quasi-drugs.

PMDA also conducts re-examinations and re-evaluations of approved drug products as well as reviews of confirmation applications prior to clinical trial notifications for genetically modified biological entities, regenerative medicine (cell- and tissue-based products) and gene therapy products.

In FY 2009, a total of 8,328 drugs were approved, of which 3,737 were prescription drugs (including 466 new drugs), 2,171 were OTC drugs, 199 were in vitro diagnostics and 2,221 were quasi-drugs.

What Are Clinical Trials?
A clinical trial refers to a research study conducted to verify the efficacy of a drug or medical device and potential adverse reactions when it is used in humans. The data collected from such studies are then submitted for regulatory reviews.

<table>
<thead>
<tr>
<th>CTC Category</th>
<th>Consultations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1 (Gastrointestinal drugs)</td>
<td>35</td>
</tr>
<tr>
<td>Category 6-2 (Hormone drugs)</td>
<td>35</td>
</tr>
<tr>
<td>Category 2 (Cardiovascular drugs)</td>
<td>52</td>
</tr>
<tr>
<td>Category 5 (Drugs for urogenital system)</td>
<td>19</td>
</tr>
<tr>
<td>In vivo diagnostics</td>
<td>1</td>
</tr>
<tr>
<td>Radiopharmaceuticals</td>
<td>5</td>
</tr>
<tr>
<td>Category 3-1 (Central/peripheral nervous system drugs)</td>
<td>42</td>
</tr>
<tr>
<td>Category 3-2 (Anesthetic drugs)</td>
<td>22</td>
</tr>
<tr>
<td>Category 4 (Antibacterial agents)</td>
<td>35</td>
</tr>
<tr>
<td>AIDS drugs</td>
<td>0</td>
</tr>
<tr>
<td>Category 6-1 (Respiratory tract drugs)</td>
<td>32</td>
</tr>
<tr>
<td>Anti-cancer drugs</td>
<td>54</td>
</tr>
<tr>
<td>Blood products</td>
<td>8</td>
</tr>
<tr>
<td>Bio-CMC</td>
<td>11</td>
</tr>
<tr>
<td>Biological products</td>
<td>16</td>
</tr>
<tr>
<td>Cell- and tissue-based products</td>
<td>1</td>
</tr>
<tr>
<td>[Re-listed] Prior assessment (pre-NDA review)</td>
<td>33</td>
</tr>
<tr>
<td>Pharmacogenomics and biomarkers</td>
<td>1</td>
</tr>
<tr>
<td>GLP/GCP compliance (for priority reviews)</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>370</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>23</td>
</tr>
<tr>
<td>Grand total</td>
<td>393</td>
</tr>
</tbody>
</table>

Note: 1. A consultation covering several categories is counted according to its main category.
2. Prior assessment consultations for drugs are conducted for the categories of quality, non-clinical: toxicology, non-clinical: pharmacology, non-clinical: pharmacokinetics, phase I study and phase II study.
3. The numbers of prior assessment consultations for drugs and consultations on pharmacogenomics/biomarkers were counted on the basis of delivery dates of consultation documents to PMDA.
4. Consultations on pharmacogenomics/biomarkers are conducted by the Omics Project Team.
5. Consultations on GLP/GCP compliance (for priority reviews) are all conducted by the Office of Conformity Audit, regardless of category.
technology and materials used in each medical device differ according to the type of product, from surgical instruments to MRI and pacemakers. It is therefore necessary to rationally regulate medical devices depending on various product characteristics, such as the usage method and level of risk.

From among the many types of medical devices, PMDA review staff mainly review applications for high-risk medical devices, such as artificial hearts, pacemakers, coronary stents, artificial blood vessels, artificial joints and artificial kidneys.

In order to enable healthcare professionals and patients to have faster access to these medical devices which are necessary in clinical practice, PMDA has set target review times and is working hard to achieve these targets.

