Pharmaceuticals and Medical Devices Agency, Japan

ANNUAL REPORT FY 2018

April 2018 to March 2019

This translation of the original Japanese text is for information purpose only (in the event of inconsistency, the Japanese text shall prevail).

THE PHARMACEUTICALS AND MEDICAL DEVICES AGENCY

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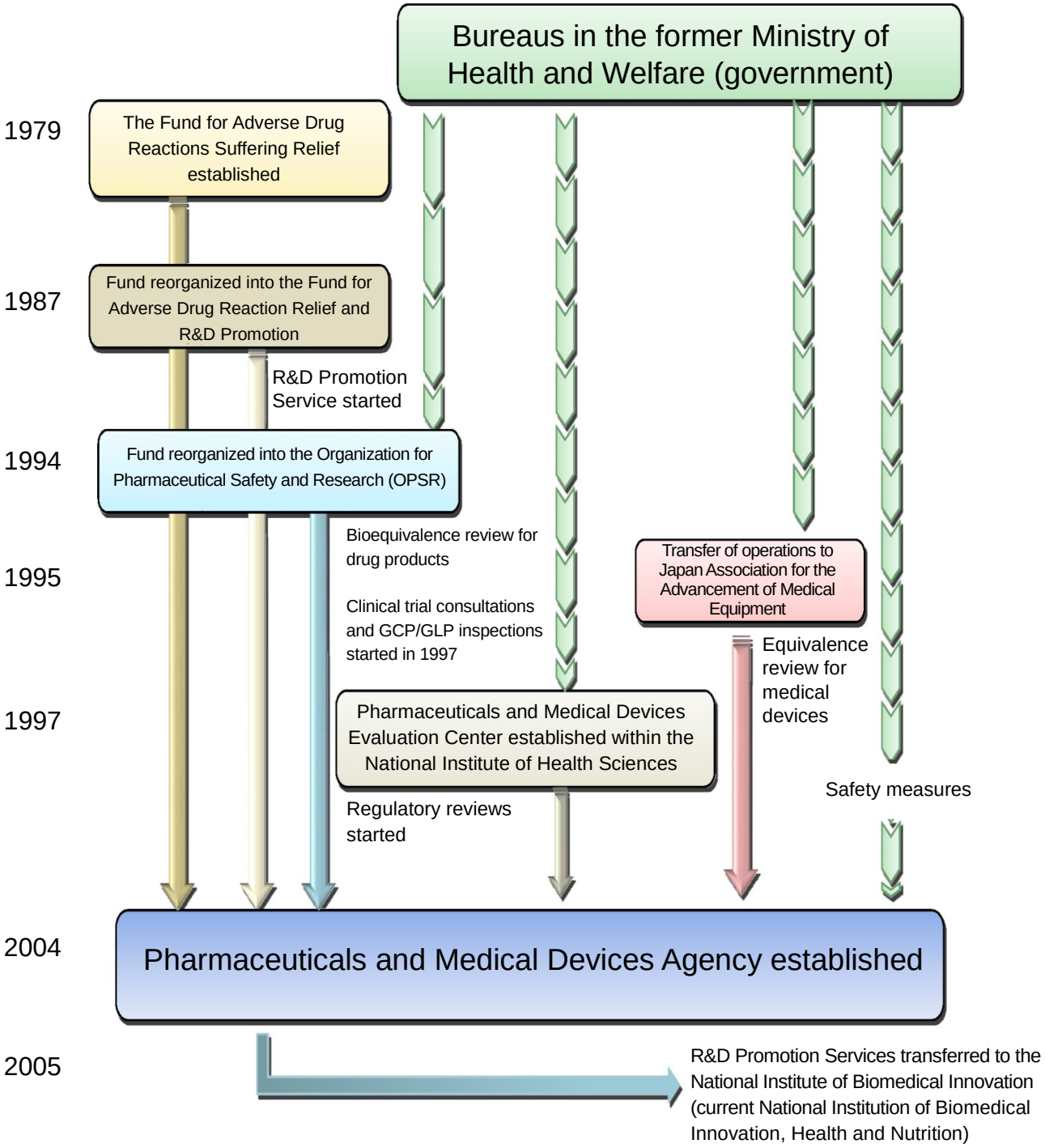
I. THE PHARMACEUTICALS AND MEDICAL DEVICES AGENCY

PART 1 History and Objectives of the PMDA

- In response to lessons learned from incidents involving drug-induced health damage, such as thalidomide-induced fetal malformations and subacute myelo-optical neuropathy (SMON), the Fund for Adverse Drug Reactions Suffering Relief was established in October 1979 for the purpose of providing prompt relief to patients suffering from adverse drug reactions (ADRs), pursuant to the provisions of the Adverse Drug Reaction Suffering Relief Fund Act (Act No. 55 of 1979). In 1987, the Fund began implementation of R&D-promoting activities, using the name, “The Fund for Adverse Drug Reaction Relief and R&D Promotion.” This fund was later reorganized into the Organization for Pharmaceutical Safety and Research (OPSR) in 1994 to play the additional role of conducting bioequivalence reviews of generic drug products. Subsequently, in 1997, this organization began providing advice related to clinical trials and conducting GCP/GLP inspections as part of the review process for new drug applications.
- In 1997, the Pharmaceuticals and Medical Devices Evaluation Center (PMDEC) was established at the National Institute of Health Sciences (NIHS) in order to develop a full-scale regulatory review system and to increase the sophistication of review activities. It was decided that reviews conducted at the Center should be conducted in teams comprised of experts specializing in the pharmaceutical and medical sciences, biostatistics, and other related fields. In addition, the Japan Association for the Advancement of Medical Equipment (JAAME) was established in 1995 as a designated investigative body under the Pharmaceutical Affairs Act tasked with conducting equivalence reviews of medical devices.
- Between 1997 and 1999, there was a systematic and drastic increase in the number of the staff involved with product review and post-marketing safety measures at the former Ministry of Health and Welfare and the three organizations above (from 121 staff members in 1996 to 241 in 1999). However, there was a limit to further increasing the number of staff members and developing the structure as governmental organizations.

  In the midst of these situations, the Cabinet adopted the Special Service Agency Restructuring Plan in December 2001, in which it was decided that the OPSR should be dissolved and that the Pharmaceuticals and Medical Devices Agency (PMDA) should be newly founded by consolidating the operations allocated to PMDEC, OPSR, and JAAME in order to further enhance reviews and post-marketing safety measures. In 2002, a bill for the Act on the Pharmaceuticals and Medical Devices Agency (PMDA) was discussed and passed at the 155th extraordinary session of the Diet, resulting in the establishment of PMDA on April 1, 2004, in accordance with the Act on the Pharmaceuticals and Medical Devices Agency (Act No.192 of 2002).
- PMDA’s mission is to contribute to the improvement in public health by providing prompt relief to people who have suffered health damage caused by adverse drug reactions or infections from biological products (Relief for Adverse Health Effects); providing guidance and reviews regarding 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 collecting, analyzing, and providing post-marketing safety information (Safety Measures).

  Previously, one of the objectives of PMDA was to promote basic research and the development of drugs and medical devices that contribute to maintaining and improving the health of the nation (Promotion of R&D). However, the Regulatory Division and the Research Promotion Division were separated, and services for promotion of R&D were transferred to the National Institute of Biomedical Innovation (now renamed to the National Institutes of Biomedical Innovation, Health and Nutrition) in April 2005, in order to allow PMDA to focus exclusively on reviews, safety measures, and relief services for harm caused by adverse events related to healthcare product use.


Bureaus in the former Ministry of Health and Welfare (government)
1979
The Fund for Adverse Drug Reactions Suffering Relief established
1987
Fund reorganized into the Fund for Adverse Drug Reaction Relief and R&D Promotion
R&D Promotion Service started
1994
Fund reorganized into the Organization for Pharmaceutical Safety and Research (OPSR)
Bioequivalence review for drug products
1995
Clinical trial consultations and GCP/GLP inspections started in 1997
Transfer of operations to Japan Association for the Advancement of Medical Equipment
Equivalence review for medical devices
1997
Pharmaceuticals and Medical Devices Evaluation Center established within the National Institute of Health Sciences
Safety measures
Regulatory reviews started
2004
Pharmaceuticals and Medical Devices Agency established
2005
R&D Promotion Services transferred to the National Institute of Biomedical Innovation (current National Institution of Biomedical Innovation, Health and Nutrition)

PART 2 Outline of Operations

2.1. Relief Services for Adverse Health Effects

- As a role inherited from the OPSR, PMDA provides benefits for medical expenses, disability pensions, and bereaved family pensions to the sufferers of illnesses or disabilities caused by adverse drug reactions (Relief Service for Adverse Drug Reaction).
- Since April 2004, PMDA has provided benefits to sufferers of adverse health effects caused by infections from drugs and medical devices manufactured using ingredients and materials of biological origin (Relief Service for Infections Acquired through Biological Products).
- Since January 2008, PMDA has also provided benefits to patients infected with drug-induced hepatitis C virus, in accordance with 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 (Act No. 2 of 2008) (Specified Relief Service).
- In November 2014, PMDA began providing relief disbursements to sufferers of adverse health effects caused by cellular and tissue-based products (as a part of Relief Service for Adverse Drug Reactions and Relief Service for Infections Acquired through Biological Products).
- PMDA is commissioned by the government of Japan and pharmaceutical companies to pay healthcare allowances and nursing care expenses to patients with SMON (Service for Healthcare Allowances). PMDA is also commissioned by the Yu-ai Welfare Foundation to make payments for healthcare expenses for patients with HIV infection or AIDS (Service for Healthcare Allowances).

2.2. Reviews

- In accordance with the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Act No. 145 of 1960, PMD Act) and based on current scientific and technological standards, PMDA evaluates the efficacy, safety, and quality of drugs and medical devices for which applications have been submitted for regulatory approval. In addition, PMDA conducts re-examinations/re-evaluations of drugs and cellular and tissue-based products, medical device use-result survey, and reviews of applications for confirmation of clinical use of genetically modified biological entities pursuant to the Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003, Cartagena Law) (Reviews).
- PMDA provides face-to-face guidance and advice on clinical trial plans to support the development of drugs, medical devices, and regenerative medical products (Regulatory Science General Consultation and Regulatory Science Strategy Consultation (R&D)).
- For products submitted for approval or re-examinations (use results survey for medical devices)/re-evaluations, on-site and document-based inspections are conducted to determine whether application data comply with Good Laboratory Practice (GLP), Good Clinical Practice (GCP), Good Post-marketing Surveillance Practice (GPSP), and the data integrity standards for product applications (GLP/GCP/GPSP Inspections).
- PMDA conducts on-site and document-based inspections to determine whether manufacturing facilities and manufacturing control methods for drugs, medical devices, and cellular and tissue-based products, etc., are in compliance with the requirements set forth in the Ministerial Ordinance on Good Manufacturing Practices/Quality Management System, whereby products of appropriate quality can be manufactured. PMDA also inspects manufacturing sites of cellular and tissue-based products to

determine whether their manufacturing facilities as well as manufacturing process and quality management system comply with the Good Gene, Cellular, and Tissue-based Products Manufacturing Practice (Act No. 85 of 2013) (GMP/QMS/GCTP Inspections).

- PMDA conducts research and organizes information to develop various standards, such as the Japanese Pharmacopoeia (JP) and certification standards of medical devices, which are set forth in the PMD Act (Research for Standards Development).

2.3. Safety Measures

- PMDA provides the following services designed to improve the safety of marketed drugs, medical devices, and cellular and tissue-based products, and also to ensure that patients and healthcare professionals can properly use drugs, medical devices, and cellular and tissue-based products, with peace of mind.

  (i) Centrally collecting and organizing information on the safety of drugs, medical devices, and regenerative medical products from a broad range of sources, such as reports from companies and medical institutions, information from foreign regulatory agencies, and reports presented at academic conferences, relating to adverse drug reactions, device malfunctions, and infections (Collection and Organization of Information).

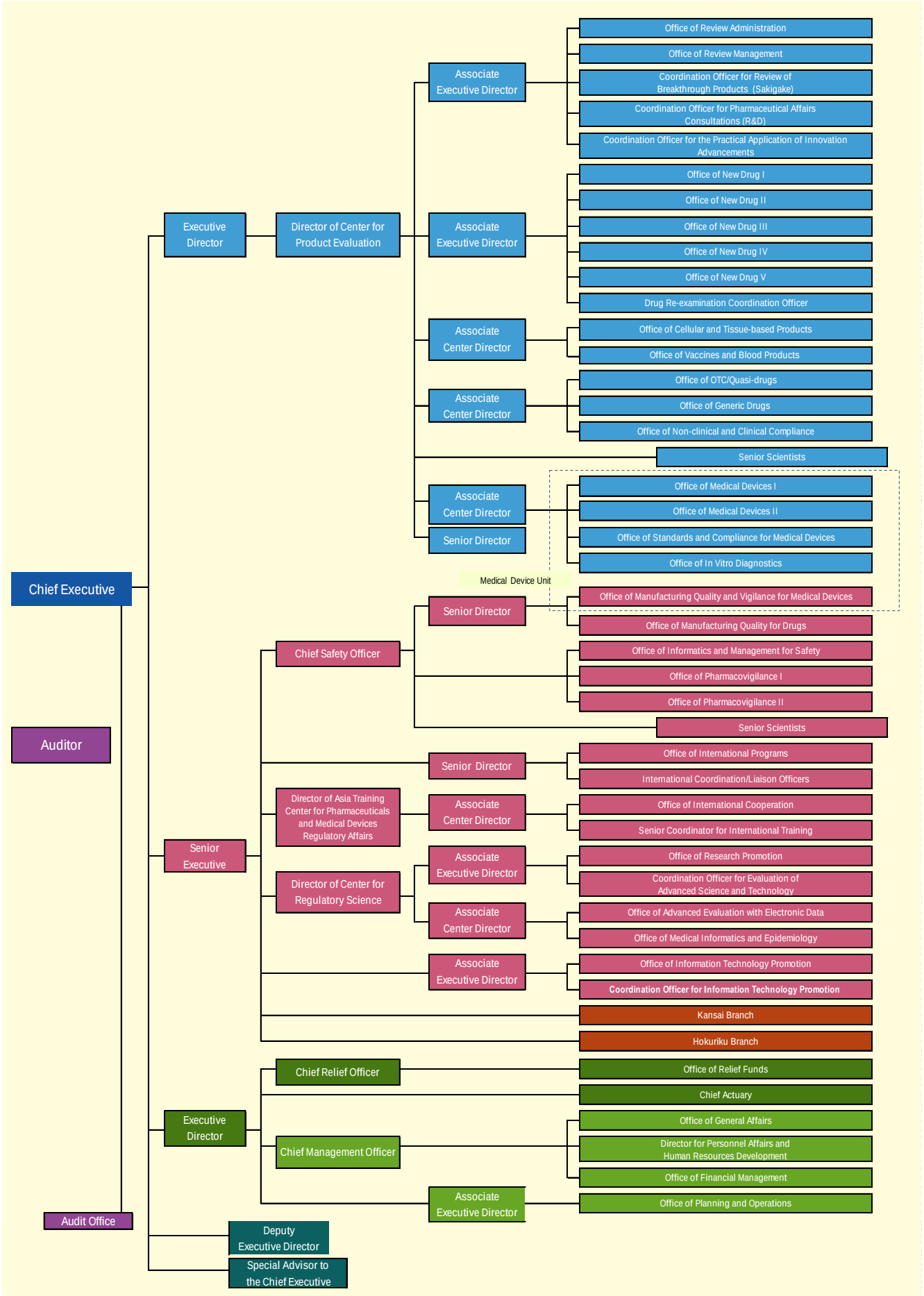
  (ii) Conducting research and reviews relating to safety measures based on the information collected in (i) above (Research and Reviews).

  (iii) Giving guidance and advice to marketing authorization holders (MAHs) as well as providing consultations to consumers upon request (Consultations).

  (iv) Providing safety information on drugs, medical devices, and cellular and tissue-based products widely to healthcare professionals, patients, companies, etc., in a timely manner (Information Provision).

- PMDA utilizes electronic medical records to conduct safety measures based on pharmacoepidemiological methods. These measures include quantitative assessments of the risk of adverse events, assessments of the impact on safety measures, and examination of the real-world implications of prescription drug use. PMDA developed medical information databases (MID-NET®) to promptly evaluate more detailed electronic medical records. MID-NET® was launched in April 2018.

PMDA Organizational Structure (as of March 31, 2019)



II. OPERATING PERFORMANCE FOR FY 2018 (April 2018 to March 2019)

PART 1 Development of Annual Plan for FY 2018 and Fourth Mid-term Plan

1.1 Development and Implementation of the Annual Plan for FY 2018 and Development of the Fourth Mid-term Plan

- PMDA, an independent administrative agency (independent administrative agency with non-civil service status), is required to develop a Mid-term Plan to implement the Mid-term Targets specified by the Minister of Health, Labour and Welfare, and to obtain Ministerial approval for this plan (effective period of the Third Mid-term Targets: April 2014 to March 2019). PMDA must develop its Annual Plan that specifies operational and management plans for each fiscal year so as to properly implement the Mid-term Plan. The Annual Plan is submitted to the Minister and released publicly.
- The Annual Plan for FY 2018 was developed at the end of FY 2017 based on the Third Mid-term Targets and Mid-term Plan, and the results of the evaluation of PMDA's operating performance for FY 2016 provided by the Minister of Health, Labour and Welfare. PMDA submitted the Annual Plan for FY 2018 to the Minister of Health, Labour and Welfare, and performed operations in accordance with the plan.
- In the FY 2018 which is the final fiscal year of the effective period of the Third Mid-term Targets, PMDA developed a new mid-term plan (effective period: April 2019 through March 2024) on the basis of the Fourth Mid-term Targets assigned by the Minister of Health, Labour and Welfare and obtained the Ministerial approval. The Annual Plan for FY 2019 was formulated based on the approved Fourth Mid-term Plan and submitted to the Minister of Health, Labour and Welfare.

1.2. Results of the Evaluation on Operating Performance for FY 2017 and Expected Results of the Evaluation on Operating Performance for the Effective Period of the Fourth Mid-term Targets

- Independent administrative agencies with non-civil service status must undergo Ministerial evaluation with regard to operating performance for the fourth fiscal year of the effective period (5 years) of the Mid-term Targets and operating performance expected at the end of the effective period of the Mid-term Targets. (Article 32 of the Act on General Rules for Independent Administrative Agencies (Act No. 103 of 1999))
- Since the last fiscal year of the effective period of the Third Mid-term Targets is FY 2018, PMDA must undergo evaluation by the Minister of Health, Labour and Welfare with regard to operating performance for FY 2017 and operating performance expected at the end of the effective period of the Third Mid-term Targets.
- The Minister of Health, Labour and Welfare released the Results of the Evaluation of Operating Performance for FY 2017 and Operating Performance for the Effective Period of the Mid-term Targets Expected at the End of the Effective Period of the Mid-term Targets on September 27, 2018, prepared based on expert committee interviews concerning the results of their evaluations of independent administrative agencies as of July 12, 2018. For operating performance for FY 2017, PMDA received 1 "S" rating, 3 "A" ratings, 10 "B" ratings and 1 "C" rating for 15 criteria evaluated. Among these, 1 "S" rating, 3 "A" ratings, and 4 "B" ratings were for "highly important" criteria.
- PMDA received a "C" rating for Operation Management due to disclosures of 5 incidents resulting from inadequate administrative practices during the fiscal year. These incidents were not considered to warrant a decrease in overall rating because PMDA voluntarily disclosed them, took measures to prevent recurrence, and has been working toward improvements. Accordingly, PMDA received an overall "B" rating ("B: Observed outcomes demonstrate progress towards achievement of the objectives specified in the Mid-term Plan") with respect to the overall assessment criteria specified in the MHLW Implementation Guidelines for the Evaluation of Independent Administrative Agencies.

- For operational results expected at the end of the effective period of the Mid-term Targets, PMDA received 1 “S” rating, 3 “A” ratings and 11 “B” ratings. Among these, 1 “S” rating, 3 “A” ratings, and 4 “B” ratings were for “highly important” criteria. Based on the consideration of the degree of decrease in overall rating warranted for the recognized events, PMDA received an overall “B” rating (“B: Observed outcomes demonstrate progress towards achievement of the objectives specified in the Mid-term Plan”) with respect to the overall assessment criteria specified in the Ministry of Health, Labour and Welfare’s Implementation Guidelines for the Evaluation of Independent Administrative Agencies.

Note: List of evaluation ratings

Individual evaluation criteria

If quantitative indices have been defined:

S: Agency operations demonstrate remarkable outcomes that both quantitatively and qualitatively exceed the expected objectives in the Mid-term Plan (quantitative criteria [when applicable]: achieved values of 120% or higher beyond the values targeted in the Mid-term Plan [or Annual Plan]; qualitative criteria: outstanding qualitative results)

A: Outcomes of agency operations exceed the expected objectives in the Mid-term Plan (quantitative criteria [when applicable]): achieved values of 120% or higher beyond the values targeted in the Mid-term Plan [or Annual Plan])

B: Outcomes of agency operations meet the expected objectives in the Mid-term Plan (quantitative criteria [when applicable]: achieved values of 100% or higher but less than 120% of the values targeted in the Mid-term Plan [or Annual Plan])

C: Outcomes of agency operations fail to meet the expected objectives in the Mid-term Plan and improvement is required (quantitative criteria [when applicable]: achieved values of 80% or higher but less than 100% of the values targeted in the Mid-term Plan [or Annual Plan])

D: Outcomes of agency operations failed to meet the expected objectives in the Mid-term Plan and drastic improvement, including discontinuation of the services, is required (quantitative criteria [when applicable]: achieved values of less than 80% of the values targeted in the Mid-term Plan [or Annual Plan], or where the competent minister deems it necessary to issue an improvement order or other necessary remedial measures)

If suitable quantitative indices cannot be defined:

S: -

A: Meets the target level established for highly difficult targets

B: Meets the target level (excluding items categorized under “A”)

C: Fails to meet the target level (excluding items categorized under “D”)

D: Fails to meet the target level, and drastic revision of operations are necessary (including cases where the competent minister deems it necessary to issue an improvement order or other necessary remedial measures)

General evaluation criteria

S: Agency operations demonstrate remarkable overall outcomes that both quantitatively and qualitatively exceed the expected objectives in the Mid-term Plan

A: Overall outcomes of agency operations exceed the expected objectives in the Mid-term Plan

B: Overall outcomes of agency operations generally achieve the expected objectives in the Mid-term Plan

C: Overall outcomes of agency operations fail to meet the expected objectives in the Mid-term Plan and improvement is required

D: Overall outcomes of agency operations fail to meet the expected objectives in the Mid-term Plan and drastic improvement, potentially including partial discontinuation of operations, is required

- The Results of the Evaluation on Operating Performance for FY 2017 and the Expected Results of the Evaluation on Operating Performance for the Effective Period of the Mid-term Targets were published on the PMDA website and reported to the Advisory Council at its meeting held on October 17, 2018.