Specifically, PMDA has greatly increased the number of reviewers who possess expertise in medical engineering, biological engineering and biomaterials to conduct professional reviews across a wide range of specialties. In addition to such engineering experts, the reviewers include experts with degrees in medicine, dentistry, pharmaceutical science, veterinary medicine, physical science and biostatistics, who participate in non-clinical, clinical and biostatistical reviews. During the review process, the reviewers exchange opinions with external experts (Expert Discussions) to enable more efficient and professional reviews.

In order to develop a globally harmonized review system for medical devices, PMDA participates in the Global Harmonization Task Force (GHTF) formed by Japan, the US, the EU, Australia and Canada. PMDA has actively incorporated the guidelines agreed upon in GHTF into its reviews, and its regulatory review system adopts standards such as those of the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC).

Since April 2009, application categories for medical devices have been re-classified as follows:

• New medical devices
• Improved medical devices (with clinical data)
• Improved medical devices (without clinical data)
• Generic medical devices (with no applicable approval standards)
• Generic medical devices (with applicable approval standards)

Meanwhile, low-risk medical devices for which certification standards have been established need to be certified by a third-party certification body under the current regulatory system, instead of receiving the Minister's approval.

In the case of general medical devices, marketing notification should be submitted to PMDA.
Reviews and Related Services

PMDA conducts inspections and reliability assessment in relation to applications for marketing approval, re-examination, or re-evaluation to assess whether the tests and clinical trials have been conducted in an ethically and scientifically appropriate way in compliance with Good Laboratory Practice (GLP), Good Clinical Practice (GCP) and Good Post-Marketing Surveillance Practice (GPMSP) or Good Post-marketing Study Practice (GPSP), and whether the submitted data comply with the reliability standards for regulatory submission documentation. PMDA also provides GLP compliance certification to testing laboratories.

Conformity Audits (GLP/GCP/GPSP inspections and data reliability assessment)

Number of Approved Medical Devices

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical devices</td>
<td>1,827</td>
<td>1,342</td>
<td>2,222</td>
<td>2,459</td>
<td>2,035</td>
</tr>
<tr>
<td>In vitro diagnostics</td>
<td>30</td>
<td>42</td>
<td>72</td>
<td>76</td>
<td>110</td>
</tr>
<tr>
<td>Total</td>
<td>1,857</td>
<td>1,382</td>
<td>2,294</td>
<td>2,535</td>
<td>2,145</td>
</tr>
</tbody>
</table>

Median Total Review Time for New Medical Devices (Priority Review Products)

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Total review time [Months]</td>
<td>14.2</td>
<td>15.7</td>
<td>28.8</td>
<td>13.9</td>
</tr>
<tr>
<td>Regulatory review time [Months]</td>
<td>5.7</td>
<td>8.6</td>
<td>5.8</td>
<td>6.0</td>
</tr>
<tr>
<td>Applicant’s time [Months]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7.7</td>
</tr>
<tr>
<td>Number of approved applications</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Note: 1. Values indicate the data for approved applications that were filed in or after April 2004.
2. Since the target for applicant’s time was set up beginning in FY 2009, no previous values were available.

Median Total Review Time for New Medical Devices (Standard Review Products)

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Total review time [Months]</td>
<td>10.3</td>
<td>15.7</td>
<td>15.1</td>
<td>14.4</td>
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<tr>
<td>Regulatory review time [Months]</td>
<td>1.8</td>
<td>3.2</td>
<td>7.7</td>
<td>9.8</td>
</tr>
<tr>
<td>Applicant’s time [Months]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Number of approved applications</td>
<td>5</td>
<td>14</td>
<td>19</td>
<td>12</td>
</tr>
</tbody>
</table>

Note: 1. Values indicate the data for approved applications that were filed in or after April 2004.
2. Since the target for applicant’s time was set up beginning in FY 2009, no previous values were available.