Results of the Evaluation on Operating Performance for FY 2017 and the Effective Period of the Mid-term Targets

Mid-term Plan (Mid-term Targets)		Fiscal year evaluation					Effective period of the Mid-term Targets	
Assessment of individual items		FY 2014	FY 2015	FY 2016	FY 2017	FY 2018	Expected operating performance	Operating Performance
I. Improvement in the quality of PMDA services in the public interest and other general operations								
	1. Provision of information on the Relief System and enhancement of the Consultation System	B	B	B	B	—	B	—
	2. Expeditious operation and systemic improvements (Relief service)	A○	B○	A○	B○	—	B○	—
	3. Execution of cross-functional collaboration and health and welfare services	B	B	B	B	—	B	—
	4. Provision of healthcare allowances for patients with SMON and patients infected with HIV through blood products	B	B	B	B	—	B	—
	5. Expeditious operation and systemic improvements (services related to drugs)	A○	S○	S○	S○	—	S○	—
	6. Expeditious operation and systemic improvements (services related to medical devices and regenerative medical products)	A○	A○	A○	A○	—	A○	—
	7. Support of the initiative to facilitate development of innovative drugs, medical devices, and regenerative medical products	B○	B○	B○	B○	—	B○	—
	8. Reinforcement of collecting, and systematization of organizing, assessing and analyzing information on adverse drug reactions/malfunctions	A○	B○	B○	A○	—	A○	—
	9. Provision of safety information to companies/healthcare professionals and follow-up, and provision of safety information to patients and consumers	B○	B○	B○	B○	—	B○	—
	10. Promotion of international activities, etc.	A○	B○	A○	A○	—	A○	—
II. Increased efficiency of operations								
	11. Operation through target management and top management, ensuring transparency by establishing deliberative bodies, strengthening the consultation system, and announcement of the Agency's services.	B	B	B	C	—	B	—
	12. Cost control efforts	A	B	B	B	—	B	—
	13. Collection and management of contributions	B	B	B	B	—	B	—
III. Fiscal improvement								
	14. Budget, income and expenditure plan, and financial plan	B	B	B	B	—	B	—
IV. Others								
	15. Personnel matters and establishment of security	A○	B○	B○	B○	—	B○	—
Overall assessment		A	B	B	B	—	B	—

* For items with a "high" level of importance, the mark "○" is added besides the rating.
For items with a "high" level of difficulty, the rating is underlined.

Note: A comprehensive Ministerial evaluation also for FY 2017 was conducted with respect to the items specified by the Independent Administrative Agency Performance Evaluation Committee, in accordance with the Guidelines for Evaluation of Performance of Incorporated Administrative Agencies.

PART 2 Improvement in Overall Management of PMDA Operations and Quality of Services

2.1. Efficient and Flexible Management of Operations

2.1.(1) Operation through target management

- In managing operations, PMDA clarifies the objectives and responsibilities of operations for each department, and strives to identify and resolve problems through managing its operational progress on a daily basis. Operations were performed with thorough operational progress management by executive directors, associate center directors, etc.

2.1.(2) Reinforcement of operational management system and top-down management

- The following organizational changes were implemented on January 1, 2019.

  To enhance the functions that support management decision making by executives including the Chief Executive and to adopt more advanced risk management approaches, the Office of Planning and Coordination was reorganized to establish the Office of Planning and Operations.

  In addition, the Medical Device Unit was formed to allow the conduct of highly specialized operation based on the characteristics of individual medical devices. The unit encompasses four offices responsible for medical device review and an office responsible for medical device vigilance. While these offices are separately supervised by multiple executive directors to ensure mutual independence, the Medical Device Unit serves as a system that promote cooperation and communication among the relevant offices.

  Furthermore, the structure of offices responsible for drug safety measures was reinforced to address the specialization and advancement of drug safety measures.

- PMDA has a systemic approach to operational management, (e.g., strategic planning capacities concerning all operations, risk management, and auditing of operations) and an organizational system in which management decision making by the Chief Executive are promptly reflected in the operations.
- To this end, the Board of Executive Directors' meeting was held on a periodic basis. The Board of Executive Directors is the highest decision-making body that supports the Chief Executive. It reviews the basic policy on management of operations, establishment and dissolution of the organization, and important matters regarding the management of operations. In addition, methods for managing the Executive Directors' Meeting were reviewed to ensure fruitful discussion and more prompt decision-making (August 2018).
- In addition, PMDA regularly (typically once per week) held the Board of Directors' meeting, attended by executives and office directors, to ensure that the Chief Executive directly comprehends operational progress and provides necessary direction.
- To realize its mission, PMDA developed the PMDA Code of Conduct to ensure that individual employees act in a moral and just way while respecting the principles of regulatory science (October 2018).

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.

- In light of the expanded organizational scale and functions etc., PMDA has been working on the "PMDA Proceeding Project" with the aim of overall improvement in governance under appropriate progress management. PMDA implemented measures that were discussed and conclusively decided in the course of the project to strengthen the organizational platform that would allow PMDA to achieve its missions in the future, and to continue its efforts to become an even far more trusted organization.

How to Actually Proceed with the PMDA Proceeding Project

1. Establish a decision-making process and management system that are appropriate for an organization with 1,300 employees
   (1) Strengthen the decision-making process and the business operation system
   (2) Review the rules to achieve a disciplined workplace
   (3) Strengthen the risk management
2. Secure and develop excellent human resources who can make accurate decisions from a scientific perspective and further improve the quality of operations
   (1) Systematically develop staff members by steadily operating the Career Development Program (CDP)
   (2) Review the personnel evaluation system and the annual salary system
   (3) Develop better workplace
   (4) Further enhance the quality of operations by effectively responding to inquiries and complaints
3. Strengthen financial governance
   (1) Establish financial governance that is appropriate for an organization where user fees and contributions make up a large portion of the income (development and operation of the system that allows prompt decision-making in light of the new product application trends and use of appropriate financial indices)
   (2) Establish a budget that allows stable long-term fiscal management (e.g., budget drafting by introducing an appropriate budget ceiling)
   (3) Disclose financial status periodically

- As a part of efforts to strengthen the IT governance, based on the "PMDA Proceeding Project," and in accordance with the investment decision process developed in FY 2016, PMDA improved the system that allowed executives to promptly make decisions on system management, by checking projects (64 projects) for IT systems that would be implemented within FY 2019, in detail in terms of the effects on operations, scale of investment, etc., at the Committee on Investment in Information Systems.
- PMDA handles highly confidential information, including application dossiers submitted by corporations etc. and claim forms for relief benefits that contain personal information. The agency provided training on information security for PMDA employees and contractors working on-site at the PMDA office, to enhance information security measures. PMDA also developed a system that allowed executives to promptly obtain information on security measures (e.g., information regarding ongoing system operations and implemented information security measures was provided every month to the Risk Management Committee at its meetings).
- In light of the severe persisting fiscal situation since the previous fiscal year, PMDA implemented a zero-based budget for FY 2019 without granting a safe-harbor exception to improve the condition of its balance sheet, and decided to make efforts to implement the FY 2019 budget as efficiently and effectively as possible while continuing to perform its operations in a stable and sustainable

manner. PMDA thus introduced a conservative budget by rationalizing and streamlining operations and reducing incidental expenses (e.g., implementing cost control by reviewing expenses for operations and IT systems and then utilizing the saved costs as a financial resource for projects prioritized upon budget compilation).

- Specifically, budget drafting by the ceiling system was continued to further reduce the total budget for FY 2019. The budgets for IT system-related expenses were allocated with a focus on urgently required items with attention to information security, in order to suppress the total investment including expenses to update existing systems and financial burdens for subsequent fiscal years, from the medium- to long-term viewpoint to the end of FY 2023.

  Although an increase in the budget for the IT system-related expenses for FY 2019 (the first fiscal year of the effective period of the Fourth Mid-term Targets) compared with that for FY 2018 is expected due to replacement of the backbone system scheduled during FY 2019, the amount of the budget increase was reduced to approximately 1.9 billion yen. This reduction was achieved by paying rental expenses in a lump sum to save the interest payment for leasing and thereby reduce the total cost during the effective period of the Fourth Mid-term Targets, reviewing the system specifications, and by other efforts.

  While there were additional factors causing an increase in the total budget (e.g., an increase in personnel cost, an increased amount of national expenditure allocated to operating expenses of PMDA), efforts to control costs (excluding payment of benefits, personnel costs, and information system costs) resulted in the total FY 2019 budget amounting to 31.5 billion yen (increased by 2.4 billion yen from FY 2018).

- To maintain sound fiscal performance and effective operations, the Financial Management Committee, chaired by the Chief Executive, held 18 meetings in FY 2018, to regularly monitor PMDA's financial condition. The Committee received reports on financial analyses including revenue and cash flow analysis of the user fees paid to each division each month and the declared amount of contributions, and discussed future financial prospects.

  To ensure that PMDA continues to play its roles securely during the Fourth and subsequent Mid-term Plan periods, the Committee discussed short-, medium-, and long-term measures to review financial expenditures, to strengthen the financial base, and to ensure effective budget implementation. The measures discussed by the Committee have been reflected in the implementation of the budget for each fiscal year, through the Plan-Do-Check-Action (PDCA) cycle, to ensure financial soundness.

  To strengthen fiscal governance, the status of PMDA's financial accounts related to reviews, etc., and other subjects were reported to the Advisory Council at all meetings of the council. In addition, the statuses of closing of accounts for the preceding fiscal year and budget for the next fiscal year were reported at the first and last meetings of the council in FY 2018, respectively.

- In the course of developing the Fourth Mid-term Plan, to ensure maintenance of the world's fastest regulatory review times and further improvement of the quality of product review so that the public can benefit from fast access to the world's most advanced drugs, medical devices, and regenerative medical products, PMDA addressed the revision of user fees for product applications and consultation services (revised in April 2019).

- PMDA held global strategy meetings on a regular basis to implement global measures comprehensively and strategically, and made decisions to implement necessary measures to carry out individual projects (9 meetings held in FY 2018).

- To provide opportunities for communication between executives and staff members, PMDA held 15 "luncheon meetings for communication with executives."

- Operational incidents that have occurred in PMDA are reported to the Risk Management Committee, which discusses individual incidents, their potential impact, and countermeasures. In order to clarify the causes of any operational incident to prevent recurrence thereof, the relevant office closely investigates and analyzes the causes of the incident and submits a report to the Risk Management Committee for discussion of countermeasures to prevent recurrence (the Committee held 15 meetings in FY 2018). Preventive measures proposed at a Risk Management Committee meeting are required to be reported at the upcoming meeting of Board of Directors. The office directors are required to verbally inform all staff members about incidents and preventive measures that have been reported to the Board of Directors. For example, not only operating procedures established at the office where the incident occurred but also those established at all offices in PMDA were reviewed to ensure prevention of recurrence.

- By utilizing a new page in its intranet for the Risk Management Committee, PMDA continues its efforts to familiarize the executives and employees with risk management best practices in accordance with the risk management rules and risk management manual.

  Operating procedures related to risk management that had been separately prepared (e.g., risk management manual and guidance on incident prevention) were integrated to enhance convenience.

- PMDA caused 2 incidents of improper conduct in FY 2018 and caused much trouble to the concerned persons. PMDA therefore announced individual incidents as well as preventive measures (date of announcement in parentheses).

  (i) Loss of periodic safety update report (February 1, 2019)
  (ii) Disciplinary action against an employee concurrently engaging in another business in violation of the internal rules (March 1, 2019)

- PMDA is seriously concerned about the fact that the agency caused these incidents of improper conduct. The Chief Executive delivered a message to all employees about promotion of strict compliance and organizational efforts to prevent recurrence of such incidents. PMDA biannually held regular risk management training programs mandatory for all staff members.

- PMDA issued a guidance document entitled “Thorough Document Management (Report)” (PMDA Notification No. 0330041, dated March 30, 2018) as preventive measures to ensure thorough document management for addressing the loss of the original application documents and submitted data that occurred in FY 2017, followed by development of a guidance document called “Thorough Document Management etc.” (dated May 8, 2018; amended on August 7, 2018) as further preventive measures. PMDA also worked on a complete overhaul of document management, including the approval, archiving, and disposal of documents. A guidance document entitled “Guidance on Thorough Document Management (March 2019)” was developed and communicated to the executives and employees.

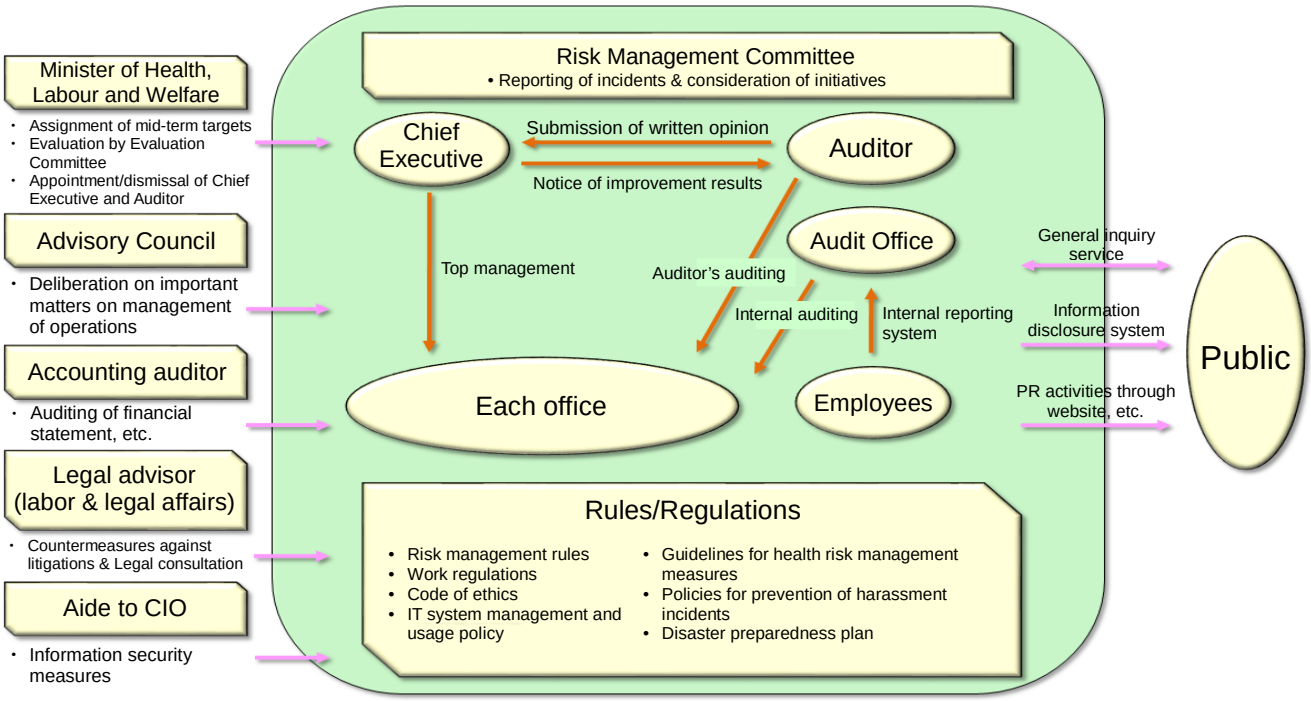
- In addition, 4 teams engaged in the “PMDA Proceeding Project”(Note) cooperated and started a discussion on whether a review of the work rules and working scheme is necessary to prevent concurrent engagement in another business in violation of the internal rules. PMDA notified relevant organizations in writing about its rules on its employee’s concurrent engagement in another business and a contact point for whistle-blowing on misconduct by PMDA employees and posted the notification on the PMDA website.

  (Note) “Review of Regulations Related to Personnel Administration” Team, “Strict Compliance” Team, “Improvement of the Process for Incident Verification and Development of Measures to Prevent Recurrence” Team, and “Implementation of IT Governance and Efficient Security Control” Team

- The Office of Audit, which reports directly to the Chief Executive, has continued to conduct internal audits and management of PMDA’s internal reporting systems.

- In order to ensure hazard and emergency readiness in the event of risks resulting from natural disasters such as earthquakes and fires, PMDA has informed all executives and employees of its disaster response manual and disaster preparedness plan.
- PMDA revised its emergency contact lists as appropriate and ensured that all concerned persons are familiarized with it. PMDA also secured emergency stock in preparation for disasters, and uploaded a Manual for Handling of Emergency Stock on the intranet to familiarize all staff members with it.
- To enhance the effectiveness of the safety confirmation/simultaneous transmission system in the event of a large-scale disaster, PMDA carried out drills for safety confirmation involving all staff members (once a month).
- The Pharmaceuticals and Medical Devices Agency's Business Continuity Plan (BCP) to Prepare for Large-Scale Natural Disasters, specifies the range of important operations that PMDA should continue to conduct in the event of a large-scale disaster (e.g., an earthquake in the Tokyo metropolitan area). PMDA installed emergency power units capable of supplying electric power for up to approximately 72 hours after the occurrence of a disaster to conduct some of the critical operations that must be conducted as promptly as possible.

Risk Management System at PMDA



★ Risks PMDA may face:

A. Risks to the organization
- Possibility of an event that damages or may damage the reputation of PMDA in society
- Possibility of an event that significantly hinders or may hinder the execution of PMDA's operations
- Possibility of an event that financially damages or may damage PMDA

B. Risks that PMDA should address as part of its tasks
- Risks relating to PMDA's operations which might cause or expand serious adverse health effects due to drugs, medical devices, etc. (including drugs, medical devices, quasi-drugs, cosmetics, and regenerative medical products, as well as agents, etc., subject to clinical trials)

- In order to systematically promote public relations (PR) activities in consideration of the public needs and international perspectives, PMDA developed the PMDA Public Relations Strategic Plan (July 11, 2008) as a basic policy for its overall PR activities. The Agency is striving to proactively provide information in line with the strategic plan. Further, in consideration of the development of PMDA's philosophy, changing socioeconomic circumstances, etc., PMDA revised the Strategic Plan in April 2015 and established the PR Committee to shape the policies of PMDA's PR activities so that PMDA will be able to implement PR activities more effectively.
- The Osaka prefectural government and other local governments located in the Kansai Innovation Comprehensive Global Strategic Special Zone, had made a request for the "arrangement of the PMDA-WEST function." In response to the request, PMDA established the Kansai Branch Office in Osaka in October 2013. The office mainly conducts Regulatory Science General Consultation Regulatory Science Strategy Consultation (R&D) and on-site GMP inspections in the Kansai region. In June 2016, the office started to offer various kinds of consultations (face-to-face consultations) with the use of a video conference system. The office started to offer video conference consultations on safety measures in November 2017.
- In July 2016, a report was published by the Advisory Panel on Promotion of Venture Companies that Play an Important Role in Medical Innovation, set up by the Minister of Health, Labour and Welfare. The report states that PMDA should launch a new office within a year to support practical application of seed-stage resources owned by small-scale business operators including medical ventures. In April 2017, PMDA thus renamed the Division of Pharmaceutical Affairs Consultation as the Division of Innovation Support and Consultations on R&D Strategy, and reorganized Pharmaceutical Affairs Consultation on R&D Strategy (introductory consultations, pre-consultations, and face-to-face consultations) into Regulatory Science General Consultation (introductory consultations; hereinafter referred to as "RS General Consultations") and Regulatory Science Strategy Consultations (R&D) (pre-consultation consultations and face-to-face consultations; hereinafter referred to as "RS Strategy Consultations (R&D)"). PMDA implemented measures for supporting the practical application of innovative drugs, medical devices, and regenerative medical products (for example, by initiating Consultations on Cooperation for Practical Application of Innovation Advancements in April 2018).
- In line with the PMDA International Strategic Plan 2015 unveiled in June 2015 as a new roadmap to guide PMDA's future international initiatives, PMDA established the PMDA Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs in April 2016.

  In addition, based on the basic policies for relocation of government-related agencies, PMDA established a Hokuriku Branch Office in Toyama Prefecture in June 2016. In the Hokuriku Branch Office, a training institute for the PMDA Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs was established. The PMDA Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs provided training for the officers of regulatory authorities in Asian countries.

2.1.(3) Advisory Council meetings

- In order to facilitate the exchange of ideas and opinions between knowledgeable individuals in various fields, PMDA convenes meetings of the Advisory Council (chaired by Dr. Masataka Mochizuki, Faculty of Pharmaceutical Sciences, Sanyo-Onoda City University), which are open to the public. The Council consists of academic experts, healthcare professionals, and representatives from relevant industries, consumers, and victims of drug and other medical product-related adverse health effects. By seeking opinions on operations and the management system, the Council serves to secure fairness and transparency of PMDA's operations, in addition

to contributing to increasing the efficiency of its operations. Under the Advisory Council, the Committee on Relief Services (chaired by Dr. Nobuyuki Miyasaka, Professor Emeritus, Tokyo Medical and Dental University) and the Committee on Review and Safety Operations (chaired by Dr. Haruhiro Okuda, Director General of the National Institute of Health Sciences) were also formed to discuss specialized operational issues. The dates of the meetings and specific agenda for FY 2018 were as follows.

Advisory Council (FY 2018)

Agenda for the 1st Meeting (June 20, 2018)

(1) Annual Report FY 2017
(2) Progress of PMDA Proceeding Project
(3) Financial Report FY 2017
(4) Employment status of personnel from the private sector
(5) Cash contributions etc., received by external experts commissioned for Expert Discussions.
(6) Commission of a Special Assistant to the Chief Executive
(7) Others

Agenda for the 2nd Meeting (October 17, 2018)

(1) Election of the Chairman and appointment of the Deputy Chairman
(2) Results of evaluation of operating performance for FY 2017 and expected results of the evaluation on operating performance for the effective period of the Mid-term Targets
(3) Status of recent major initiatives
(4) Progress of PMDA Proceeding Project
(5) PMDA's financial condition of accounts for reviews, etc.
(6) Direction of the Fourth Mid-term Plan (draft)
(7) Employment status of personnel from the private sector
(8) Cash contributions etc., received by external experts commissioned for Expert Discussions

Agenda for the 3rd Meeting (January 28, 2019)

The Fourth Mid-term Plan (draft)

Agenda for the 4th Meeting (March 25, 2019)

(1) Measures in response to recent incidents of improper conduct
(2) Annual Plan for FY 2019 (draft)
(3) Progress of PMDA Proceeding Project
(4) PMDA's financial condition of accounts for reviews, etc.
(5) Budget (draft) for FY 2019
(6) PMDA's activities in response to suggestions from the Advisory Council
(7) Employment status and extension of interim restrictions on posts of personnel from the private sector
(8) Cash contributions etc., received by external experts commissioned for Expert Discussions
(9) Cash contributions etc., from the industry received by the Special Assistant to the Chief Executive
(10) Others

Committee on Relief Services (FY 2018)

Agenda for the 1st Meeting (June 18, 2018)

(1) Annual Report FY 2017
(2) Annual Plan for FY 2018, etc.
(3) PR on the Relief System for Adverse Health Effects

(4) Others

Agenda for the 2nd Meeting (December 19, 2018)
(1) Election of the Chairman and appointment of the Deputy Chairman
(2) Results of evaluation of operating performance for FY 2017 and expected results of the evaluation on operating performance for the effective period of the Mid-term Targets
(3) Operating performance so far in FY 2018 and current situation of recent major initiatives
(4) Direction of the Fourth Mid-term Plan (draft)
(5) Others

Committee on Review and Safety Operations (FY 2018)

Agenda for the 1st Meeting (June 18, 2018)
(1) Annual Report FY 2017
(2) Annual Plan for FY 2018, etc.
(3) Employment status of personnel from the private sector
(4) Cash contributions etc., received by external experts commissioned for Expert Discussions.
(5) Others

Agenda for the 2nd Meeting (December 19, 2018)
(1) Election of the Chairman and appointment of the Deputy Chairman
(2) Results of evaluation of operating performance for FY 2017 and expected results of the evaluation on operating performance for the effective period for the Mid-term Targets
(3) Operating performance so far in FY 2018 and initiatives to be addressed newly
(4) Direction of the Fourth Mid-term Plan (draft)
(5) Employment status of personnel from the private sector
(6) Cash contributions etc., received by external experts commissioned for Expert Discussions.

- The above meetings were open to the public, and the minutes and materials for the meetings of the Advisory Council and its sub-committees were published on the PMDA website (Japanese-language only).
- PMDA held an idea exchange session with the Japan Federation of Drug-Induced Sufferers Organizations in November 2018.
- PMDA held a joint idea exchange session on new drugs and safety measures with members of the pharmaceutical industry in December 2018.

  PMDA supported the operation of MHLW-hosted regular idea exchange sessions focusing on the review, vigilance, etc. of medical devices and in vitro diagnostics (held in August 2018).

2.1.(4) Establishment of an efficient operational management system

- PMDA aims to establish an efficient operational management system through flexible personnel allocation tailored to situations, as well as through effective use of external experts.
- In the review divisions necessitating flexible processes, PMDA continued its team review system under which review teams are led by Review Directors who report to the Office Director.
- PMDA has commissioned external experts to seek their professional opinions relating to scientifically significant matters on reviews and safety measures.
  (1,200 external experts are commissioned as of March 31, 2019.)
- PMDA has also commissioned external experts to seek their opinions on the relief service for health damage caused by adverse drug reactions and infections acquired through biological

products.
(125 external experts are commissioned as of March 31, 2019.)

- The list of commissioned external experts is available on the PMDA website.
- Based on the need to secure impartiality and transparency of judgments offered by external experts, PMDA developed the Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency (December 25, 2008; amended on December 26, 2018). The establishment of these rules enables PMDA to ensure the transparency by releasing review reports and information on conflict of interest of commissioned external experts, and also allows outside parties to check the decision-making process at Expert Discussions. The statuses of cash contributions and contract payments received by external experts are disclosed immediately after confirmation of approval of designated products, implementation of safety measures, or development of approval standards or review guidelines for drugs, etc., and are reported to the Advisory Council and the Committee on Review and Safety Operations.

  In addition, PMDA has implemented a scheme to ensure that cash contributions and contract payments received by external experts are declared by using the information disclosed by companies.
- In carrying out operations, PMDA has also commissioned lawyers as advisors to handle operations that require legal expertise. In addition, the Agency has made use of private companies for operational management of information systems and minimized the increase in the number of its regular staff.
- PMDA has continued to appoint an outside specialist with advanced expertise in information systems as an aide to the Chief Information Officer (CIO), to ensure consistency and coordination of services across the Agency's information systems.

2.1.(5) Standardization of operating procedures

- PMDA has continued to develop, examine, and, if necessary, revise standard operating procedures (SOPs) for its major tasks. The purpose is to implement operations properly and consistently by standardizing each operating procedure, and to limit the number of regular staff by effectively employing non-regular staff. Routine operations are conducted by non-regular staff.

2.1.(6) Development of databases

- PMDA promoted the standardization of procedures for the management and maintenance of all information systems for operations and assessed incidents occurring in individual systems using a common indicator. The Office of Information Technology Promotion is engaged in centralized management of incident information that is stored in an incident database. The database serves as a management tool to identify the status of occurrence of incidents in all systems used in PMDA as well as actions taken to address them.
- PMDA promoted streamlining of operations across the organization by switching personal computers for employees from desktops to laptops and introducing a wireless LAN network into all office rooms including meeting rooms to allow digitization of meeting hand-out materials and thereby saving work for preparation of paper materials as well as printing costs thereof.

2.1.(7) Promotion of the optimization of operations and IT systems

- Based on the total budget ceiling for IT systems set in FY 2016, PMDA reduced investment cost of operations and IT system projects and terminated some operations and IT system projects, to

ensure that expenditures remain below the budget ceiling for FY 2018. PMDA discussed the optimal IT system infrastructure within the ceiling.

Elsewhere, to ensure that the individual IT systems are operated stably and to ascertain and classify the functions that should be further enhanced, PMDA confirmed the status of various system improvements as well as the details of monthly reports obtained from operational support companies. Based on this information, PMDA took actions to the extent possible within the scope of the current contract.

2.2. Cost Control through Increased Efficiency of Operations

2.2.(1) Retrenchment of general and administrative expenses

- The Mid-term Plan set a target that the Mid-term Plan budget relating to general administrative expenses, covered by administrative subsidies, should be reduced by at least 15% from FY 2014 to the end of the effective period of the Mid-term Plan/Targets (FY 2018). To achieve the target, PMDA has been making ongoing efforts to improve operations and increase management efficiency.
- In FY 2018, PMDA enhanced the efficiency of its operations by optimizing IT systems and reducing unnecessary expenditure, as in the previous year. PMDA also made efforts to reduce procurement costs by adopting general competitive bidding, resulting in a 16.9% reduction against the FY 2014 figure, with the exception of new services starting in FY 2016 or later.

  PMDA also made efforts to effectively implement new services covered by administrative subsidies that were distributed in association with increases in newly entrusted business by the government, such as strengthening of the system for safety measures and GMP inspections, promotion of optimal uses of innovative pharmaceuticals, etc.
- PMDA outsourced arrangements for travel tickets, etc., on a trial basis in FY 2018. Since the results of cost-effectiveness verification suggested that an expected reduction in expenses would exceed the initial investment cost, PMDA decided to continue the outsourcing in the next fiscal year and thereafter (cost control achieved by using package tours or inexpensive travel services exclusive to corporate employees, available on the website of the contracted travel agency).

  * Operating expenses are reduced in a similar manner.

2.2.(2) Cost control of operating expenses

- The Mid-term Plan set a target that Mid-term Plan budget relating to operating expenses, covered by administrative subsidies, should be reduced by at least 5% from FY 2014 to the end of the effective period of the Mid-term Plan/Targets (FY 2018). To achieve the target, PMDA has been making ongoing efforts to improve operations and increase management efficiency.
- Like the measures taken for general administrative expenses, PMDA enhanced the efficiency of its operations, such as optimization of systems, promotion of digitalization, and reduction of unnecessary expenditure in FY 2018. PMDA also made efforts to reduce procurement costs by concluding contracts through general competitive bidding, resulting in a 26.1% reduction against the FY 2014 figure, except for new services starting in FY 2016 or later.

  PMDA also made efforts to effectively implement new services covered by administrative subsidies that were distributed in association with increases in newly entrusted business by the government, such as strengthening of the system for safety measures and GMP inspections, promotion of optimal use of innovative pharmaceuticals, etc.

2.2.(3) Competitive bidding

- In FY 2018, the percentage of competitive contracts (including competitive requests for proposals and invitations to bid) among the total contracts decreased by 2.8% in number of bids and by 3.0% in monetary value, compared with FY 2017.

  The decreased percentage of competitive contracts in number of bids was attributable to 6 unsuccessful competitive bids changed to and counted as non-competitive optional contracts, though there was an increase in the total number of competitive contracts (i.e., an increase of 9 compared with FY 2017).

  In FY 2018, the monetary amount of competitive contracts increased, whereas the monetary amount of optional contracts increased as well for the following reasons: (a) maintenance services for office environment were available only from a limited provider; (b) there was an increase in services for which only optional contracts were available because a number of contracts were changed to optional contracts after bidding, as was the case with percentage of contracts in number of bids.

		FY 2017	FY 2018	Change
General competitive bidding (including competitive planning competition and invitations to bids)		90 bids (75.6%) 2,467 million yen (82.9%)	99 bids (72.8%) 5,734 million yen (79.9%)	9 bids (-2.8%) 3,267 million yen (-3.0%)
Non-competitive optional contracts		29 bids (24.4%) 511 million yen (17.1%)	37 bids (27.2%) 1,443 million yen (20.1%)	8 bids (2.8%) 933 million yen (3.0%)
	Excluding contracts in relation to office lease	26 bids (21.8%) 453 million yen (15.2%)	33 bids (24.3%) 1,193 million yen (16.6%)	7 bids (2.5%) 740 million yen (1.4%)
Total		119 bids 2,977 million yen	136 bids 7,177 million yen	17 bids 4200 million yen

Note: Since the figures are rounded to the nearest whole number, the figures in "Total" may not equal the sum of the individual figures.

2.2.(4) Contract Review Committee meetings, etc.

- PMDA established its Contract Review Committee in accordance with the Inspection/Review of the Contract Status of Independent Administrative Agencies ordinance (adopted by the Cabinet on November 17, 2009). The Committee consists of 3 external experts and 2 internal auditors. During Committee meetings, PMDA underwent a pre-inspection regarding the appropriateness of the transaction schemes and adjustment measures for ensuring the competitiveness of procurement and similar cases involving contracts planned to be executed during FY 2018. PMDA is making efforts to improve the issues commented on by the Contract Review Committee at future procurement practices.

  The Committee held 4 meetings in FY 2018 and summaries of its reviews are available on the PMDA website.

  In addition, PMDA established an internal Committee for Discussion on Rationalization of Procurements, etc., in accordance with the Promotion of Rationalization of Procurements, etc. in Independent Administrative Agencies ordinance (adopted by the Minister of Internal Affairs and Communications, dated May 25, 2015). The Committee addresses urgent procurement cases

where there is rational justification and where such cases are preliminarily investigated based on criteria similar to those applied by the Contract Review Committee, and subsequently reports its results to the Contract Review Committee.

2.2.(5) Collection and management of contributions

- Contributions from marketing authorization holders (MAHs) in industry enable PMDA to secure the major part of the financial resources necessary for PMDA's Relief Service for adverse health effects (e.g., adverse reactions to drugs and regenerative medical products, infections acquired through biological products and regenerative medical products) and other operations to improve the quality, efficacy, and safety of drugs and medical devices. Specifically, contributions to the adverse drug reaction fund ("ADR contributions") are declared and made by MAHs of approved drugs or approved regenerative medical products related to adverse reaction relief compensation. Contributions to the relief fund for infections acquired through biological products ("infection contributions") are made and declared by MAHs of approved biological products or approved regenerative medical products related to infection relief benefits. Contributions to post-marketing safety measures are declared and made by MAHs of drugs, medical devices, regenerative medical products, and *in vitro* diagnostics.
- Basic data such as those concerning newly approved products and money transfers are automatically processed by the contribution collection management system, which is able to manage these contributions in an integrated fashion. Thus, PMDA was able to efficiently collect and manage these contributions through various methods, such as the calculation of products' transaction value, which constitutes the basis of the contribution amount, and the management of data concerning unpaid contributions. PMDA also maintained contributors' convenience through continuing consignment contracts with five major banks for receipt of contributions, resulting in the prompt transfer of funds.
- In its Mid-term Plan, PMDA designated its target collection rates of owed contributions related to ADRs, infections, and post-marketing safety measures to be no less than 99%. In FY 2018, the collection rates achieved for ADR, infection, and post-marketing safety measure-related contributions were 99.6%, 100%, and 99.6%, respectively.
- The rate of contributions for post-marketing safety measures was changed from that in the preceding fiscal year, as was the case in FY 2017, to cover the cost of improving information security and enhancing safety measures related to medical devices. The adjusted contribution rate became effective on April 1, 2018.

FY 2018 Contribution Collection Results

Category		Number of parties obligated to make contributions	Number of parties who made contributions	Collection Rate	Contribution amount (Million yen)
ADR contributions	MAHs of approved drugs, etc.	680	680	100%	4,179
	MAHs of pharmacy-compounded drugs	4,291	4,273	99.5%	4
	Total	4,971	4,953	99.6%	4,184
Infection contributions	MAHs of approved biological products, etc.	100	100	100%	118
Post-marketing Safety measures etc., contributions	MAHs of drugs, etc.	3,195	3,188	99.7%	3,804
	MAHs of pharmacy-compounded drugs	4,290	4,272	99.5%	4
	Total	7,485	7,460	99.6%	3,808

Note: Since the figures for contribution amount are rounded to the nearest million yen, the figures in "Total" may not equal the sum of the individual figures.

- PMDA took the following efforts to efficiently improve contribution collection rates:

  1) PMDA continued to commission the Japan Pharmaceutical Association (JPA) to collect contributions from MAHs of pharmacy-compounded drugs.

  2) PMDA placed advertisements on the PMDA website and in relevant trade journals, and continued its efforts to raise awareness of the contribution procedure among the relevant parties obligated to make contributions by preparing and distributing a handbook. PMDA also dispatched written requests to all the contributors who have not yet made contributions.

(i) Collected ADR contributions and trends in the liability reserve

a. ADR contributions

- In order to fund the relief service for adverse drug reactions, PMDA has collected ADR contributions from MAHs of approved drugs, etc. In FY 2018, the contribution rate applied to such MAHs was set at 0.27/1000 and the collected amount was 4,184 million yen.

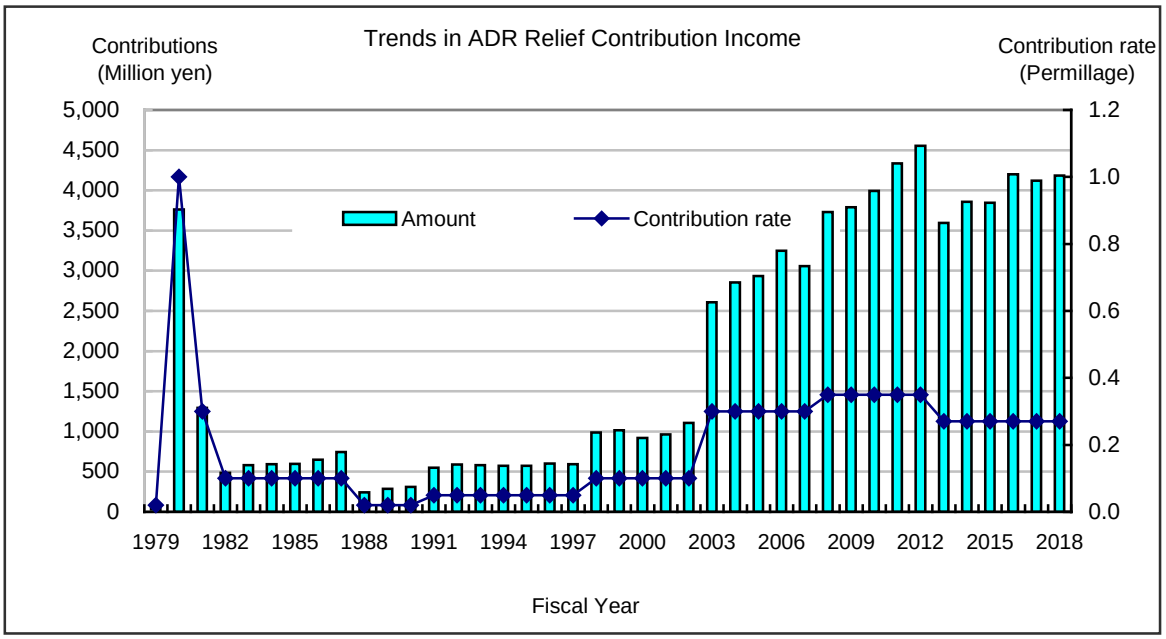
(Million yen)

Fiscal year	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Contributions from MAHs of approved drugs*	3,852 [692]	3,841 [688]	4,193 [693]	4,116 [679]	4,179 [680]
Contributions from MAHs of pharmacy-compounded drugs	6 [5,658]	5 [5,439]	5 [4,974]	5 [4,683]	4 [4,273]
Total	3,857	3,847	4,198	4,120	4,184
Contribution rate	0.27/1000	0.27/1000	0.27/1000	0.27/1000	0.27/1000

Note: Since the figures for contribution amount are rounded to the nearest million yen, the figures in "Total" may not equal the sum of the individual figures.

** The figures for FY 2013 and 2014 represent the amount of contributions paid by MAHs of drug. The figures for FY 2015, 2016, and 2017 represent the amount of contributions paid by MAHs of approved drugs and MAHs of approved regenerative medical products related to ADR contributions. The figures in brackets represent the number of MAHs.*

- The ADR contribution income and the contribution rate since the establishment of this service are shown below.



b. Collected contributions for relief for infections acquired through biological products

- In order to fund the relief service for infections acquired through biological products, PMDA has collected infection contributions from MAHs of approved biological products, etc. In FY 2018, the contribution rate applied to such MAHs was set at 0.1/1000 and the collected amount was 118 million yen.

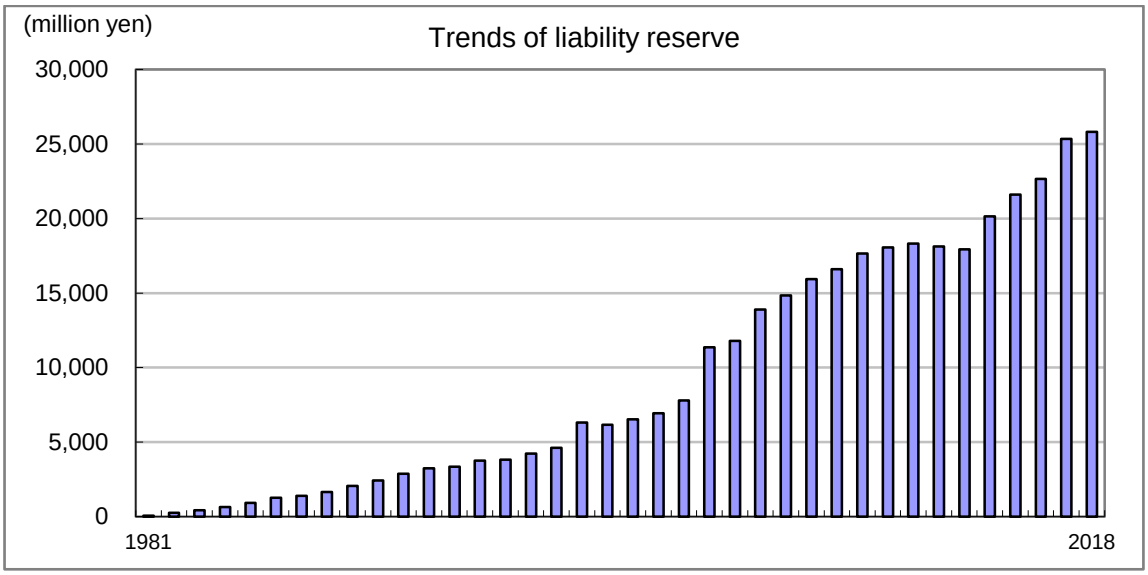
(Million yen)

Fiscal year	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
MAHs of approved biological products, etc.*	93 [92]	93 [96]	102 [100]	110 [100]	118 [100]
Contribution rate	0.1/1000	0.1/1000	0.1/1000	0.1/1000	0.1/1000

** The figures for 2014 represent the amount of contributions paid by MAHs of approved biological products. The figures for FY 2015, 2016, 2017, and 2018 represent the amount of contributions paid by MAHs of approved biological products and MAHs of approved regenerative medical products related to infection contributions. The figures in brackets represent the number of MAHs.*

c. Liability reserve

- In order to cover the estimated costs for relief benefits that eligible persons will receive in the future, PMDA calculates the amount that it should possess at the end of every fiscal year and accumulates funds accordingly. The liability reserve at the end of FY 2018 was 25,823 million yen.



(ii) Collected contributions for post-marketing safety measures

- In order to fund services for improvements in the quality, efficacy, and safety of drugs, etc., PMDA has collected contributions to post-marketing safety measures from MAHs of drugs, medical devices, regenerative medical products, and *in vitro* diagnostics. In FY 2018, the contribution rate applied to such MAHs was 0.231/1000 for drugs, 0.143/1000 for medical devices, and 0.115/1000 for *in vitro* diagnostics and regenerative medical products; the collected amount was 3,808 million yen.

(Million yen)

Fiscal year	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
MAHs of drugs, etc.*	2,972 [3,099]	2,952 [3,139]	3,231 [3,141]	3,697 [3,146]	3,804 [3,188]
MAHs of pharmacy-compounded drugs	6 [5,658]	5 [5,439]	5 [4,974]	5 [4,639]	4 [4,272]
Total	2,977	2,958	3,236	3,701	3,808
Contribution rate	0.22/1000 (Drugs excluding *in vitro* diagnostics) 0.11/1000 (Medical devices and *in vitro* diagnostics)	0.22/1000 (Drugs excluding *in vitro* diagnostics) 0.11/1000 (Medical devices, *in vitro* diagnostics, and regenerative medical products)	0.22/1000 (Drugs excluding *in vitro* diagnostics) 0.11/1000 (Medical devices, *in vitro* diagnostics, and regenerative medical products)	0.231/1000 (Drugs excluding *in vitro* diagnostics) 0.127/1000 (Medical devices) 0.115/1000 (*in vitro* diagnostics and regenerative medical products)	0.231/1000 (Drugs excluding *in vitro* diagnostics) 0.143/1000 (Medical devices) 0.115/1000 (*In vitro* diagnostics, and regenerative medical products)

Note: Since the figures for contribution amount are rounded to the nearest million yen, the figures in "Total" may not equal the sum of the individual figures.