Number of GLP/GCP/GPSP Inspections

<table>
<thead>
<tr>
<th></th>
<th></th>
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<tbody>
<tr>
<td>Document-based inspections/ reliability assessment</td>
<td>136</td>
<td>426</td>
<td>774</td>
<td>942</td>
</tr>
<tr>
<td>Drugs</td>
<td>135</td>
<td>251</td>
<td>234</td>
<td>293</td>
</tr>
<tr>
<td>Medical devices</td>
<td>1</td>
<td>175</td>
<td>540</td>
<td>649</td>
</tr>
<tr>
<td>GLP inspections</td>
<td>39</td>
<td>31</td>
<td>27</td>
<td>43</td>
</tr>
<tr>
<td>Drugs</td>
<td>37</td>
<td>23</td>
<td>23</td>
<td>32</td>
</tr>
<tr>
<td>Medical devices</td>
<td>2</td>
<td>8</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>GCP inspections</td>
<td>131</td>
<td>149</td>
<td>132</td>
<td>198</td>
</tr>
<tr>
<td>New drugs</td>
<td>120</td>
<td>137</td>
<td>122</td>
<td>182</td>
</tr>
<tr>
<td>Generic drugs</td>
<td>11</td>
<td>12</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Medical devices</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>GPSP inspections</td>
<td>82</td>
<td>103</td>
<td>107</td>
<td>79</td>
</tr>
</tbody>
</table>

Note: 1. Values for GLP, GCP and GPSP inspections in or after FY 2005 are the number of notifications after the evaluation was conducted.
2. The numbers of inspections from FY 2005 to FY 2008 indicate those conducted as GPMSP inspections, while the number for FY 2009 includes GPMSP or GPSP inspections.
3. GLP: Good Laboratory Practice
4. GCP: Good Clinical Practice
5. GPMSP: Good Post-marketing Surveillance Practice
6. GPSP: Good Post-marketing Study Practice
When manufacturing a drug or a medical device, all products should be of the same quality as that of the product which was approved. To ensure this, the manufacturing site should have appropriate manufacturing facilities, and the manufacturing process and quality management system should be maintained and controlled properly.

PMDA conducts on-site and document-based inspections of manufacturing sites that require a license from the Minister of Health, Labour and Welfare, such as manufacturing sites of new drugs, new medical devices or vaccines, as well as those of high-risk (Class IV) medical devices, in order to ascertain whether their manufacturing facilities and manufacturing controls comply with standards such as the Good Manufacturing Practice/Quality Management System (GMP/QMS), and whether the manufacturing sites have a system for manufacturing products of adequate quality.

PMDA also conducts inspections of the licensing of manufacturing sites located in Japan that require a license from the Minister and inspections relating to accreditation of foreign manufacturers.

GMP/QMS Inspections

When manufacturing a drug or a medical device, all products should be of the same quality as that of the product which was approved. To ensure this, the manufacturing site should have appropriate manufacturing facilities, and the manufacturing process and quality management system should be maintained and controlled properly.

PMDA conducts on-site and document-based inspections of manufacturing sites that require a license from the Minister of Health, Labour and Welfare, such as manufacturing sites of new drugs, new medical devices or vaccines, as well as those of high-risk (Class IV) medical devices, in order to ascertain whether their manufacturing facilities and manufacturing controls comply with standards such as the Good Manufacturing Practice/Quality Management System (GMP/QMS), and whether the manufacturing sites have a system for manufacturing products of adequate quality.

PMDA also conducts inspections of the licensing of manufacturing sites located in Japan that require a license from the Minister and inspections relating to accreditation of foreign manufacturers.

Number of GMP/QMS Inspections

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs*</td>
<td>53</td>
<td>783</td>
<td>893</td>
<td>738</td>
<td>2,000</td>
</tr>
<tr>
<td>In vitro diagnostics</td>
<td>9</td>
<td>32</td>
<td>84</td>
<td>78</td>
<td>107</td>
</tr>
<tr>
<td>Quasi-drugs</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Medical devices</td>
<td>32</td>
<td>300</td>
<td>1,021</td>
<td>915</td>
<td>1,285</td>
</tr>
<tr>
<td>Total</td>
<td>94</td>
<td>1,120</td>
<td>1,998</td>
<td>1,734</td>
<td>3,395</td>
</tr>
</tbody>
</table>

*Excludes in vitro diagnostics

Note: 1. Figures in parentheses indicate the number of on-site inspections.
2. GMP: Good Manufacturing Practice
3. QMS: Quality Management System
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 and medical devices.
PMDA collects information on the quality, efficacy and safety of drugs and medical devices from marketing authorization holders and medical institutions in an integrated manner, which it then uses for scientific research and reviews in order to accurately implement safety measures in conjunction with the Ministry of Health, Labour and Welfare. PMDA also provides appropriate information to healthcare professionals, drug manufacturers, and users of drug products and medical devices. Through such activities, PMDA is committed to improving the quality, safety and reliability of the medical environment by integrating the entire process, from clinical trial consultations to post-marketing safety measures.
Post-marketing Safety Measures

Drugs and medical devices are essential for a healthy, happy life. Thanks to advancements in science and technology, humans have conquered many difficulties over the years; the drugs and medical devices created by human ingenuity have allowed us to overcome many diseases.

However, the drugs and medical devices 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 drugs and medical devices properly at all times; safety is achieved through the ceaseless efforts of people who are involved in all stages of the life cycle of drugs and medical devices. And it is this safety that gives users peace of mind.

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

Collecting, Organizing, and Consolidating Safety Information

It is important to collect the necessary safety information on drugs and medical devices at appropriate times and from a wide range of sources.

PMDA collects safety information promptly and efficiently by using information technology; safety staff electronically receive reports from companies when cases of adverse drug reactions (ADRs) and infections caused by drugs as well as malfunctions of medical devices are detected during the development and post-marketing periods.

PMDA also consolidates all essential safety information from a broad range of fields, such as information on ADRs, infections, or malfunctions as reported by healthcare professionals to MHLW, information from international sources, such as ICH, and conference papers and research reports related to medical and pharmaceutical sciences. The collected information is then promptly compiled into a database and shared with MHLW.

Number of Adverse Drug Reaction Reports

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Companies (Japanese)</td>
<td>24,751</td>
<td>26,560</td>
<td>28,257</td>
<td>32,306</td>
<td>30,928</td>
</tr>
<tr>
<td>Companies (foreign)</td>
<td>65,316</td>
<td>77,346</td>
<td>95,036</td>
<td>116,622</td>
<td>141,386</td>
</tr>
<tr>
<td>Healthcare professionals</td>
<td>3,992</td>
<td>3,669</td>
<td>3,891</td>
<td>3,816</td>
<td>3,721</td>
</tr>
</tbody>
</table>

Number of Medical Device Malfunction Reports

<table>
<thead>
<tr>
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<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Companies (Japanese)</td>
<td>6,222</td>
<td>9,310</td>
<td>13,842</td>
<td>4,301</td>
<td>4,116</td>
</tr>
<tr>
<td>Companies (foreign)</td>
<td>5,012</td>
<td>2,880</td>
<td>2,708</td>
<td>2,014</td>
<td>2,332</td>
</tr>
<tr>
<td>Healthcare professionals</td>
<td>445</td>
<td>424</td>
<td>434</td>
<td>444</td>
<td>363</td>
</tr>
</tbody>
</table>
In research and reviews of safety information, it is important to scientifically evaluate the collected information promptly and thoroughly. PMDA therefore strives to improve the quality of safety measures by using the latest scientific evaluation methods, such as epidemiological analysis, and by building the expertise of its safety staff through training.

PMDA conducts research and reviews of the collected information through scientific analyses by its highly specialized staff, interviews with companies, and discussions with experts as necessary, to determine whether any cases require urgent measures, whether the risk/benefit profile is favorable, and the optimum safety measures to be taken. All these efforts help increase the safety of drugs and medical devices.