** The figures for FY 2014 represent the amount of contributions paid by MAHs of drugs (including in vitro diagnostics) and medical devices. The figures for FY 2015, 2016, 2017, and 2018 represent the amount of contributions paid by MAHs of drugs, medical devices, regenerative medical products, and in vitro diagnostics. The figures in brackets represent the number of MAHs.*

2.2.(6) Promotion of measures for reduction of unnecessary expenditures

- To steadily implement measures for Reinforcement of efforts to reduce unnecessary expenditures (formulated in FY 2014), PMDA promoted efforts for cost-cutting, along with “Standard practice for taking more efficient cost-cutting measures” (formulated in FY 2009).
- In FY 2018, PMDA made efforts to reduce the amount of paper printed by copiers. As a result, the amount and cost of paper was reduced by 12.5% and 9.7%, respectively, over FY 2017. PMDA also thoroughly reduced unnecessary expenditures by cutting various administrative expenses based on unified management of supplies.
- Also in FY 2018, PMDA implemented budget control measures by reducing expenditures to improve its overall balance sheet. To enhance its effectiveness, PMDA strived to implement the budget efficiently without waste under strict management. Further, by standardizing this implementation process, PMDA established a budget control system and reinforced its efforts to reduce unnecessary expenditures.

  In preparing the annual budget for FY 2019, PMDA reviewed service operations without granting a safe-harbor exception under the budget ceiling system as it has done in the previous fiscal year and make efforts to implement the budget efficiently without waste by further reducing the total budget.

  In addition, as a part of the Work-style reform project starting in June 2016, a scheme for turning a 3-step cycle involving reality check on operations, factor analysis, and actions was developed to promote an initiative to reduce overtime work.

2.3. Improvement of Services to the Public

2.3.(1) General inquiry service

- Based on the General Inquiry Guidelines that specify how to handle inquiries directed to PMDA and how to make use of comments and opinions to improve its operations, PMDA provides a general inquiry service and makes questionnaires available at the reception desk, enabling the collection of comments and opinions of visitors regarding its overall operations. In addition, PMDA receives opinions etc., via telephone, facsimile, and the PMDA website.
- Since June 2010, PMDA has gathered input from the public (Public Voices) and has disclosed them on the PMDA website at regular intervals. The input gathered is used to improve the agency’s operational management practices.
- In FY 2018, PMDA received 2,976 inquiries, of which 873 (approximately 30%) were related to applications and consultations for drugs, medical devices, etc.

	Inquiry	Complaint	Opinion/Request	Others	Total
FY 2018	2,966 (871)	5 (1)	5 (1)	0 (0)	2,976 (873)

Note 1: Figures in parentheses represent the number of cases related to consultations and applications for marketing approval of drugs, medical devices, etc. They are included in the total numbers shown in the upper row.

Note 2: The Office of Review Administration also accepts inquiries on consultations and applications for marketing approval of drugs, medical devices, etc., separately from this general inquiry service.

2.3.(2) Responses to inquiries, complaints, and claims of dissatisfaction from companies regarding product reviews and product safety operations

- In addition to responding to inquiries and complaints from general consumers, PMDA also addresses complaints from relevant companies regarding product reviews and product safety operations.
- In FY 2004, PMDA established a system where, if an applicant files a complaint or other claim regarding product reviews and product safety operations, the responsible office director (the Director of the Center for Product Evaluation or the Chief Safety Officer, if the second claim of dissatisfaction has been filed in the same case) is to directly conduct an investigation and respond to the applicant within 15 working days. After experiencing a number of subsequent large-scale organizational changes, PMDA is currently investigating for clarification of the contact point for whistle-blowing and review of the scheme compatible with the current status of the organization.
- In addition, PMDA is discussing a system to sincerely respond to complaints etc. from related companies in the “PMDA Proceeding Project.”

2.3.(3) Enrichment of the PMDA website

- PMDA has enhanced the content of its website. For example, new information and updates of existing content are sequentially posted on the PMDA website in order of requests from relevant departments. Further, the PMDA website has a table that lists notifications issued by the MHLW. The list includes only those relevant to the Agency’s operations or those that should be broadly disseminated to the public.
- PMDA completely redesigned its official website in March 2015 so that the public, healthcare professionals, stakeholders, etc. can easily access safety and efficacy information of pharmaceuticals and medical devices, and it continues working to enhance information provision in and outside of Japan. Of the most frequently visited pages for information search, e.g., package inserts (prescription drugs, medical devices, behind-the-counter (BTC) drugs, over-the-counter (OTC) drugs, and *in vitro* diagnostics), the pages for searching package inserts of prescription drugs have been renovated in FY 2018 to address the introduction of a new package insert format based on “Guidelines for Preparation of Package Inserts of Prescription Drugs” (to be implemented on April 1, 2019) and change in electronic data format for package insert data (from SGML to XML).
- Article 5 of the Act for Eliminating Discrimination against Persons with Disabilities (Act No. 65 of 2013) requires that the administrative organs, etc., must appropriately ensure reasonable accommodation to implement the elimination of social barriers. PMDA has posted its web accessibility policy on the PMDA website and preferentially renovated the most frequently accessed contents of this website (40 pages) to improve their accessibility.

2.3.(4) Proactive PR activities

- The PMDA Public Relations Strategic Plan (announced on July 11, 2008; revised on April 1, 2015) was developed with the aim of systematically promoting the Agency’s overall PR activities. In line with the Plan, PMDA intends to take a proactive approach to information provision through implementing PR activities anticipated to be useful to individual stakeholders and improve its services to the public. In FY 2018, the following activities were implemented in accordance with this Plan.

- In FY 2018, on the occasion of the “Drug and Health Week,” PMDA conducted PR activities for the general public by distributing brochures on relief systems, leaflets describing drug/medical device consultation services for consumers and give-away goods, etc., in cooperation with pharmaceutical associations and associations of OTC-drug counselors in 28 prefectures.
- In addition, PMDA revised brochures on its services to facilitate public understanding thereof, by, for example, using language as plain as possible in the text and providing more detailed explanations.
- PMDA introduced its operations to researchers and healthcare professionals by making booth exhibitions at academic conferences.
- PMDA also held a press meeting in January 2019 to introduce the PMDA’s roles and recent activities, including the Fourth Mid-term Plan (draft).
- PMDA issued an e-mail magazine to introduce PMDA’s operations to prospective employees. The Chief Executive delivered presentations and speeches as public relations activities in and outside Japan (15 times in Japan and 14 times overseas).

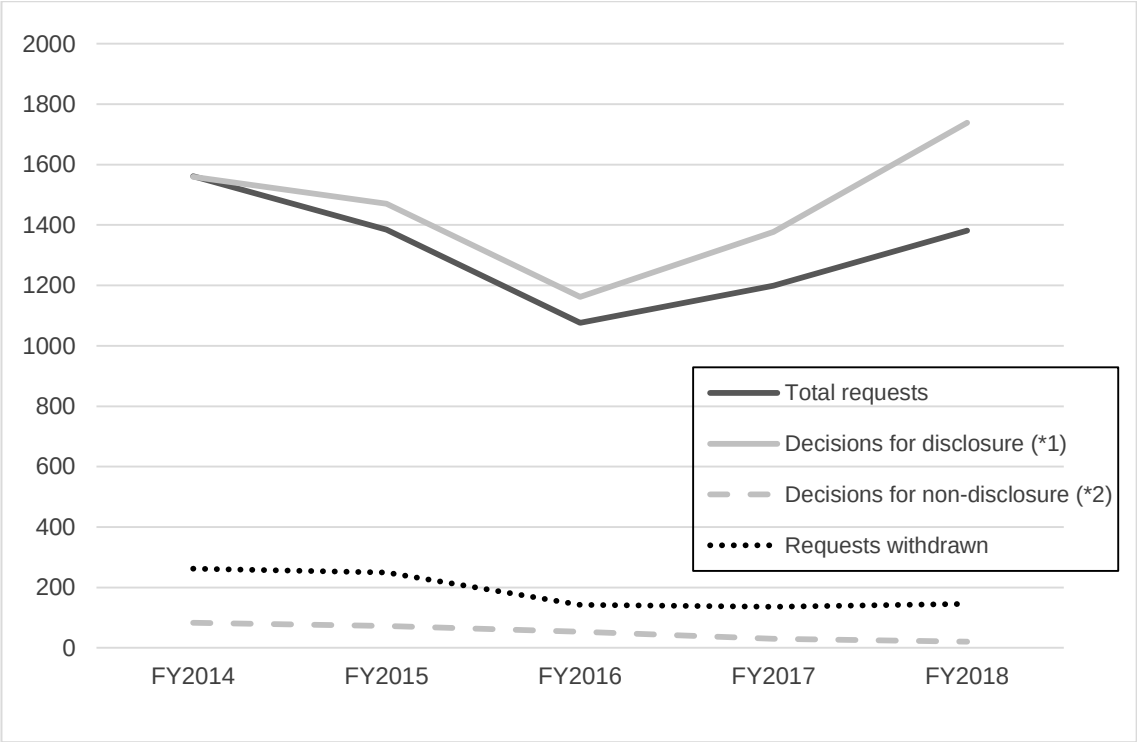
2.3.(5) Disclosure requests for internal agency documents

- The status of requests (over the last 5 years) for disclosure of documents under the Act on Access to Information Held by Independent Administrative Agencies is shown below. In FY 2018, the number of requests increased by 15.2% and the number of disclosures decided increased by 26.3% compared to FY 2017. PMDA appropriately processed requests in accordance with the relevant laws and regulations.

Number of Requests for Disclosure of Internal Agency Documents

	Total requests	Requests withdrawn	Decisions *					Requests for examination
			Full disclosure	Partial disclosure	Non-disclosure	Non-existing documents	Refusal to answer whether the document exists	
FY 2014	1,562	262	176	1,384	0	82	1	0
FY 2015	1,385	249	66	1,404	0	70	2	5
FY 2016	1,076	142	70	1,092	6	47	0	0
FY 2017	1,199	136	164	1,213	4	26	0	9
FY 2018	1,381	146	170	1,569	0	20	0	0

* *A single request does not necessarily receive a single decision for disclosure etc., but may receive multiple decisions on separate occasions. The figures show the number of decisions, not the number of requests.*



**1)* *The number of decisions for disclosure includes full and partial disclosure.*

**2)* *The number of decisions for non-disclosure includes cases of non-existing documents and refusals to answer whether the documents exist.*

Number of Requests for Disclosure of Agency Documents by Operational Category of Document

Operational category	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018	Examples
Review	1,457	1,295	990	1,087	1,174	Marketing notification for products not subject to approval, Notification of the results of GCP inspections
Post-marketing vigilance	97	82	70	109	207	ADR reports etc.
Others	8	8	16	3	0	
Total	1,562	1,385	1,076	1,199	1,381	

Note: The figures include requests withdrawn, requests rejected (decision for non-disclosure), requests for non-existing documents, or requests for which PMDA refused to answer whether the requested document exists.

2.3.(6) Disclosure requests for personal information

- The table shown below describes the status of requests for disclosure of personal information made within the previous five years as permitted under the Act on the Protection of Personal Information Held by Independent Administrative Agencies.

Number of Requests for Disclosure of Personal Information

	Total requests	Requests withdrawn	Decisions					Requests for examination
			Full disclosure	Partial disclosure	Non-disclosure	Non-existing documents	Refusal to answer whether the documents exist	
FY 2014	8	1	0	9	0	0	0	0
FY 2015	8	0	2	4	0	0	0	0
FY 2016	8	0	8	1	1	0	0	0
FY 2017	3	0	2	1	0	0	0	0
FY 2018	6	1	1	3	0	0	0	0

2.3.(7) Auditing

- PMDA undergoes audits conducted by an accounting auditor in accordance with the general rules for independent administrative agencies and by the Agency's auditors. PMDA also conducts internal auditing systematically through the Audit Office for operations and accounts, from the perspective of internal control. The results of these audits are publicly reported to ensure transparency in the Agency's management and operations.
- In FY 2018, PMDA conducted internal audits on the status of document management, inventory and asset management, cash and deposit management, commission of external experts, attendance management of all employees, disbursement of competitive research funds etc., as well as the status of compliance with restrictions on work assignments of personnel with prior experience in the private sector. The audit results were released on the PMDA website.

  PMDA also reported audit results on the status of compliance with restrictions on work assignments of personnel with prior experience in the private sector to the Advisory Council etc., and released meeting materials of the Council on its website.
- Based on the guidance document entitled "Thorough Document Management (Report)," PMDA conducted unannounced internal audits on the status of implementation of preventive measures to be implemented by individual offices in compliance with "Guidance on Thorough Document Management, etc.", and released audit results on the PMDA website.

2.3.(8) Report on financial standing

- To ensure the transparency of expenditures, PMDA disclosed its financial standing for FY 2017 (including the utilization of user fees and contributions) in government gazettes and on the PMDA website. PMDA also released its budget for FY 2018 on the PMDA website.

2.3.(9) Development and release of the Plan to Rationalize Procurement, etc.

- The Minister of Internal Affairs and Communications adopted a policy entitled, "Promotion of Rationalization of Procurements, etc. in Independent Administrative Agencies" on May 25, 2015. In accordance with this policy, the Committee for Discussions on Rationalization of Procurements, etc. developed the Plan to Rationalize Procurement, etc. by the Pharmaceuticals and Medical Devices Agency for FY 2018, as was also done during FY 2017. The purpose of this Plan is to streamline procurement processes autonomously and continuously through application of the "PDCA cycle" in view of the characteristics of the clerical and business operations, while ensuring fairness and transparency. The plan was posted on the PMDA website in June 2018.

2.4. Personnel Matters

2.4.(1) Personnel performance evaluation system

- According to the Mid-term Targets, PMDA is required to evaluate personnel fairly and consistently by taking factors related to the performance of individual employees into consideration. Moreover, in implementing the Third Mid-term Plan (FY 2014 to FY 2018), PMDA also intends to adjust its personnel performance evaluation system such that the results of performance evaluations and the attainment of individual goals are appropriately reflected in remuneration, pay raises, and promotions, to enhance employee morale.
- To this end, PMDA reflected the results of personnel performance evaluation during the period from April 2017 to March 2018 in pay raises etc., as of July 2018. In order to ensure the proper implementation of this personnel performance evaluation system, PMDA provided briefing sessions for all employees, and explained the “personnel performance evaluation system” to the new recruits as a subject of their training course.
- Interviews between secondary evaluators and evaluees are conducted, to familiarize evaluators with daily working conditions and to promote good communication and relationships between evaluators and evaluees (since FY 2013).
- PMDA is striving to develop a personnel performance evaluation system and an annual salary system that contributes to the development of excellent human resources who empathize with the “PMDA Philosophy” and to the growth of individual employees as well as maximization of organizational performance. In the course of efforts to achieve these goals, a new personnel performance evaluation system was launched first (enforced in April 2019).

  Appropriate performance evaluation can help increase the satisfaction of employees. PMDA therefore provided an evaluator training program aiming at “promotion of understanding of the outline of the evaluation system as well as basic concepts and methods of evaluation” as a part of evaluator education mainly targeting new managerial staff.

2.4.(2) Systematic implementation of staff training

- The science and technology of drug and medical device development are dynamic and advance at a rapid pace. As such, highly specialized and current expertise is necessary in the course of PMDA’s review, safety, and relief service operations.
- To improve the quality of operations, PMDA must systematically provide training opportunities tailored to the objectives of each specific operation geared towards not only technical staff but also administrative staff who support organizational management. PMDA’s staff training programming is divided into two courses:

  (1) The General Training Course, which consists of programs on staff duties, basic workplace knowledge, and various other topics (e.g., IT best practices and business etiquette) deemed necessary in light of the specialized nature of PMDA’s operations

  (2) The Specialized Training Course, which consists of programs focusing on development of expertise in the evaluation of quality, efficacy, and safety of drugs, medical devices, etc. as well as other more technical matters related to the products regulated by PMDA

  Commensurate with educational background and prior work experience, staff have the option to participate in both courses to aid in cultivating the knowledge and expertise needed for their work assignments. In FY 2018, staff participated in necessary programs in a planned manner, using a training system and chart that promote easier comprehension of the role of each training program.

In addition, to provide efficient and effective and role-specific training offerings, PMDA recruits the support of a variety of external organizations and subject matter experts, enriching training content and thereby improving staff capabilities. PMDA also encourages employees to participate in both domestic and overseas academic conferences and other similar events to improve their breadth of knowledge and technical expertise.

PMDA reviewed its training system for administrative staff in order to develop their management ability and necessary skills, with the expectation that these staff will support the foundation of PMDA, and clarified the persons and offices to be targeted by each training program. As a result, a 3-year training course was established for administrative staff, and 7 training sessions on regulatory affairs, agency management, financial management, etc., were held in FY 2018 as the first year of the training course.

- To conduct each training course, the Training and Academic Degree Acquisition Support Study Committee formulated plans in view of staff need. Implemented training programs are listed below. All training programs were reviewed by collecting opinions from attendees, directors of individual offices, or training proponents on later days according to the individual contents thereof. Each offering was generally highly praised with opinions that they were useful for business operations. PMDA reflected the results of program review to formulate training plans for FY 2019.

  1) General Training Course programs

     The implementation status of major general training course programs is shown in the table below ([Major Training Programs Implemented in FY 2018]). Major activities are as follows.

     - As in previous years, a lecture-based training program was provided by lecturers invited from patient advocacy groups, such as those related to patients suffering from adverse drug reactions (two sessions as part of the mental attitude training program for new staff and one session as part of the training program on adverse drug reactions).
     - As for new staff training sessions, attendees were required to score all lectures in terms of lecture contents and explicitness of slides, and feedback was then provided to lecturers with scores and rankings to improve the quality of training.
     - Training programs tailored to different job levels were provided. Executive directors delivered lectures to raise the staff motivation and awareness. Because prior educational training should be provided to staff who are expected to be promoted to managerial levels, PMDA provided a training session before the promotion to a managerial level, primarily to reform the awareness from players to managers.
     - PMDA provided a training program of good practice for writing scientific papers in English offered by in-house staff to enhance the motivation of all employees to learn English and raise their awareness of presentations.
     - PMDA provided two lecture-based training programs for risk management in addition to new staff training programs with a subsequent comprehension check (test) to further increase all executives/employees' awareness of legal and compliance obligations, including protection of personal and/or proprietary information.
       PMDA also provided a new training program on ethics as a part of new staff training and training programs tailored to different job levels in order to educate the employees about ethical obligations they must comply with.
       PMDA further provided a training program concerning compliance and insider trading for new staff. This training program was provided also in the form of video clips uploaded on the PMDA intranet so that any staff who has failed to attend the original lecture-based training session can attend the program session, as necessary, by accessing these video clips on-line.

2) Specialized Training Course programs

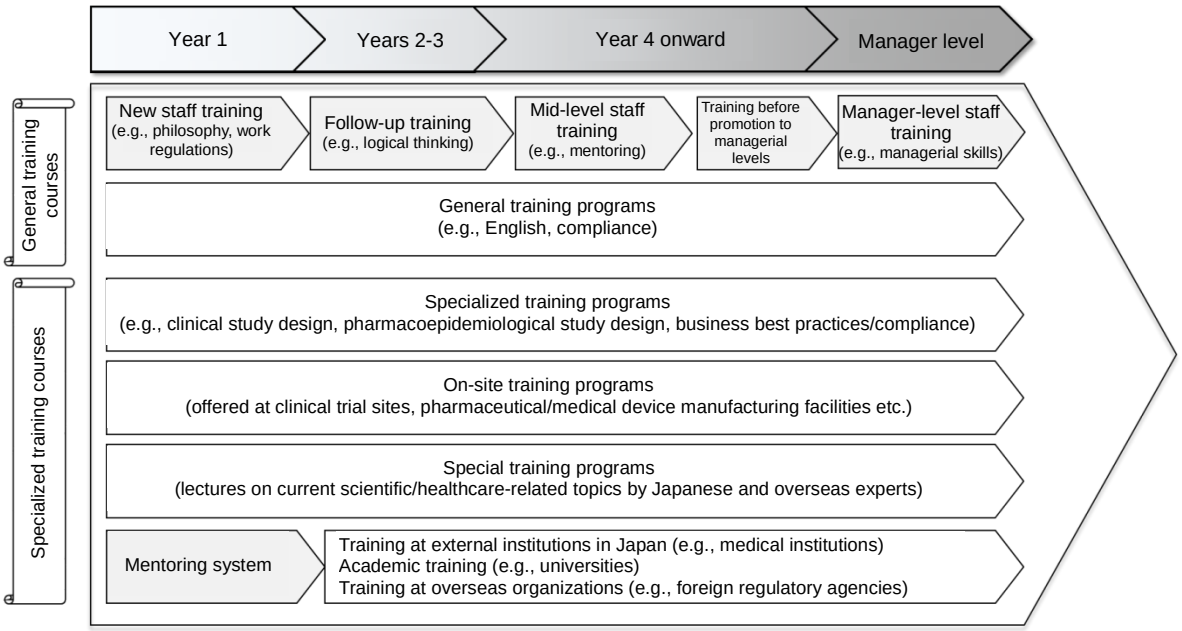
The implementation status of major specialized training course programs is shown in the table below. The major activities are as follows.

- PMDA provided a pharmacometrics expert training program to employees in charge of clinical pharmacology and ADME evaluations in the new drug review process. The purpose of this program is to improve the quality of review/consultation services by ensuring that those employees enhance their expertise by acquiring pharmacometrics-related knowledge and analysis techniques.
- PMDA designed and provided a visit-based training program focusing on institutional review board meetings and ethics committee meetings held at medical institutions concluding a comprehensive partnership agreement with PMDA. This program enables employees to sit in on an institutional review board or ethics committee meeting concerning clinical trials and clinical research conducted in medical institutions, thereby leading to further improvement of the quality of operations such as product review, consultation, and planning of safety measures.
- PMDA provided a training program for research ethics in line with the revised guidance document entitled “Ethical Guidelines for Medical and Health Research Involving Human Subjects.”
- PMDA provided a visit-based training program with focus on the study of clinical study management operations at medical institutions.
- PMDA provided a visit-based training program at GLP-compliant contract test facilities to ensure that its employees increase their expertise for improvement of the quality of operations such as review and assessment by learning the outlines of individual testing methods used in non-clinical studies (mainly GLP studies) required for regulatory submission for drugs, medical devices, etc., and by seeing the process of studies and operation of facilities first hand.
- PMDA provided a training program on medical writing for efficient preparation of review reports, etc., to improve the quality of documents prepared for its operations.

Major Training Programs Implemented in FY 2018

Training program title, etc.			Implementation (No. of sessions[Note)] etc.)
General Training Course	Training programs tailored to different job levels	New staff training	1 session (April to May 2018)
		Follow-up training	1 session
		Mid-level staff training	1 session
		Training before promotion to manager level	1 session
		Manager-level staff training (i.e., attitude of mind)	1 session
	General training programs	English language training program for employees scheduled to be dispatched overseas for a long period	2 employees
		Practical English training program for international conferences	17 employees
		English language training program (good practice for learning English etc.)	1 session
		Training in risk management	3 sessions (including 1 session as part of new staff training) * With subsequent comprehension check (test)
		Training on compliance and insider trading controls	1 session
		Training on adverse health effects (e.g., adverse drug reactions)	1 session
Specialized Training Course	Specialized training programs	Training in clinical study design	15 sessions
		Training in pharmacoepidemiology	11 sessions
		Training in CDISC* overview * CDISC: Clinical Data Interchange Standards Consortium	2 sessions
		Training in pharmacokinetics/clinical pharmacology and modeling & simulation training	4 sessions
		Training in research ethics	1 session
		Training on medical writing	1 session
		Training in ME technology	Type 1: 3 employees Type 2: 9 employees
		Regular course provided by the Pharmaceuticals Promotion Association	8 employees
		Training for accounting workers from government-related organizations at the Accounting Center of the Ministry of Finance	2 employees
	On-site training programs	Visits to pharmaceutical and medical device manufacturing sites (pharmaceutical manufacturing plants, medical device manufacturing plants, and nuclear medicinal facilities)	4 sessions (41 employees in total)
		Visits to see institutional review board meetings of medical institutions	5 sessions (25 employees in total)
		Visits to see ethics committee meetings of medical institutions	2 session (6 employees)
		Visits to study cancer chemotherapy in outpatient settings and operations of pharmacists	1 session (2 employees)
		Training to study medical device products	2 sessions (29 employees in total)
		Visits to see GLP-compliant contract test facilities	1 session (20 employees)
	Special training programs (lecturers on the latest topics pertaining to drug development/production, medical accident investigation system)		4 sessions
	Training at external institutions in Japan	Practical training for clinical engineers in hospitals	2 employees
		Visit-based training to learn clinical study management operations	5 employees
		Training in radiation technology	Beginner: 8 employees Intermediate: 1 employee Advanced: 1 employee
		Pharmacometrics expert training program	Beginner: 2 sessions (4 employees), Intermediate: 2 sessions (4 employees), Advanced: 1 session (3 employees)
		Training in hygiene control provided by the National Institute of Public Health	1 employee
		Seminars on pharmacoepidemiology provided by the Union of Japanese Scientists and Engineers	3 employees

Note: If identical training sessions took place on several occasions, the sessions are counted as 1 session.



Note: Training courses indicated in color are mandatory for all eligible employees.

2.4.(3) Support of acquisition of an academic degree

- The Career Development Program (CDP) was established in October 2016 to strengthen the overall PMDA functions through systematic development of human resources, training provision, and personnel allocation. Based on the CDP, PMDA put in place a support system for technical staff to acquire a doctoral degree. In FY 2018, the users of this system included 6 employees for sabbatical leave etc., 3 employees for short-term dispatch training in Japan (other than medical skills acquisition), and 1 employee for training at academia. In addition, candidates for programs for FY 2019 were recruited and selected by the Training and Academic Degree Acquisition Support Study Committee (6 employees for sabbatical leave etc., 6 employees for short-term dispatch training in Japan [support of doctoral degree acquisition, including 3 employees concomitantly utilizing sabbatical leave etc.], 1 employee for training at academia).

2.4.(4) Appropriate allocation of personnel

- In order to secure the expertise of staff members, operational continuity, and the most effective and efficient use of limited resources, PMDA seeks to conduct appropriate personnel allocation practices in line with the basic policy of the Third Mid-term Plan.

  To achieve this target, PMDA deploys personnel while taking into consideration the knowledge and work experience of individual staff members. PMDA also conducts medium- and long-term rotation of personnel.

- As part of the CDP, PMDA created a new personnel rotation policy that further focused on the expertise of employees etc., to realize optimal human resource allocation so that individual employees could use their skills and abilities more effectively. Since FY 2017, personnel changes have been implemented in line with this policy.

- PMDA developed a new IT system that allows unified management of necessary personnel information and information sharing between employees and their superiors, to facilitate CDP-based development of human resources. The system was launched in FY 2017. Information contained in this system was effectively used to get the right people in the right place (personnel relocation).

2.4.(5) Open recruitment of human resources

- The recruitment of capable staff with appropriate professional expertise, with full consideration to PMDA's neutrality and impartiality, is an essential task to ensure the efficient and accurate execution of PMDA's review, vigilance, and relief service operations.
- In accordance with the Act for Partial Revision of the Pharmaceutical Affairs Act, which reflects the content of the Japan Revitalization Strategy, the Healthcare and Medical Strategy, and the final recommendations of the Committee for Investigation of Drug-induced Hepatitis Cases and Appropriate Regulatory Administration to Prevent Drug-induced Suffering, the Third Mid-term Plan specified that the number of executives and regular employees should reach 1,065 by the end of the effective period (end of FY 2018). PMDA is required to recruit capable persons in relevant areas, based on the recruitment plan for each job category. To this end, PMDA held information sessions on career opportunities, and conducted open recruitment of technical employees twice (and once for administrative employees) in FY 2018 by making use of its website as well as job information websites.

Employment through Open Recruitment (as of April 1, 2019)

1) Technical (specialist) employees (open recruitment conducted twice [once for those who start working on April 1, 2019])
   - Number of applicants 344
   - Number of persons employed 45
   - (Breakdown)
     - Those who start working in April 2019 30 employees
     - Those who start working by March 2018 3 employees
     - Those who start working in April 2020 (doctor's degree) 12 employees

2) Administrative regular staff members (open recruitment conducted once)
   - Number of applicants 116
   - Number of new hires 9
   - (Breakdown)
     - Those who start working in April 2019 7 employees
     - Those who start working by March 2018 2 employees

Open Recruitment of New Employees Who Start Working in April 2020 (Major Activities in FY 2018)

○ Information sessions on career opportunities

Technical employees: Six sessions in Tokyo and one session each in Osaka and Sendai (a total of 397 participants) in March 2019

Administrative employees: Two sessions in Tokyo and one session in Osaka (a total of 149 participants) in March 2019

○ Activities performed in collaboration with directors/employees

- Lectures at universities etc., and a business introduction during the lectures given by directors/employees
- Attendance in on-campus seminars at university, etc.
- Encouragement of alumni-student visit activities by young PMDA employees
- Attendance in joint seminars, etc. sponsored by job information websites
- Implementation of internship (February 2019)

○ Recruitment tools

- Brochures and posters for recruitment were sent out to approximately 400 institutions including medical schools of universities, medical institutions such as university hospitals, faculties of pharmaceutical science of universities, pharmacy departments of hospitals, faculties relevant to biostatistics and veterinary science, and research institutions. Also, the brochures were distributed at recruitment information sessions etc.

○ Information posted on online job boards, etc.

- Websites presenting job offers for new graduates (*My Navi 2020* and *Rikunavi 2020*)
- Posting of recruitment advertisements on joint job recruitment systems for universities, etc. such as *Career+ UC* and *Kyujin-uketsuke NAVI*

- Staff were recruited as needed in 9 job categories: Toxicology, IT systems, clinical medicine, biostatistics, epidemiology, clinical pharmacology/pharmacokinetics, GLP, GMP, and QMS. As a result, 11 individuals were employed on an as-needed basis.

Numbers of Executives and Regular Staff

	April 1, 2004	April 1, 2009	April 1, 2014	April 1, 2015	April 1, 2016	April 1, 2017	April 1, 2018	April 1, 2019	The target number of regular staff at the end of the effective period of Third Mid-term Plan (end of March 2018)
Total	256	521	753	820	873	906	915	936	1,065
Review Department	154	350	492	532	560	578	575	561	
Safety Department	29	82	152	165	185	190	198	224	
Relief Department	18	32	33	36	37	39	39	39	

Note 1: The "Total" includes 6 executives (including 1 part-time auditor).
However, the number of executives is 5 as of April 1, 2014.

Note 2: The Review Department consists of Director of Center for Product Evaluation, Director of Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs, Associate Executive Directors or Associate Center Directors (excluding the ones responsible for Office of Planning and Operation, for Office of Information Technology Promotion, for Office of Research Promotion, and for Offices of Manufacturing Quality), Office of International Programs, Office of International Cooperation, Office of Advanced Evaluation with Electronic Data, International Coordination/Liaison Officers, Office of Review Administration, Office of Review Management, Coordination Officer for Review of Breakthrough Products (SAKIGAKE), Coordination Officer for Pharmaceutical Affairs Consultations on R&D, Coordination Officer for Practical Application of Innovation Advancements, Offices of New Drugs I to V, Drug Re-examination Coordination Officer, Office of Cellular and Tissue-based Products, Office of Vaccines and Blood Products, Office of OTC/Quasi-Drugs, Office of Generic Drugs, Offices of Medical Devices I and II, Office of Standards and Compliance for Medical Devices (other than Division of Registered Certification Body Assessment), Office of In Vitro Diagnostics, Office of Non-clinical and Clinical Compliance, Chief of Kansai Branch, Consultation Division of Kansai Branch, Principal Senior Scientists, Senior Scientists, and International Senior Training Coordinator, and International Training Coordinator.

Note 3: The Safety Department consists of the Chief Safety Officer, Associate Executive Director or Senior Director (responsible for Offices of Manufacturing Quality), Office of Medical Informatics and Epidemiology, Office of Standards and Compliance for Medical Devices (Division of Registered Certification Body Assessment only), Office of Informatics and Management for Safety, Offices of Pharmacovigilance I and II, Office of Manufacturing Quality for Drugs, Office of Manufacturing Quality and Vigilance for Medical Devices, Inspection Division of Kansai Branch, and Senior Scientists.

2.4.(6) Appropriate personnel management based on employment regulations

- PMDA strives to carefully manage its personnel even more appropriately than ever in order to mitigate any suspicion of impropriety or inappropriate interactions with the private sector. PMDA accomplishes this by imposing certain restrictions on recruitment and allocation of executives and employees as well as on employment by the private sector after resignation from PMDA. In May 2018, PMDA amended its work regulations for employees to extend the scope of executive directors to be obligated to report re-employment after resignation.

- For this purpose, PMDA's employment regulations specify submission of a signed pledge by new hires for compliance with employment regulations, staff allocation policy, policy concerning restrictions on employment by the private sector after resignation, restrictions on work assignment to staff with family members employed in a related industry, and other rules. PMDA conducts appropriate personnel management by creating a staff handbook that provides a summary of

related regulations, Q&A, and other information, posting the information on the PMDA intranet, and familiarizing staff members on the occasions of new staff training.

- PMDA also mandates that applicable employees submit reports concerning actual and potential conflicts of interest as well as any donations or financial support received under its staff code of ethics to ensure appropriate management of conflicts of interest.
- PMDA has maintained mechanisms for the effective prevention and smooth resolution of workplace bullying and harassment-related incidents. These mechanisms include the placement of a staff counselor in each office based on the regulations and manuals related to the prevention of harassment.

2.4.(7) Compensation policy optimization

- PMDA compared its personnel compensation system for FY 2017 with that for national government employees in order to facilitate public understanding of its compensation levels, and released the results on the PMDA website.
- PMDA should determine its compensation levels considering those for national government employees and private business employees. Accordingly, in reference to the recommendations of the National Personnel Authority in FY 2018, PMDA narrowed disparities in compensation levels between PMDA and the private sector.

2.4.(8) Development of a better workplace

- To promote work-life balance, PMDA engaged in tasks to reduce overtime and introduced a flexible working hour system as a part of the Work-style Reform initiatives on May 1, 2018. Further, the Telework Extension Project Team has been investigating the possibility of extension of the scope of telework jobs, and developing approaches to the realization of streamlined operations and a diversified work-style, leading to a better work-life balance.
- The average monthly overtime hours per non-managerial employee were 28 hours in FY 2013, 27 hours in FY 2014, 26 hours in FY 2015, 20 hours in FY 2016, and 17 hours in FY 2017. The overtime hours have been around 20 hours since PMDA started the Work-Style Reform project in June 2016. In FY 2018, PMDA continued to make efforts to achieve the following targets:

  (1) To be achieved by September 2018:
  No employees (including managerial-level staff) work in the office after 22:00 for ≥10 days per month.
  To be achieved by March 2019:
  No employees work in the office after 22:00.

  (2) To be achieved in FY 2018:
  Not more than 24 non-managerial employees work ≥45 hours overtime per month (monthly average).

- To create a better work environment, and as part of the Work-style Reform initiatives, PMDA undertook office layout change to revitalize staff communications and to make business operations more efficient.
- Starting in April 2017, PMDA continued the activities of the “Work-Life Balance Promotion Committee” operated by committee members chosen by the in-house staff recruitment system (17 members) to discuss activities to promote the work-life balance of the employees (12 meetings held in FY 2018).

The “Flexible Working Hours System” was proposed by the Work-Life Balance Promotion Committee in 2015. The Committee made recommendations on how to design the system in FY 2017, contributing to its implementation in May 2018. The Committee then started operation of an “Opinion Box” to widely accept proposals for improving staff’s business operations. This successfully improved practical operations.

Furthermore, to enhance communication levels between employees, the Committee held events planned mainly by committee members, and prepared a new manual entitled “Good Practices for Adding Comments on Documentation and Handout Materials” to ensure that all employees are familiar with it together with the pre-existing manuals, i.e., the “Guide to e-mailing,” “Guide to Meeting Arrangement and Operation/Checklist,” “Checklist for Communication,” “Checklist for Handover of Business Operations,” etc.

2.4.(9) Development of the System to Secure Diversified Human Resources

- To secure diversified human resources, PMDA established a system that allows its employees and the employees of other organizations to implement PMDA’s operations and operations of other organizations as persons authorized to work in both positions (Cross-appointment System) based on agreements with these organizations. In FY 2018, PMDA accepted one person from another organization utilizing this system.

2.5. Ensuring Security

2.5.(1) Entry/exit access control

- To ensure security and protect confidential information, PMDA has installed a door access control system for each office to reinforce internal security.
- Specifically, the ID card based-”access control system” installed at each office can log every entry through designated doors and prevent non-staff from freely entering.

  In May 2010, to reinforce security, PMDA designated restricted floors in its office locations that cannot be accessed by elevators unless the passengers (PMDA executives and employees, etc.) have appropriate ID cards. In June 2017, PMDA introduced a system that did not allow employees to access other offices than their own on holidays. In May 2018, PMDA prohibited tailgating and ensured that staff attend the entry of outside vendors, etc.
- PMDA has taken all reasonable efforts to thoroughly inform its staff of the office access restrictions through the PMDA intranet and new staff training programming.

2.5.(2) IT security measures

- In accordance with its FY 2018 plan, PMDA has been striving to maintain and improve the security of its IT systems and is operating a security management service, introduced in FY 2016. System configurations were modified and updated in response to the results of IT audits and guidance information provided by the National Center for Incident Readiness and Cybersecurity Strategy (NISC).
- In addition, PMDA ensured that related staff received cautionary advice (information on suspicious mail) from NISC provided by MHLW, and implemented security measures as necessary.
- Based on the “Common Standards for Information Security Measures for Government Agencies and Related Agencies” (2018 version) revised in 2018, PMDA worked on revision of the PMDA

Information Security Policy, and implemented IT security audits and provided IT security training programs according to the revised Security Policy.

- PMDA has recorded and stored data backups for its IT systems at remote locations since FY 2007.
- In conjunction with its expanded use of secure e-mail services for audio transcription and recording activities during industry consultation sessions, PMDA has taken steps to further strengthen its “Electronic certificate issuance service for PMDA secure E-mail IDs” network security protocol, which was first implemented in January 2016. This service maintained stable functionality in FY 2018.

Numbers of Users/Issued Certificates within the Secure E-mail System

	Number of registered companies	Certificates issued
Outside PMDA	9	44
Within PMDA		95

Note: The numbers of registered companies and certificates issued as of the end of FY 2018

PART 3 Improvements in Operational Management and Quality of Services Offered by Each Division

3.1. Relief Services for Adverse Health Effects

PMDA, as part of its relief services, conducts various activities (1) to provide adequate and swift relief to victims of adverse health effects caused by drugs and regenerative medical products and infections resulting from use of biologics and regenerative medical products; and (2) to ensure public awareness of the Relief System for Sufferers from Adverse Drug Reactions and the Relief System for Infections Acquired through Biological Products (collectively, the Relief System). These activities are detailed below.

3.1.(1) Expansion and review of dissemination of information regarding the Relief System

3.1.(1).(i) Disclosure of information (e.g., cases concluding in disbursement) on the PMDA website

- PMDA promptly discloses the results of reviews of claims for relief benefits while exercising due care with respect to the protection of claimants' personal information. Every month, claims approved or rejected during the previous month are posted on the PMDA website.

  When posted on the PMDA website, information on claims approved or rejected is also publicized through the "PMDA Medi-Navi," PMDA's free E-mail notification service.

- The PMDA website contains a trial web page entitled "Patient Reports of Adverse Drug Reactions." The purpose of the web page is to improve safety measures for drugs, by identifying trends in occurrence of adverse drug reactions. The web page has a link to the "Relief System for Adverse Health Effects" web page.

3.1.(1).(ii) Improvement of PR materials, etc.

- In order to deepen public understanding of the Relief System and promptly offer relief benefits, PMDA has made the following efforts:

  a) The leaflet on the Relief System features either of the following taglines: For patients, "Remember this system whenever you take medicine." For healthcare professionals, "A system that all healthcare professionals should be familiar with." In addition, the back of the leaflet provides answers to basic questions about the Relief System in a Q&A format. This helps readers who pick up the leaflet to understand the outline of the Relief System.

     Further, the design of the leaflet was improved to highlight the name of the system by increasing its visual impact, by using a *Mincho* font across 3 columns, and by displaying in red the Japanese characters meaning "sufferers from adverse reactions" in the middle column.

     In addition, the poster for the Relief System with the same design (in PDF format) is available on the PMDA website for users' convenience.

  b) PMDA has been making efforts to inform the general public that claim forms can be downloaded from the PMDA website. PMDA provides instructions on how to fill out the forms of various medical certificates on the PMDA website, for the greater convenience of claimants, physicians, etc. In FY 2018, these instructions were also introduced at such events as lectures for healthcare professionals.

◆Claim forms (Japanese only) can be downloaded from: http://search.pmda.go.jp/fukusayo_dl/

3.1.(2) Proactive PR activities of the Relief System

PMDA implemented the following activities for proactive and efficient PR for the Relief System.

Major activities conducted in FY 2018

(i) As a PR campaign on TV, 15-second and 30-second commercials were aired through 39 nationwide TV stations, including *Nippon Television network, TBS network, Fuji Television network, TV Asahi network,* and *TV Tokyo network*, to familiarize the general public with the Relief System. The commercials appeared during the "Drugs and Health Weeks" (for 2 weeks from October 17-30, 2018). Also, 30- to 60-second publicity infomercials (spot commercials) were run through 37 nationwide TV stations.

The TV commercial videos are available on a special promotional website featuring an original mascot character "Doctor Q" of the PMDA website.

Commercial videos for download are available on the members' only page on the official website of the Japan Pharmaceutical Association, with its cooperation.

(ii) A 1/6 page monochrome advertisement was placed in the morning editions of 5 national newspapers (*Yomiuri Shimbun, Asahi Shimbun, Sankei Shimbun, Nikkei Shimbun,* and *Mainichi Shimbun*) on October 17, 2018.

(iii) The following PMDA advertisements have been placed on the Internet:

- Banner advertisements were distributed through major portal sites including Yahoo! News as well as newspapers and magazines.
- Commercial videos were distributed on "YouTube" during the period when the commercial videos were broadcast on TV.
- News videos featuring the Relief System were produced separately for the general public and healthcare professionals and distributed on the special PMDA site as well as online services including "News TV Network" and "Twitter."

(iv) A 30-second commercial was shown on 1,785 TV monitors in 1,525 medical institutions/pharmacies nationwide during the period from November 1 to 30, 2018.

Other new activities introduced in FY 2018 included the following:

- Distribution of "still image commercials" using 1,094 TV monitors placed in 942 post offices located in areas where the number of claims per person is small (Aomori, Iwate, Tokushima, and Okinawa Prefectures) (October 17 to 30, 2018)
- Distribution of CM videos using ATMs placed in convenience stores national wide (October 17 to 30, 2018)
- Distribution of CM videos using TV monitors placed in 436 "SUSHIRO" sushi restaurants nationwide (October 17 to 30, 2018)
- Distribution of leaflets at pharmacies (by handing them over to patients with medicine envelopes) (November 1 to 20, 2018)

(v) For better penetration of the Relief System into the community of healthcare professionals, videos featuring this system were produced and provided to medical institutions, etc.

(vi) An advertisement was placed in 7 major medical publications during the month of October or November 2018 (one advertisement per newspaper etc.).

On-site activities

(i) Dispatching lecturers to employee training workshops held by medical institutions and other organizations

In order to encourage healthcare professionals to support the utilization of the Relief System and to foster public awareness, PMDA actively dispatches members of its staff to serve as lecturers at employee training courses organized by medical institutions or other organizations.

In FY 2018, in response to requests from medical and related institutions, PMDA dispatched staff to 34 medical institutions, 39 related organizations, etc., to explain the Relief System and provide examples of how some institutions effectively disseminate information regarding the Relief Systems. PMDA also sent PR materials to 118 medical institutions.

PMDA has been distributing the following questionnaires to medical institutions receiving lecture presentations from PMDA staff: (a) a questionnaire designed to identify the level of awareness about the Relief System and to collect comments and suggestions to help PMDA staff improve their lectures (administered immediately after training sessions); and (b) a questionnaire to learn how medical institutions have changed their attitudes and systems after receiving the training sessions (administered 3 months after training sessions).

(ii) Lectures delivered at training sessions for designated mental health doctors

PMDA gave lectures and distributed information materials on the Relief System and the proper use of antipsychotic drugs at 11 training sessions for designated mental health doctors (for new doctors and for those renewing their certification) held in 3 prefectures (Tokyo, Osaka, and Fukuoka).

(iii) Academic conferences

PMDA carried out PR activities by distributing its leaflets etc. at the Japan College of Rheumatology, Annual Meeting of the Japanese Dermatological Association, Annual Meeting of the Japanese Society of Nephrology, Annual Meeting of the Japanese Society of Psychiatry and Neurology, Annual Meeting of the Japanese Society for Cutaneous Immunology and Allergy, and Annual Meetings of the Japanese Society for AIDS Research.

(iv) Requests for cooperation to governmental entities, relevant organizations, etc.

PMDA informed 31 governmental entities and other relevant organizations of the current level of awareness of the Relief System, and requested their cooperation on PR-related activities.

(v) Others

PMDA distributed leaflets on the Relief System at the 20th Forum on Eradication of Drug-induced Suffering (sponsored by the Japan Federation of Drug-Induced Sufferers Organizations).

Others

(i) PMDA maintained a promotional website for the Relief System, featuring its original mascot character Doctor Q, on the PMDA website.