To establish effective safety measures, the safety staff work together with the review and relief divisions as needed, as well as with MHLW.

In order for drugs and medical devices to be used safely and with a sense of trust, it is important to provide the required information whenever needed.

PMDA actively provides the following information on the quality, efficacy and safety of drugs and medical devices on the Medical Product Information page of its website: http://www.info.pmda.go.jp

- Package inserts of drug products and medical devices
- Recalls
- Urgent safety information issued by manufacturers (‘Dear Healthcare Professional’ Letters)
- Ministry of Health, Labour and Welfare press releases
- Approval of new drugs
- Quality information for prescription drugs
- Pharmaceuticals and Medical Devices Safety Information
- PMDA Medical Safety Information

The funds necessary for safety measures carried out by PMDA come from contributions made by the marketing authorization holders of drugs and medical devices.

In accordance with the Act on the Pharmaceuticals and Medical Devices Agency, marketing authorization holders of drugs or medical devices under the Pharmaceutical Affairs Act as of April 1 in any given year are required to make a declaration and pay a contribution to PMDA by July 31 of the same year based on the total quantity of their products shipped in the previous fiscal year.

<table>
<thead>
<tr>
<th>Contributions to Safety Measures</th>
<th>(Unit: Millions of yen)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marketing authorization holders (MAHs) of approved drug products and medical devices (Number of MAHs)</td>
<td>1,143</td>
</tr>
<tr>
<td></td>
<td>[2,982]</td>
</tr>
<tr>
<td>MAHs of pharmacy-compounded drug products (Number of MAHs)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>[9,907]</td>
</tr>
<tr>
<td>Total contributions</td>
<td>1,153</td>
</tr>
<tr>
<td>Contribution rate</td>
<td>0.11/1000</td>
</tr>
<tr>
<td>0.22/1000*</td>
<td></td>
</tr>
<tr>
<td>0.11/1000**</td>
<td></td>
</tr>
</tbody>
</table>

*For drug products (excluding in vitro diagnostics)
**For medical devices and in vitro diagnostics
Fundamentals of Safety Measures - Standards Development

Safety measures for drugs and medical devices are grounded in various standards, such as the Japanese Pharmacopoeia, which are set forth in the Pharmaceutical Affairs Act.

PMDA collects, organizes and investigates information on those standards which are relevant to the quality, efficacy and safety of drugs and medical devices, and submits its findings to MHLW.

For the Japanese Pharmacopoeia in particular, PMDA has established expert committees on individual fields such as chemical drugs, biological drugs and general test methods. These committees mainly evaluate the quality of drugs and develop drafts for the Japanese Pharmacopoeia. Public comments are sought regarding items nominated for entry into the Japanese Pharmacopoeia and its draft monographs on the PMDA website: http://www.pmda.go.jp

Post-marketing Safety Measures by Data Mining

In FY 2008, PMDA established a safety measures operation support system incorporating data mining methods. This computer-based system conducts statistical analyses of information on adverse drug reactions as reported by companies and detects signals for which safety measures may be required.

The new operational flow with data mining allows the staff to analyze safety information not only from pharmacological aspects but also from quantitative aspects.

In line with the Mid-term Plan, PMDA intends to proactively make use of the data mining methods in organizing, evaluating, and analyzing information on adverse drug reactions and make improvements on an as-needed basis, in order to detect any adverse drug reaction at an early stage and take measures to prevent further events.

In FY 2009, PMDA examined the detection method of duplicate reports so as to further enhance the accuracy and reliability of signal detection by data mining. The Agency also studied the method of capturing time-series changes in the number of adverse drug reaction reports. The method has been adopted on a trial basis to verify the effectiveness of the safety measures taken in some cases.
In line with the Mid-term Plan, PMDA intends to develop the access infrastructure for the medical record databases by FY 2013 so as to perform pharmacoepidemiological analyses and quantitatively evaluate pharmaceutical risk.