(ii) PMDA ran a PR campaign using a brochure aimed at healthcare professionals: “Know it better than anyone else and pass it on to other people: Relief System for Sufferers from Adverse Drug Reactions.”

The brochure in PDF format is available on the PMDA website.

(iii) PMDA updated its presentation slides entitled “What is the Relief System for Sufferers from Adverse Drug Reactions?” to accelerate the use of the slides in lectures, training sessions, etc., on the Relief System at universities and hospitals.

(iv) PMDA posted the following images of its public relations materials on the PMDA website: A poster for the Relief System to be displayed in pharmacies and a medicine envelope printed with information on the Relief System.

(v) PMDA published the "Summary of the Relief System for Sufferers from Adverse Drug Reactions and Request for Cooperation for the System" in the "Pharmaceuticals and Medical Devices Safety Information No. 357 (October 2018)."

(vi) With the cooperation of the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ), PMDA sent leaflets to pharmaceutical companies so that medical representatives could distribute them to doctors to promote their knowledge and understanding of the Relief System.

(vii) With the cooperation of the FPMAJ, PMDA published information on the Relief System in the FPMAJ's journal "Drug Safety Updates" and distributed the journal to medical institutions nationwide.

(viii) In collaboration with MHLW, PMDA included flyers concerning the Relief System with its brochures entitled, "Pharmaceuticals and Medical Devices Safety Information Reporting System." The posters included with the brochures were distributed to relevant organizations and other stakeholders.

(ix) Information on the Relief System was provided in a leaflet "Useful Information about Medicines" distributed during the "Drugs and Health Week." (The leaflet is published by MHLW and the Japan Pharmaceutical Association (JPA).)

(x) PMDA asked the JPA to retain the banner ad for the Relief System on the JPA's public-facing web page in order to raise awareness of the system.

(xi) PMDA surveyed the level of awareness of the Relief System among the general public and healthcare professionals to make PR activities more effective.

Survey period: December 21-28, 2018.

(xii) The claim forms for relief benefits were modified to gather information regarding how claimants knew the Relief System:

- In April 2016, all claim forms for relief benefits were modified to include a multiple-choice question asking claimants how they knew (or who informed them of) the Relief System, with the following options: "Physicians," "Dentists," "Pharmacists," "Other medical institution staff," "Newspaper, TV, etc.," and "Others." The most common answer in FY 2018 was "Physicians" (444 answers [30.5%]), followed by "Others (Internet)" (245 answers [16.8%]), "Newspaper/TV, etc." (140 answers [9.6%]), and "Pharmacists" (136 answers [9.3%]) (multiple answers allowed).
- In June 2014, the adverse drug reaction reporting form (which is sent from healthcare professionals to PMDA, as part of the Pharmaceuticals and Medical Devices Safety Information Reporting System) was modified to include a question asking healthcare professionals whether the patient involved will claim relief benefits for the adverse reaction concerned. In FY 2018, PMDA received 4,926 answers (multiple answers allowed): "The patient plans to claim benefits" (62 answers [1.3%]); "Already informed the patient of the Relief System" (166 answers [3.4%]); "The patient has no plan to claim benefits" (3,655 answers [74.2%]); "Not covered by the Relief System" (1,136 answers [23.1%]); and "Unknown/Others" (725 answers [14.7%]).

PMDA promotional website

Promotional website for the Relief System

http://www.pmda.go.jp/kenkouhigai_camp/index.html

TV commercial

Newspaper Ad: 1/6 Page monochrome advertisement placed in national newspapers (*Yomiuri Shimbun, Asahi Shimbun, Sankei Shimbun, Nikkei Shimbun, and Mainichi Shimbun*)

Promoting the Relief System through TV monitors placed in hospitals and pharmacies

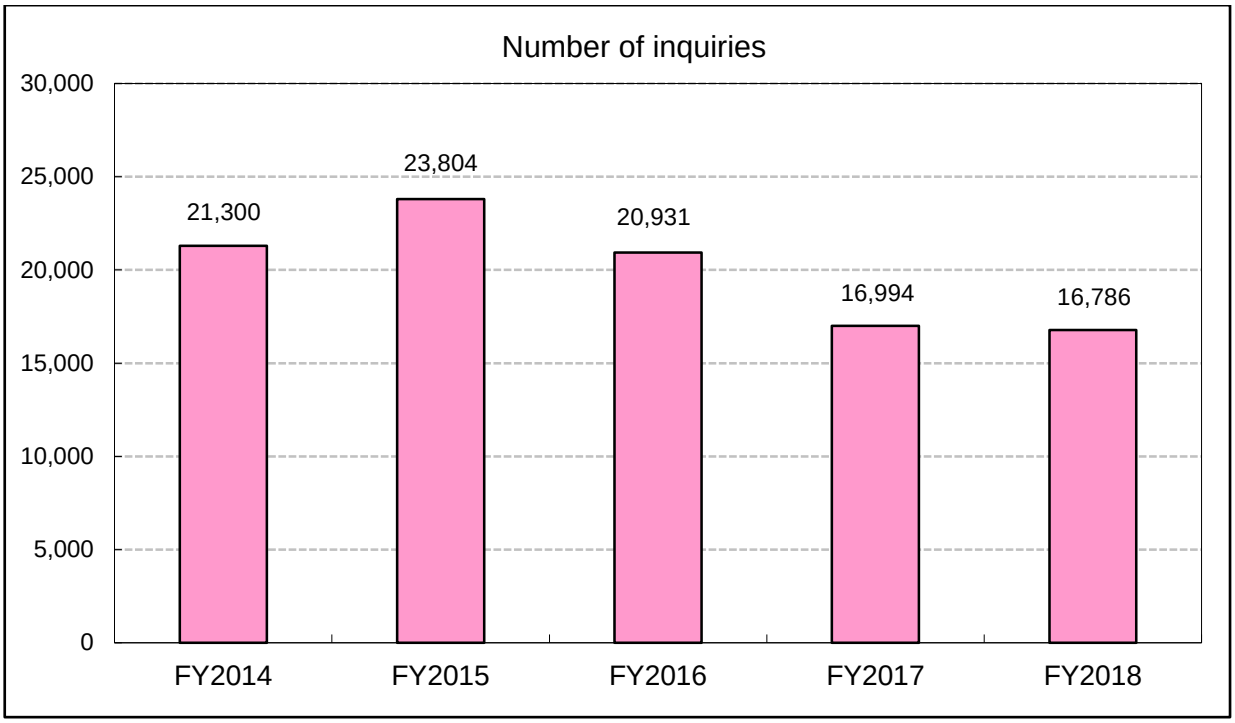
Promoting the Relief System through TV monitors placed in post office lobbies and displays on ATMs placed in convenience stores

Distribution of leaflets on the Relief System with drugs dispensed at pharmacies

3.1.(3) Maintaining efficient management of the inquiry service

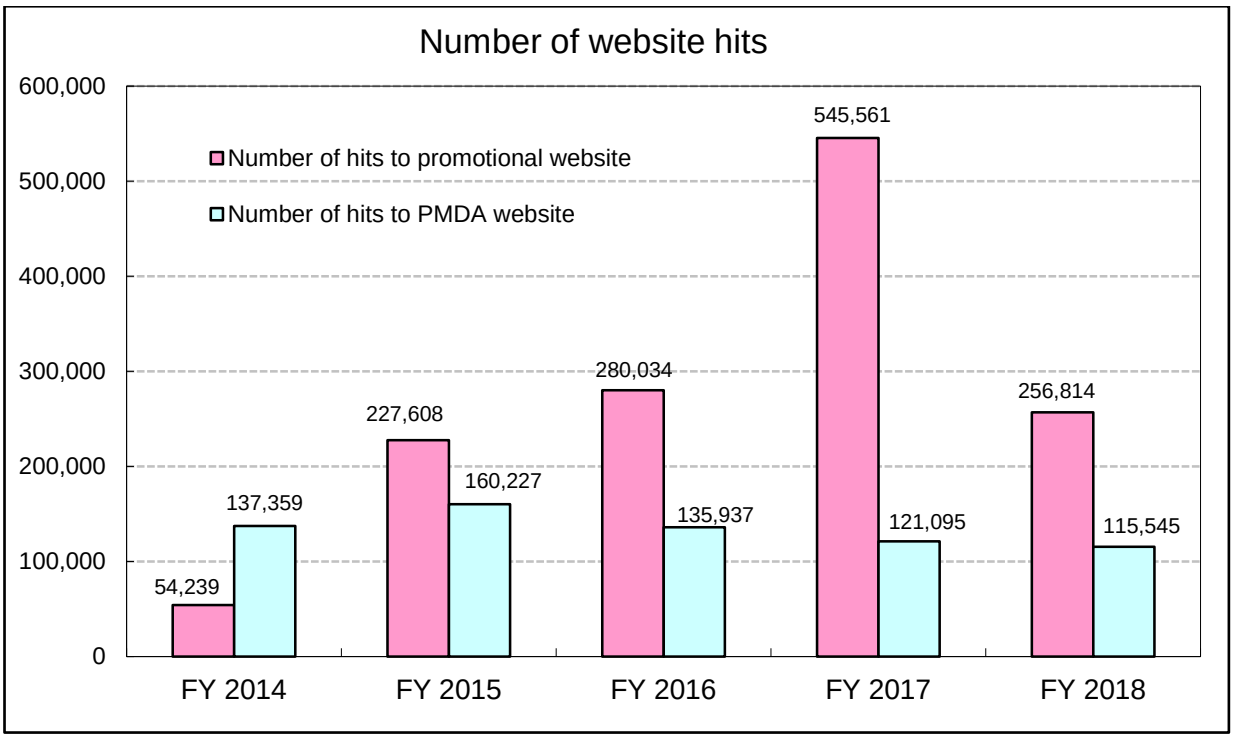
- In FY 2018, the Relief System Inquiry Service received 16,786 inquiries, which represents 98.8% versus FY 2017 (16,994 inquiries).

Fiscal year	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018	Versus FY 2017
Number of inquiries	21,300	23,804	20,931	16,994	16,786	98.8%



- In FY 2018, the PMDA website was accessed 115,545 times, which represents 95.4% versus FY 2017 (121,095 hits).
- The promotional website for the Relief System was accessed 256,814 times, which represents 47.1% versus FY 2017 (545,561 hits).

Fiscal year	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018	Versus FY 2017
Number of hits to PMDA website	137,359	160,227	135,937	121,095	115,545	95.4%
Number of hits to promotional website	54,239	227,608	280,034	545,561	256,814	47.1%



Relief System Inquiry Service

- ♦ Toll-free number: 0120-149-931
  (Office hours: Monday-Friday [excluding public holidays and the New Year's holidays] 9:00 -17:00)
- ♦ Relief System Inquiry Service E-mail address: kyufu@pmda.go.jp

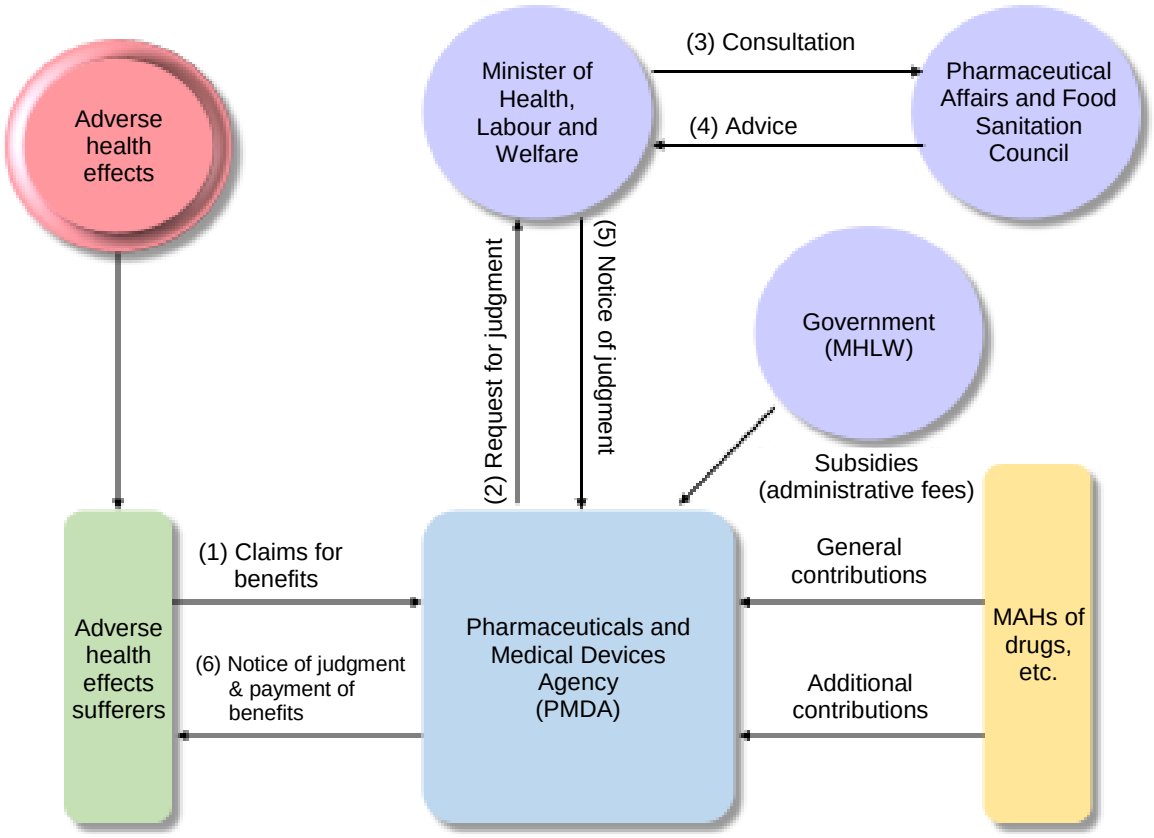
3.1.(4) Promotion of efficient database-backed services

- Information on relief benefit services for adverse reactions was stored in a database and used to expedite relief benefit services based on past cases.

3.1.(5) Promotion of expeditious administrative processing of relief benefit claims

- Upon receiving a claim for relief benefits, PMDA investigates and analyzes related facts and processes administrative paperwork (e.g., investigation of related facts, preparation of case narrative summaries and investigation reports). The agency then submits a request to the Minister of Health, Labour and Welfare to make a judgment on the medical and pharmaceutical matters associated with the claim. This process flow helps ensure that claimants receive relief benefits without delay.

Process Flow for Adverse Health Effect Relief Services



* Claimants who are not satisfied with the outcome of the judgment regarding their claim(s) for relief benefits may submit a request to the Minister of the MHLW to review the judgment.

- Although the number of claims is expected to increase, the Third Mid-term Plan specifies that at least 60% of claims should be judged (approved/rejected) within 6 months of filing. To achieve this target, in FY 2018, PMDA strove to process benefit claims received as quickly as possible, as in previous years.

  The number of claims submitted in FY 2018 decreased compared to the previous fiscal year, but exceeded the figure in the first year of the effective period of the Third Mid-term Plan (FY 2014). PMDA has processed many of these claims, as in previous years. Among 1,519 claims received in FY 2018, PMDA processed 998 claims, accounting for 65.7%, within 6 months of filing. The achievement rate exceeded the target level (60%).

  PMDA received 86 HPV-related claims in FY 2018 and processed 111 of the total claims ever received.

  The amount of benefits paid for claims reached a record high (approximately 2.353 billion yen).

HPV-associated claims

Fiscal year	FY 2010	FY 2011	FY 2012	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018	Total
Number of claims filed	2	10	7	25	39	152	334	141	86	796
Number of claims judged	0	5	9	8	4	75	314	223	111	749

3.1.(5).(i) Relief Service for adverse drug reactions

PMDA provides benefits to victims of diseases, disabilities, and deaths occurring on or after May 1, 1980 that were determined to have been the result of adverse reactions to drugs (and regenerative medical products on or after November 25, 2014) that were used appropriately. These benefits consist of medical expenses, medical allowances, disability pensions, pensions for raising handicapped children, bereaved family pensions, lump-sum benefits for bereaved families, and funeral expenses.

3.1.(5).(i).a. Performance of the Relief Service for adverse drug reactions

The performance for FY 2018 is shown below.

Fiscal year			FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Number of claims filed			1,412	1,566	1,843	1,491	1,419
Number of claims judged			1,400	1,510	1,754	1,607	1,519
		Approved	1,204	1,279	1,340	1,305	1,263
		Rejected	192	221	411	298	250
		Withdrawn	4	10	3	4	6
	Within 6 months	Number of claims	867	915	1182	1,113	998
		Achievement rate[*1]	61.9%	60.6%	67.4%	69.3%	65.7%
Claims in progress[*2]			922	978	1,067	951	851
Median processing time (months)			5.7	5.6	5.3	5.3	5.4

**1 The number of claims judged within 6 months of filing / The total number of claims judged in each fiscal year*

**2 The numbers of claims under review at the end of each fiscal year.*

3.1.(5).(i).b. Number of claims by type of benefit

The numbers of claims filed in FY 2018 by type of benefit are shown below.

Fiscal year		FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Number of claims filed		1,412	1,566	1,843	1,491	1,419
Types of benefit	Medical expenses	1,221	1,341	1,595	1,289	1,246
	Medical allowances	1,290	1,428	1,693	1,354	1,311
	Disability pensions	95	109	111	117	87
	Pensions for raising handicapped children	12	7	8	9	2
	Bereaved family pensions	41	37	56	46	33
	Lump-sum benefits for bereaved families	65	61	71	57	67
	Funeral expenses	103	100	128	102	101

Note: More than one type of benefits may be claimed within a single claim.

3.1.(5).(i).c. Approval by type of benefit

The number of approved claims and amounts of benefits paid in FY 2018 by type of benefit are shown below.

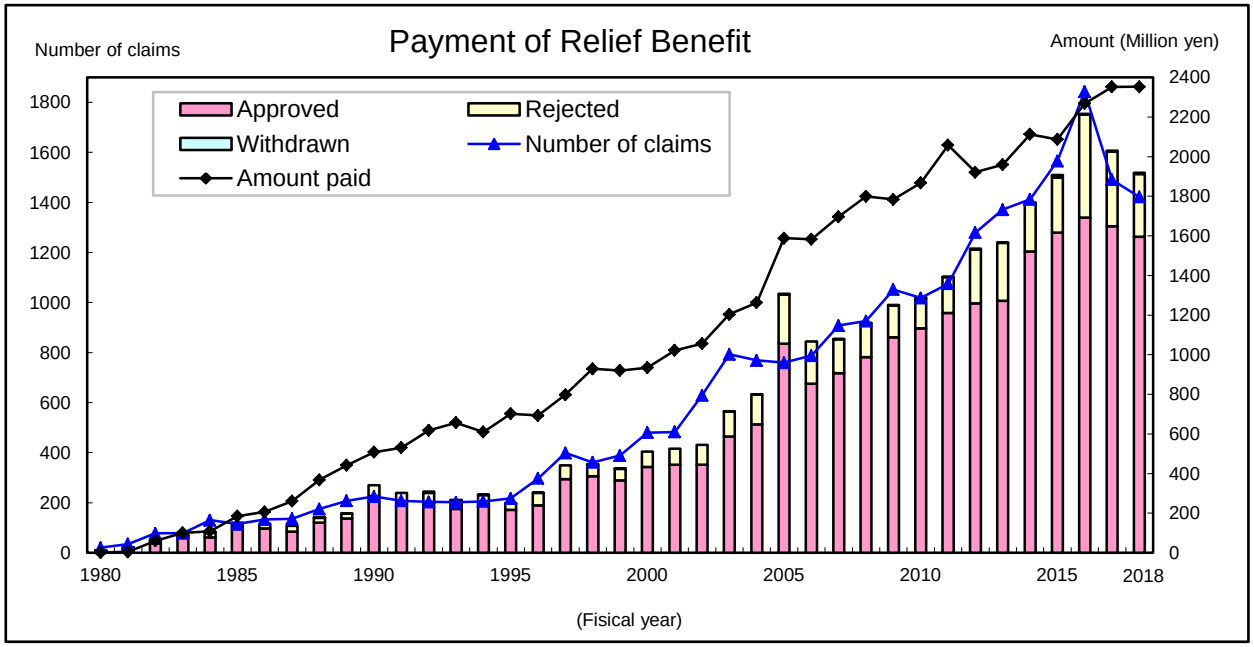
(Unit: Thousand yen)

Type	FY 2014		FY 2015		FY 2016	
	No. of claims	Amount paid	No. of claims	Amount paid	No. of claims	Amount paid
Medical expenses	1,108	123,987	1,146	118,235	1,190	136,997
Medical allowances	1,151	95,457	1,220	112,040	1,269	120,109
Disability pensions	37	943,939	47	1,002,305	53	1,082,599
Pensions for raising handicapped children	2	38,965	8	43,675	6	42,153
Bereaved family pensions	31	585,626	23	580,934	31	607,497
Lump-sum benefits for bereaved families	45	310,806	32	218,891	38	263,243
Funeral expenses	72	14,507	53	10,822	73	14,944
Total	2,446	2,113,286	2,529	2,086,902	2,660	2,267,542

Type	FY 2017		FY 2018	
	No. of claims	Amount paid	No. of claims	Amount paid
Medical expenses	1,178	118,173	1,156	117,788
Medical allowances	1,240	109,652	1,206	100,214
Disability pensions	45	1,156,881	35	1,194,996
Pensions for raising handicapped children	4	35,676	2	32,673
Bereaved family pensions	36	642,861	27	642,762
Lump-sum benefits for bereaved families	38	272,887	35	252,050
Funeral expenses	75	15,415	62	12,742
Total	2,616	2,351,545	2,523	2,353,225

Note 1: "No. of claims" is the number of approved claims. "Amount paid" is the amounts of benefits paid to both new and existing recipients.

Note 2: Since the amounts are rounded off to the nearest thousand yen, the figures in "Total" may not equal the sum of the individual figures.



3.1.(5).(i).d. Number of current status reports from pension recipients

In FY 2018, PMDA received 659 (624) current status reports from pension recipients: 400 (378) from those receiving disability pension, 34 (37) from those receiving pensions for raising handicapped children, and 225 (209) from those receiving bereaved family pension.

* The figures in parentheses represent the number of reports received in FY 2017.

3.1.(5).(ii) Relief service for infections acquired through biological products

PMDA provides benefits to victims of diseases, disabilities, or deaths occurring on or after April 1, 2004, due to infections caused by biological products (and regenerative medicine products on or after November 25, 2014) that were determined to have been used in accordance with their approved labeling and prescribing information. These benefits consist of medical expenses, medical allowances, disability pensions, pensions for raising handicapped children, bereaved family pensions, lump-sum benefits for bereaved families, and funeral expenses.

3.1.(5).(ii).a. Performance of relief service for infections

The performance for FY 2018 is shown below.

Fiscal year		FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Number of claims filed		3	6	1	3	7
Number of claims judged		7	2	5	2	7
	Approved	6	1	3	2	6
	Rejected	1	1	2	0	1
	Withdrawn	0	0	0	0	0
Claims in progress*1		1	5	1	2	2
Achievement rate*2		42.9%	50.0%	20.0%	50.0%	85.7%
Median processing time (months)		6.3	7.5	10.0	10.2	4.6

**1 Claims yet to be judged at the end of each fiscal year.*

**2 The number of claims judged within 6 months of filing / The total number of claims judged in each fiscal year*

3.1.(5).(ii).b. Number of claims by type of benefit

The numbers of claims filed in FY 2018 by type of benefit are shown below.

Fiscal year		FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Number of claims filed		3	6	1	3	7
Types of benefit	Medical expenses	2	5	1	1	7
	Medical allowances	3	5	1	2	7
	Disability pensions	0	0	0	0	0
	Pensions for raising handicapped children	0	0	0	1	0
	Bereaved family pensions	1	2	0	0	0
	Lump-sum benefits for bereaved families	1	0	0	0	1
	Funeral expenses	2	2	0	0	1

Note: More than one type of benefits may be claimed within a single claim.

3.1.(5).(ii).c. Approval by type of benefit

The number of approved claims and amounts of benefits paid in FY 2018 by type of benefit are shown below.

(Unit: Thousand yen)

Type	FY 2014		FY 2015		FY 2016		FY 2017		FY 2018	
	No. of claims	Amount paid	No. of claims	Amount paid	No. of claims	Amount paid	No. of claims	Amount paid	No. of claims	Amount paid
Medical expenses	5	336	1	0	3	92	2	339	5	155
Medical allowances	6	566	1	170	3	210	2	248	6	251
Disability pensions	–	–	–	–	–	–	–	–	–	–
Pensions for raising handicapped children	–	–	–	–	–	–	–	–	–	–
Bereaved family pensions	–	2,338	–	2,393	–	1,005	–	–	–	–
Lump-sum benefits for bereaved families	–	–	–	–	–	–	–	–	1	7,225
Funeral expenses	–	–	–	–	–	–	–	–	1	206
Total	11	3,239	2	2,563	6	1,306	4	587	13	7,838

Note: As benefit amounts are rounded to the nearest thousand yen, the figures in figures in "Total" may not equal the sum of the individual figures.

3.1.(6) Promotion of appropriate information communication through interoffice collaboration

- The Office of Relief Funds and the Offices of Pharmacovigilance conducted joint meetings approximately once a month to promote information sharing.
- The Office of Relief Funds periodically provides the following information to the Offices of Pharmacovigilance, after taking appropriate measures to protect personal information in order to ensure that this information can be reflected in safety measures in accordance with Article 68-10 of the PMD Act: Information on diseases, disorders, and/or death of persons who filed claims for relief benefits for adverse reactions and/or infections, and information on the decision on approval/rejection of claims.
- The Office of Relief Funds provides the Offices of Pharmacovigilance with detailed information concerning adverse reactions not listed in package inserts (unknown adverse reactions) and on adverse events that have been repeatedly reported despite warnings in package inserts.

- PMDA calls users' attention to the cases of drug-related health damage using information obtained from claims submitted for relief benefits with respect to adverse events that have occurred repeatedly despite precautions that were already provided in package inserts. Information concerning such cases is posted on PMDA's website (on a web page entitled "PMDA Request for Proper Use of Drugs"). This document provides healthcare professionals with simple and clear advice on how to use drugs safely in order to further promote the proper use of drugs.

  Reference: "PMDA Request for Proper Use of Drugs" is disseminated to healthcare professionals, etc. through the "PMDA Medi-Navi," the agency's E-mail notification service.

- The Office of Relief Funds and the Office of Informatics and Management for Safety work in tandem through their defined roles and responsibilities related to the "Relief System Inquiry Service" and "Drugs and Medical Devices Inquiry Service."

3.1.(7) Appropriate management of health and welfare services

- To provide more immediate relief from health damage due to adverse drug reactions, PMDA offers health and welfare services to victims of adverse health effects who require such services in addition to relief benefits. (These services are offered in accordance with the Act on the Pharmaceuticals and Medical Devices Agency.)

3.1.(7).(i) Investigative research to improve the quality of life of sufferers from serious and rare adverse health effects caused by drug products

PMDA established an Investigative Research Group for Improvements in the Quality of Life (QOL) of Sufferers from Serious and Rare Adverse Health Effects Caused by Drug Products in April 2006. The group launched an investigative research initiative to examine methods for offering necessary services and how to improve the QOL of victims of serious and rare adverse health effects who are unable to obtain adequate support from general assistance programs for disabled people. This research project was carried out based on the results of a survey on adverse health effects due to adverse drug reactions (March 2006).

In FY 2018, PMDA summarized the group's operating performance during FY 2017, prepared an investigative research report, and conducted investigative research targeting 67 individuals presenting with serious adverse health effects, including Stevens-Johnson syndrome, Reye's syndrome, and conditions similar to Reye's syndrome.

Research Method

Sufferers from adverse health effects were asked to provide detailed data on their daily living by completing a survey form. The data are analyzed and evaluated (67 volunteers at the end of FY 2018).

Research Group

Group Leader:	Atsushi Ozawa	Professor, Graduate School of Comprehensive Human Sciences, University of Tsukuba (Master's Program in Lifespan Developmental Science)
	Takao Takahashi	Professor, School of Medicine, Keio University (Department of Pediatrics)
	Kazuo Tsubota	Professor, School of Medicine, Keio University (Department of Ophthalmology)
	Chieko Matsunaga	Professor, School of Health and Welfare, International University of Health and Welfare

3.1.(7).(ii) Consultation services to address mental health problems etc.

The results of the survey on adverse health effects caused by adverse reactions to drug products indicated the necessity of care for persons presenting with deep mental trauma due to diseases and disabilities caused by adverse drug reactions, as well as the importance of consultation support for persons experiencing significant restrictions to their normal activities of daily living due to such adverse health effects. PMDA therefore held numerous discussions with support groups for adverse drug reaction sufferers and other organizations on how to offer support services to persons who have received benefits under the Relief System. Accordingly, PMDA initiated Consultation Services to Address Mental Problems etc. in January 2010.

Through these consultation services, social welfare experts provided advice on mental health care and on the use of welfare services to persons who are suffering from adverse health effects caused by adverse drug reactions or infections acquired through biological products (and their families). In FY 2018, 112 consultation sessions were held.

3.1.(7).(iii) Distribution of benefit recipient cards

In January 2010, PMDA began issuing wallet-sized certificate cards to recipients of adverse reaction relief benefits for their convenience at their request. The card displays specific information including the name of the drug(s) that were determined or suspected to have caused the adverse reaction to the card holder. In FY 2018, PMDA issued such certificates to 765 recipients.

3.1.(7).(iv) Investigative research concerning improvements to the QOL of patients with hepatitis C infection caused by treatment for congenital diseases

PMDA established an Investigative Research Group for Improvements in the QOL of Patients with Hepatitis C Infection Caused by Treatment for Congenital Diseases in August 2010. The group initiated research to study the actual living conditions of sufferers from infections acquired through biological products and thereby obtain information to examine how to improve the QOL of sufferers and provide necessary services to them.

In FY 2018, PMDA summarized the operating performance for FY 2017, prepared an investigative research report, and conducted research in 151 subjects.

Research Method

Among individuals with hepatitis C infection caused by treatment for congenital diseases, those with serious infections are asked to complete a survey form to provide detailed data on their daily living. The data are analyzed and evaluated (147 volunteers at the end of FY 2018).

Research Team

Group Leader:	Kugahisa Teshima	Former Professor, Graduate School of Social Service, Japan College of Social Work
	Namiki Izumi	Director, Musashino Hospital, Japanese Red Cross Society
	Midori Shima	Professor, Department of Pediatrics, Nara Medical University
	Akira Terashima	Advisor, Japanese Society for Rehabilitation of Persons with Disabilities

3.1.(8) Appropriate provision of healthcare allowances for patients with SMON and patients infected with HIV through contaminated blood products

- PMDA has been commissioned to provide healthcare allowances to patients with subacute myelo-optic neuropathy (SMON) and patients infected with human immunodeficiency virus (HIV) through contaminated blood products, giving due consideration to the confidentiality of personal information.

3.1.(8).(i) Services for patients with SMON (commissioned payment of healthcare allowances)

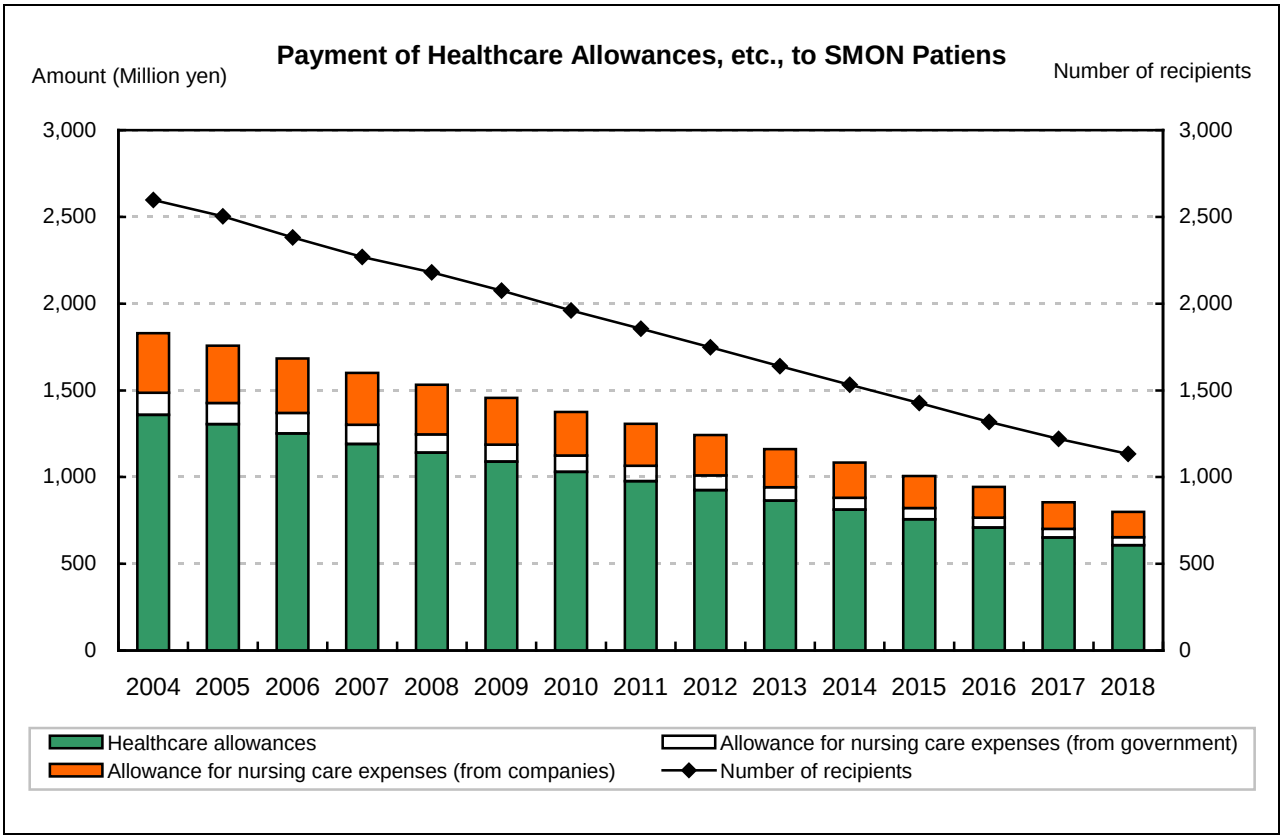
- PMDA provides healthcare allowances and nursing care expenses to patients with SMON for whom a settlement was reached in court. In FY 2018, a total of 800 million yen was paid to 1,134 patients.

  * SMON arising from use of quinoform products

  SMON is a disease caused by quinoform products (antiflatulents) that leads to numbness, ambulatory difficulties, visual disturbances, etc. According to the report provided by a research group, an estimated 10,000 individuals have been affected by SMON.

Fiscal year		FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Number of recipients		1,533	1,428	1,319	1,221	1,134
Amount paid (thousand yen)		1,082,992	1,006,135	942,828	855,351	799,692
Breakdown	Healthcare allowances	811,727	757,285	709,290	651,407	606,580
	Allowance for nursing care expenses (from companies)	201,919	185,319	176,639	154,037	146,219
	Allowance for nursing care expenses (from national government)	69,346	63,532	56,899	50,267	46,893

Note: As benefit amounts are rounded to the nearest thousand yen, the figures in "Amount paid" may not equal the sum of the individual figures in "Breakdown."



3.1.(8).(ii) HIV-related services (commissioned payment of healthcare allowances)

- PMDA provides the following three services for patients infected with HIV through blood products (services commissioned by the *Yu-ai* Welfare Foundation). In FY 2018, 496 HIV-positive patients received allowances under the investigative research, 120 patients with AIDS received allowances under the healthcare support service, and 3 patients with AIDS received special allowances. In total, 619 patients received allowances under the three services (503 million yen in total).

  a. Payment of healthcare allowances for HIV-positive patients without AIDS, as part of the investigative research
  b. Payment of healthcare allowances for patients with AIDS for whom a settlement has been reached in court, as the healthcare support service
  c. Payment of special allowances etc., for patients with AIDS for whom a settlement has not been reached in court

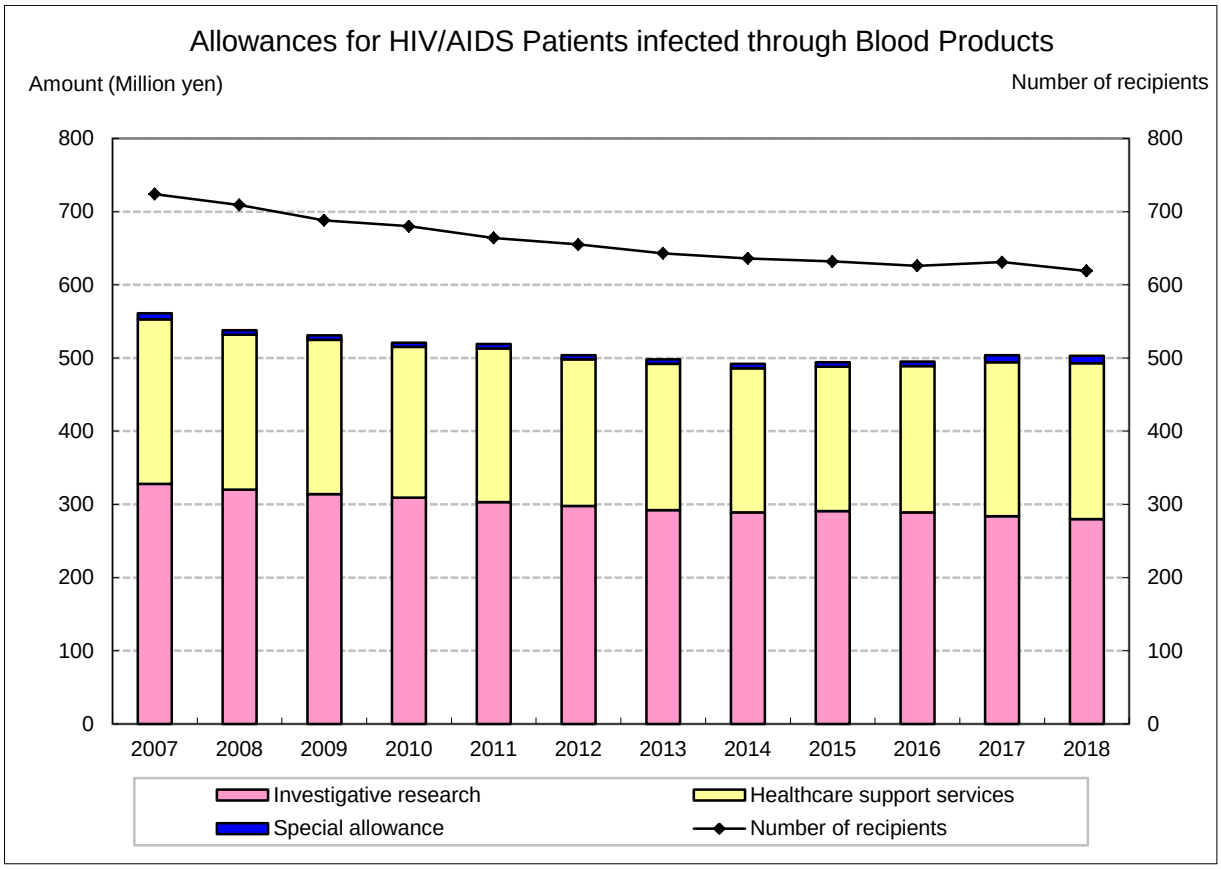
* HIV infection due to blood products

Patients with hemophilia, etc. were infected with HIV after receiving unheated blood coagulation-factor products manufactured from blood donated by people in the US.

Fiscal year	FY 2014		FY 2015		FY 2016	
	Number of recipients	Amount paid (thousand yen)	Number of recipients	Amount paid (thousand yen)	Number of recipients	Amount paid (thousand yen)
Investigative research	524	288,736	520	290,935	513	288,703
Healthcare support services	110	197,400	110	197,400	111	199,650
Special allowance	2	6,190	2	6,336	2	6,384
Total	636	492,325	632	494,671	626	494,737

Fiscal year	FY 2017		FY 2018	
	Number of recipients	Amount paid (thousand yen)	Number of recipients	Amount paid (thousand yen)
Investigative research	509	283,700	496	280,062
Healthcare support services	119	209,700	120	213,450
Special allowance	3	9,565	3	9,612
Total	631	502,965	619	503,124

Note: As benefit amounts are rounded to the nearest thousand yen, the figures in in "Amount paid" may not equal the sum of the individual figures.



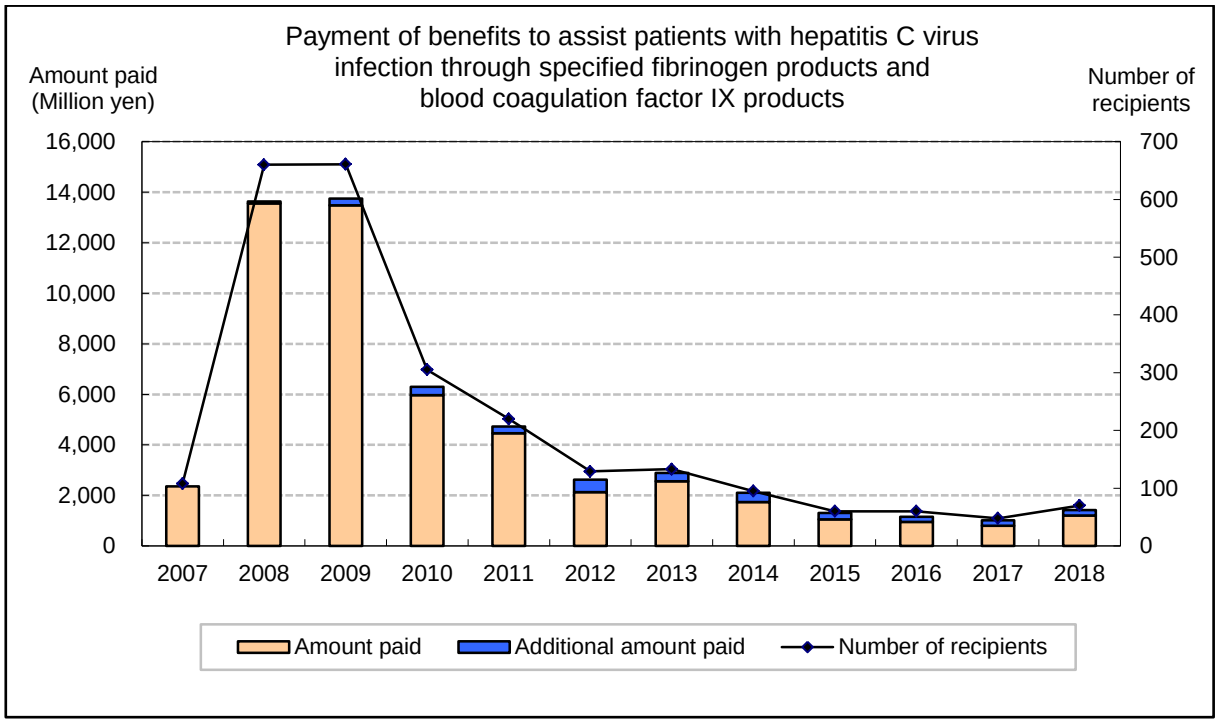
3.1.(9) Appropriate provision of benefits to individuals infected with hepatitis C through specified fibrinogen products and specified blood coagulation factor IX products

- Starting on January 16, 2008, PMDA has provided benefits to individuals infected with hepatitis C virus through specified fibrinogen products, in accordance with the Act on Special Measures concerning the Payment of Benefits to Relieve Patients with Hepatitis C Infection through Specified Fibrinogen Products and Specified Blood Coagulation Factor IX Products.* In FY 2018, 70 patients received benefits (of whom, 12 patients received additional benefits), and the total amount of benefits paid was 1.416 billion yen (of them, the amount of additional benefits was approximately 0.216 billion yen).

  * A revised Act went into effect on December 15, 2017, and thereby the time frame for claiming benefits was extended by 5 years (Until January 16, 2023).

	FY 2009	FY 2010	FY 2011	FY 2012	FY 2013
Number of recipients	661	305	220	129	133
(Number of these recipients receiving additional payment)	(22)	(20)	(20)	(28)	(18)
Amount paid (thousand yen)	13,748,000	6,293,000	4,732,000	2,624,000	2,888,000
(Amount of additional payment)	(272,000)	(324,000)	(268,000)	(488,000)	(332,000)
Number of inquiries	894	1,286	674	982	473

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Number of recipients	95	60	60	48	70
(Number of these recipients receiving additional payment)	(20)	(14)	(14)	(13)	(12)
Amount paid (thousand yen)	2,100,000	1,308,000	1,156,000	1,020,000	1,416,000
(Amount of additional payment)	(368,000)	(252,000)	(208,000)	(224,000)	(216,000)
Number of inquiries	660	834	1,087	2,508	1,189



3.2. Reviews and Related Services

Based on the Japan Revitalization Strategy (adopted by the Cabinet on June 14, 2013), Healthcare and Medical Strategy (adopted by the Cabinet on July 22, 2014), 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), and the Act on the Safety of Regenerative Medicine, PMDA made every effort to accelerate the review process, achieve "zero" review lag*, and upgrade the quality of reviews by evaluating drugs, medical devices, and regenerative medical products according to their respective characteristics; and to support the elimination of development lag* by providing Regulatory Science General Consultation and Regulatory Science Strategy Consultation (R&D); and to promote first-in-the-world practical application of innovative medical products through the SAKIGAKE designation system. Detailed activities are described sections below.