In July 2009, PMDA established the “Study committee on the application of electronic medical records to safety measures,” which is composed of external experts, under the initiative called the MIHARI Project. The project involves a series of investigations on advantages and disadvantages, etc. of data, such as health insurance claim data and hospital information system data, according to the data type.

PMDA investigated the characteristics of claim data and what analysis is applicable to safety evaluation by using a commercially-available database of claims, and conducted a pilot study on anaphylaxis in FY 2009. The results of the study were posted on the PMDA website. The Agency continues to undertake pilot studies on different themes and to investigate analysis methods.

With regard to hospital information systems, PMDA conducted a pilot study on the detection of information on adverse drug reactions, in line with more than one theme such as “rhabdomyolysis caused by statin drugs,” from 5 medical institutions that are equipped with the standard storage based on the SS-MIX (Standardized Structured Medical Information Exchange project by the MHLW) standards. In this study, PMDA identified technical challenges for the secondary use of data from more than one hospital information system in terms of differences in data among institutions, potential for integration of retrieved and detected data, and preparation of data sets for analysis, which served as a basic investigation to make improvements in the future.

PMDA continuously examines the usability of other electronic medical records.
Post-marketing Safety Measures

Development of System for Evaluating Medical Device Malfunctions

As a safety measure for medical devices, PMDA is developing scientific evaluation methods by analyzing the incidence, etc. of medical device malfunctions that may unavoidably occur at a certain rate due to the nature of the device rather than to structural defects (for example, malfunctions resulting from handling or the usage period of the medical device, or from the patient’s pathological condition).

A study on coronary stents (a prospective five-year follow-up study of over 16,000 patients as a target number, in 26 institutions) has been conducted since February 2008 to collect data. In December 2009, the second interim analysis was performed using some of the data collected.

In line with the Mid-term Plan, PMDA intends to build a system for gathering and evaluating data on the operation status of medical devices such as the incidence of malfunctions over time, regarding high-risk implantable medical devices subject to tracking, in order to properly use such a system for safety measures.

The first release of a web-based entry system called J-MACS for the registry of implantable artificial heart assist systems was finished at the end of March 2010, based on the implementation structures/protocols that were considered in detail under the industry-government-academia collaboration. The preparation for post-marketing registry of patients at 6 participating medical institutions was completed.

Pharmaceuticals and Medical Devices Information E-mail Services

PMDA distributes the latest safety information by e-mail, including the urgent safety information, to registered healthcare professionals.

Information provided:

- Urgent safety information (“Dear Healthcare Professional” Letters)
- Pharmaceuticals and Medical Devices Safety Information
- Instructions for revision of precautions in package insert
- Drug safety update (DSU)
- Notification for self-check and recalls (Class I)
- PMDA Medical Safety Information

For details, please visit the Medical Product Information web page: http://www.info.pmda.go.jp
Registration for this e-mail service is free.

Publication of Drug Guide for Patients

The “Drug Guide for Patients” is an explanation for patients, which helps them better understand prescription drugs, leading to earlier detection of serious adverse drug reactions. This guide is available on the Medical Product Information web page. It focuses on prescription drugs that contain warnings in their package inserts and that require special instructions relating to proper use by patients.

Package Insert of Prescription Drugs and Drug Guide for Patients

- Package Insert
  - Described in technical terms
  - Fully comprehensive description of ADRs
  - Information that needs attention of doctors and pharmacists
- Drug Guide for Patients
  - Using clear and simple terms that a high school student can understand
  - Showing subjective symptoms of serious ADRs and such ADRs by body parts
  - Information that requires patients’ attention on dosage and application of drugs and what should be done in case of missing to take them
- Physicians, pharmacists, etc
  - Can obtain accurate and comprehensive information on the drugs
  - Can get necessary information for appropriate use of the drugs
- Patients and their family
  - Can detect serious ADRs early
  - Can access to information on appropriate use of drugs including application and storage condition
The PMDA International Strategic Plan (finalized on February 6, 2009) was formulated as a basic policy for overall international activities during the period of the Second Mid-term Plan. PMDA actively carries out international activities in line with the strategic plan.

To build closer partnerships with the EU and the US, PMDA dispatched International Liaison Officers to the European Medicines Agency (EMA) in November 2009 and to the US Pharmacopeia in February 2010.

Regarding activities in East Asia, the Tripartite Health Ministers Meeting has been held annually since FY 2007 and the Director-General Meeting on Pharmaceutical Affairs since FY 2008, with the participation of the three health authorities from Japan, China and South Korea. As part of working-level talks, the Japan-China-Korea Working Group Meetings were held twice in FY 2009, in which the following plan was decided: MHLW/PMDA are responsible for coordinating the joint research project on ethnic factors in clinical data and the Korean Food and Drug Administration (KFDA) is responsible for coordinating the exchange of information on clinical trials of drugs.

PMDA has also been strengthening ties with regulatory agencies in the US, the EU and Asian countries with respect to reviews and safety measures through the exchange of trainees.

In addition to participating in the International Conference on Harmonization (ICH), Global Harmonization Task Force (GHTF) and International Organization for Standardization (ISO) to facilitate international harmonization of test methods as well as standards for preparing data for reviews, PMDA also takes part in the Pharmacopoeia Discussion Group (PDG) to promote international harmonization of the Japanese Pharmacopoeia. Moreover, the Agency is actively involved in the “Harmonization By Doing” activities and has launched the US-Japan Pilot Program regarding Medical Device Collaborative Consultation and Review of Pre-marketing Applications.

PMDA hosts international symposia every year. In October 2009, the 4th PMDA International Symposium on Biologics was held on the “Clinical evaluation of cell/tissue-based products,” with speakers from a regulatory agency in the EU and industry and medical institutions in Japan discussing the activities and trends in Japan and foreign countries. The 2010 China-Japan Symposium on Global Clinical Trials and Ethnic Factors 2010 was held in Beijing in May. Speakers from regulatory authorities, academia and the pharmaceutical industry in China and Japan were invited to discuss the current and future trends of global clinical trials in East Asia, and why and how ethnic factors should be clarified.

PMDA continues to expand its English website to provide the latest information to an international audience.
PMDA’s mission is to continually evaluate various conflicting issues and appropriately assess and balance the risks and benefits, in the most beneficial manner for the public, based on the latest scientific knowledge. Regulatory decisions can then be made on a scientific basis.

PMDA strives to enhance training programs for improving the expertise of its staff as well as to promote communication with external scientists in order to advance regulatory science. One such initiative is the Joint Graduate School Program, in which the Agency is actively promoting collaboration with educational institutions. PMDA has agreements with the Yokohama City University Graduate School of Medicine; the Graduate School of Life and Environmental Sciences, the University of Tsukuba; and the Yamagata University Graduate School of Medical Science as of July 2010.

Revised conventional training programs fundamentally by reference to FDA’s training programs and put into practice stepwise from the latter half of FY 2007.

First year  
Training program for new recruits

Second year  
Training program for mid-level employees
  
  General training program (e.g., English language and communication skills)
  
  Specialized training program (case study, medical writing)
  
  Facility visit (medical institutions which clinical trials take place, factories of drug manufacturers)

Third year onwards  
Training program for managerial staff (e.g., management skills)

Management level  
Participation in international conferences such as DIA (as speakers and attendees)
  
  Dispatching of lecturers to universities
  
  Special training program (discussion on the latest technological topics with experts invited from Japan and foreign countries)
  
  Participation in and presentation at academic conferences in Japan and foreign countries

Mentoring system (established by reference to FDA’s Orientation Mentoring Program)

Training at external institutions in Japan (medical institutions, research institutions)
  
  Long-term training at overseas organizations (such as overseas regulatory agencies)
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