*Drug lag and device lag are roughly classified into two types of lag: "Review lag," caused by the difference in the review time (from submission to approval of marketing applications) between the US and Japan; and "development lag," caused by the difference in timing which medical companies submit marketing applications to regulatory agencies in the US and Japan (quoted from the Japan Revitalization Strategy). Resolution of the issues associated with review lag and development lag will lead to the overall elimination of lag during the approval process.

The Science Board was established in May 2012 as a committee that is independent of the PMDA's operations. The Science Board discusses the scientific aspects of reviews of drugs, medical devices, and regenerative medical products to provide advice that assists PMDA in more appropriately evaluating products employing advanced technologies. In FY 2018, PMDA continuously utilized the Science Board to improve the quality of its operations ranging from reviews/consultations to post-marketing safety measures, taking the practical application of advanced technology into account.

3.2.(1) Accelerated access to drugs and medical devices

3.2.(1).A. New drugs

- Various measures were implemented or reviewed with the aim of accelerating reviews and improving the quality of reviews, based on the Japanese government's policy documents including the "Japan Revitalization Strategy" and the "Healthcare and Medical Strategy."

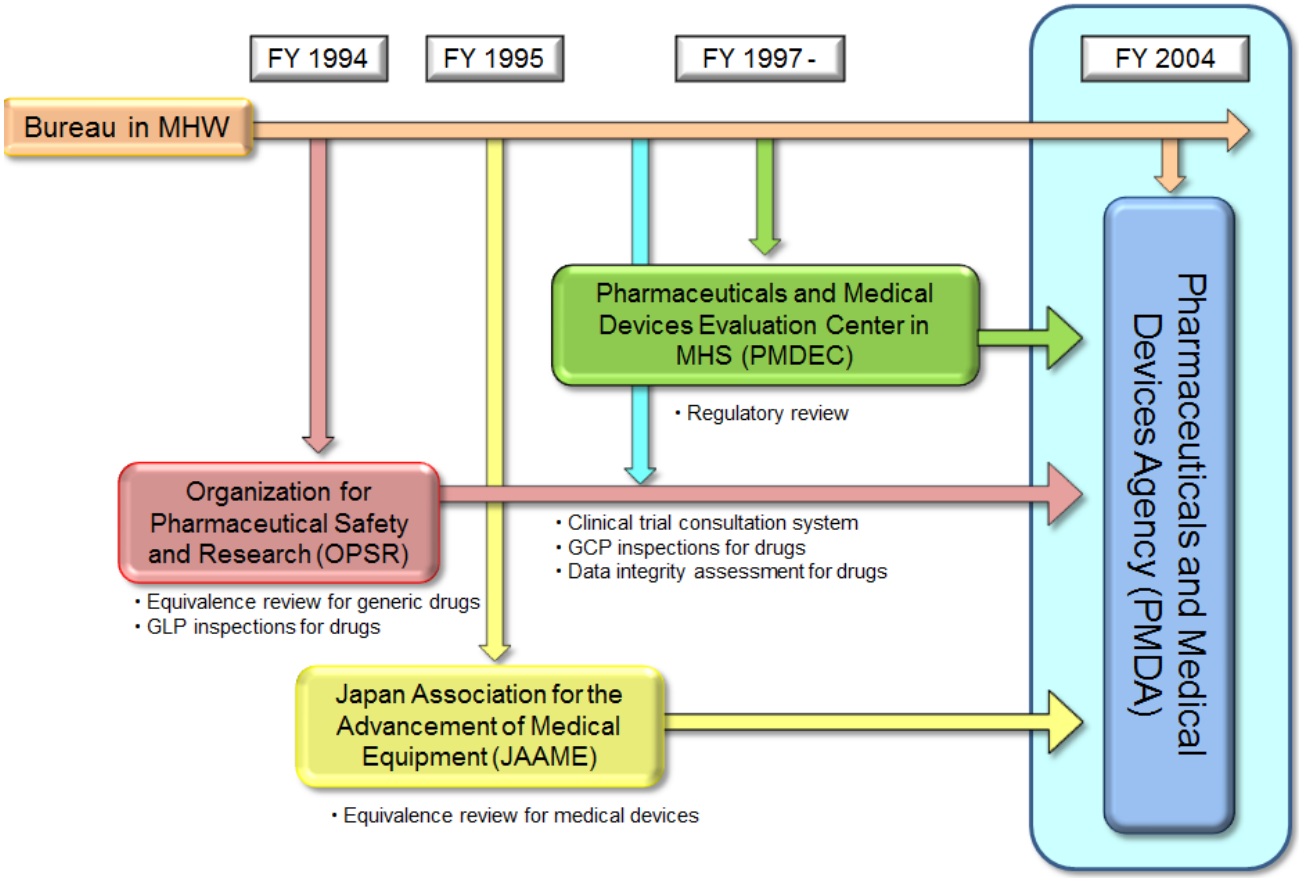
3.2.(1).A.(i) Appropriate and prompt reviews

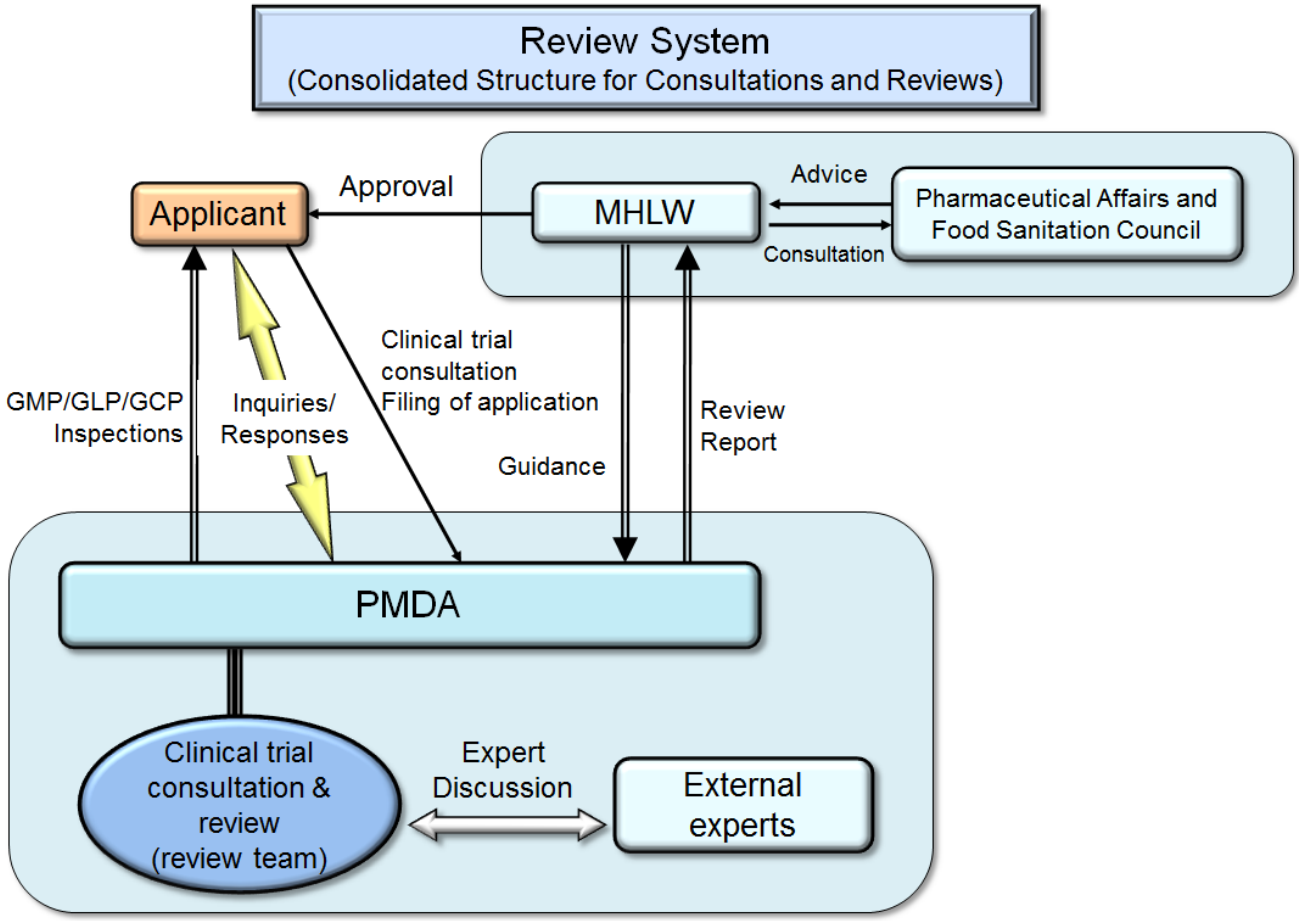
3.2.(1).A.(i).a. Structure for clinical trial consultations and reviews

- Since its inception in FY 2004, PMDA has continued to improve its review system by taking the following measures:

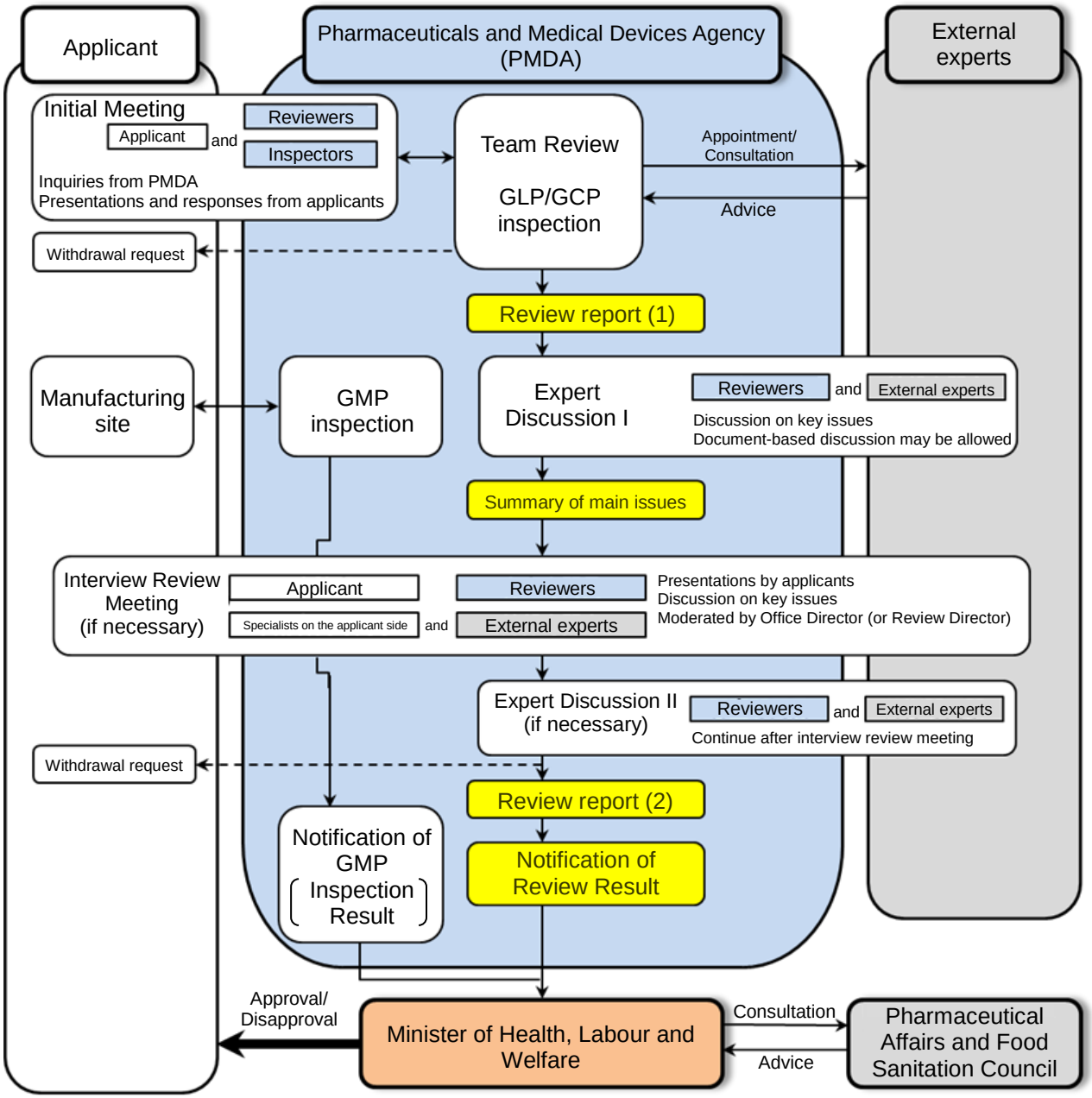
  1) Substantial increase in the number of staff including reviewers.
  2) Introduction of a coherent system in which the process from clinical trial consultations until reviews is conducted by the same team with the same staff members.
  3) Enhancement of reviews of biological and biotechnology-derived products.
  4) Reinforcement of functions for reviewing medical devices.
  5) Acceptance and analysis of electronic data for new drug applications.

Transition of review system for drugs and medical devices





Flowchart of review process

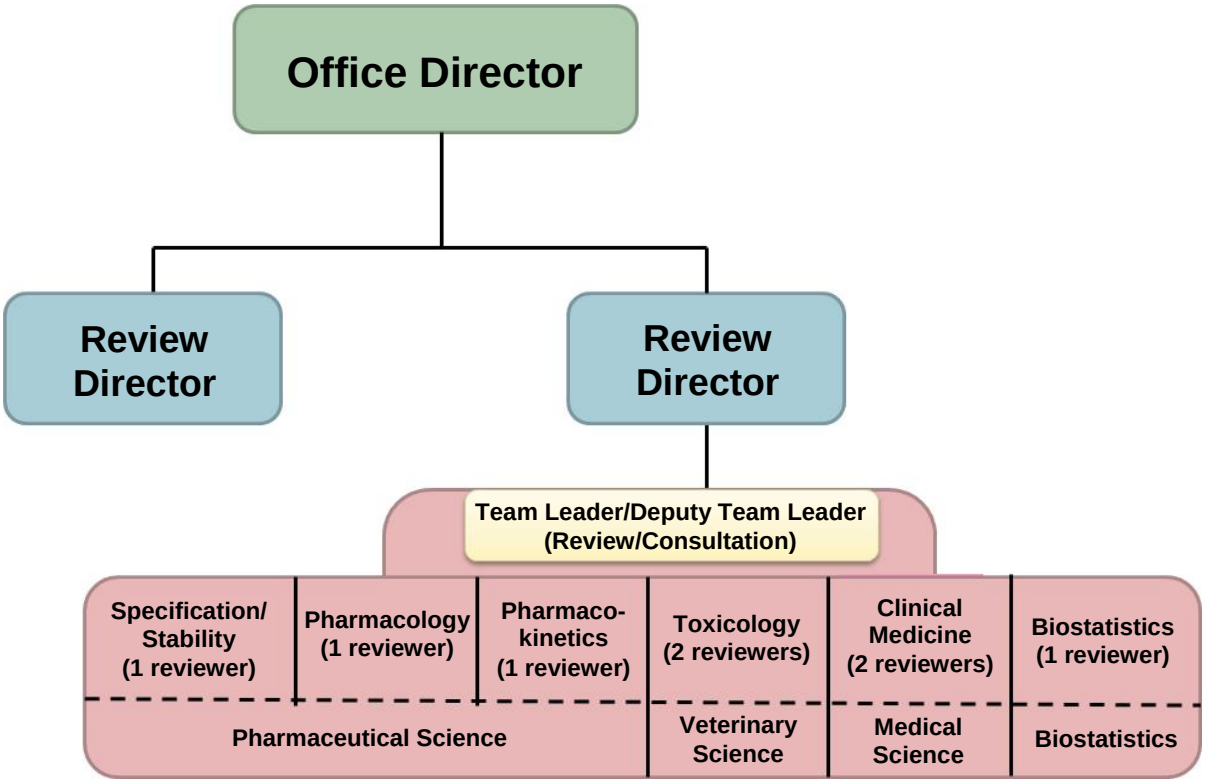


Review Performance for FY 2018 (drugs)

(1) Number of Expert Discussions conducted: 254 (212 document-based discussions, 42 meetings)
(2) Applications reviewed by the Drug Committees (under Pharmaceutical Affairs and Food Sanitation Council [PAFSC]): 71
Applications reported to the Drug Committees (under PAFSC): 48

- Reviews of new drugs were conducted by review teams under the guidance of an office director and a review director. As a general rule, each review team consists of experts holding academic degrees in pharmacology, veterinary medicine, clinical medicine, biostatistics, and other specialized fields. Each review team is typically comprised of a team leader, deputy team leader(s), and reviewers specializing in the areas of quality, toxicology, pharmacology, pharmacokinetics, clinical medicine, and biostatistics.

Organization Chart for Reviews of New Drugs



- In order to enhance its review system, PMDA increased the number of reviewers allocated to the categories receiving large numbers of new drug application filings where delays in the review process were most likely.

- Reviews of new drug applications are shared among the responsible offices and teams according to the review categories by therapeutic area. The review categories are as follows:

Review Categories Covered by the Offices of New Drugs

Office	Review Categories	
Office of New Drug I	Category 1	Gastrointestinal drugs, dermatologic drugs, immunosuppressive drugs, and others (not classified as other categories)
	Category 6-2	Hormone drugs, drugs for metabolic disorders (including diabetes mellitus, osteoporosis, gout, and inborn errors of metabolism)
Office of New Drug II	Category 2	Cardiovascular drugs, antiparkinsonian drugs, anti-Alzheimer's drugs
	Category 5	Reproductive system drugs, drugs for urogenital system, combination drugs
	Radiopharmaceuticals	Radiopharmaceuticals
	In vivo diagnostics	Contrast agents, reagents for function tests (excluding *in-vitro* diagnostics)
Office of New Drug III	Category 3-1	Central/peripheral nervous system drugs (excluding anesthetic drugs)
	Category 3-2	Anesthetic drugs, sensory organ drugs (excluding drugs for inflammatory diseases), narcotics
Office of New Drug IV	Category 4	Antibacterial drugs, antiviral drugs (excluding AIDS drugs), antifungal drugs, antiprotozoal drugs, anthelmintic drugs
	Category 6-1	Respiratory tract drugs, anti-allergy drugs (excluding dermatologic drugs), sensory organ drugs (drugs for inflammatory diseases)
	AIDS drugs	Anti-HIV drugs
Office of New Drug V	Oncology drugs	Antineoplastic drugs
Office of Cellular and Tissue-based Products	Cellular and tissue-based products	Cell/tissue-processed products among regenerative medical products
	Gene therapy products	Gene therapy products among regenerative medical products, Cartagena
	Bio-CMCs	Quality of biologics, biosimilars
	Biological devices (quality)	Biological devices (quality)
Office of Vaccines and Blood Products	Vaccines	Vaccines (only those to be used for prevention of infection), antitoxic serum, etc.
	Blood products	Blood products (including alternatives for blood products)

- PMDA conducted face-to-face or document-based clinical trial consultations on new drugs based on the team-reviewed advice plan drafted by the Review Director as well as the consultation leader and the deputy consultation leader in charge, who were appointed from among the review team members.

3.2.(1).A.(i).b. Reinforcement and improvement in the transparency of the progress management of reviews

- Product managers responsible for progress management and coordination of reviews of new drugs were assigned in each Office of New Drug. PMDA reviewers continuously made efforts to further accelerate reviews and related services in FY 2018 as well.

- The PMDA's Progress Management Committee for Reviews and Related Services is intended to ensure that PMDA executives have an accurate understanding of the progress status of reviews and related services and improve the progress as needed. The "Review Segment Committee for Progress Management" is headed by the Director of the Center for Product Evaluation. The two committees held joint meetings to manage the progress of reviews, in order to achieve the target review times specified in the Mid-term Plan. In the meetings, the committee members shared information regarding the overall review status for new drugs and associated issues including GCP and GMP inspections, discussed measures to address challenges and future approaches, and checked the progress of reviews for new drugs and other products. (11 meetings held in FY 2018.)

  At these joint meetings, (1) the PMDA executives, the Director of the Center for Product Evaluation, and the responsible Associate Center Director, etc., provided necessary guidance after reviewing reports from the office directors of review divisions, and (2) each review segment was notified of the content of discussion regarding measures to address issues associated with the products that had required prolonged review.

- In accordance with the "Approach to Explaining Progress in the Review of New Drug Applications" (PMDA Notification No. 1227001, dated December 27, 2010), the progress of the PMDA review is to be communicated to applicants in each review stage. The relevant office director appropriately held meetings with applicants upon their request to explain the progress and outlook of the review to them. If reviewing a new drug application is difficult, review-related issues including reasons for the difficulty and the possibility of approving the drug are to be provided in writing to the applicant, in order to increase the transparency of the review process. If applicants take time to respond to inquiries for product review, such time should be excluded when calculating the total review time.

3.2.(1).A.(i).c. Standardization of review

- To clarify review standards, reviewers were informed of the "Points to be Considered by the Review Staff Involved in the Evaluation Process of New Drug" released in FY 2008, which provides basic considerations for review. The document is posted on the PMDA website. In addition, target review times for priority review products and standard review products were presented for each review process in "Timeline in the Standard Process of New Drug Application" (PFSB/ELD Administrative Notice of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Division, MHLW, dated January 30, 2015). This document is also posted on the PMDA website.

3.2.(1).A.(i).d. Consultations and reviews based on medical care needs

- PMDA actively exchanged opinions with healthcare professionals by participating in academic conferences etc., in and out of Japan, to comprehend their needs. The Agency conducted consultations and reviews, taking into account the information obtained in this manner.

- The Investigational Committee on Medically Necessary Unapproved Drugs and Off-Label Use Drugs (chaired by Dr. Tomomitsu Hotta, Honorary President of National Cancer Center) was established in MHLW in February 2010, and since then has been active. The purpose of committee is to request that pharmaceutical companies develop drugs and indications that have been approved in Europe and the U.S. but not in Japan. In FY 2018, the committee convened three times. PMDA continuously supports the committee, and offers clinical trial consultations and reviews based on the results of the investigations by the committee.

- In order to resolve a delay in the introduction of unapproved drugs and off-label use drugs with high medical needs, PMDA promptly and timely collected information on the approval status at the

United State (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA), gathered and organized evidence information, etc., and expanded the unapproved drug database to compare the approval status between Japan and the US or Europe. Of drugs with a new active ingredient approved by the US FDA or EMA in or after April 2009, 182 (US FDA) and 118 (EMA) have not been approved in Japan as of March 2019. The list of the unapproved drugs is available on the PMDA website.

3.2.(1).A.(i).e. Consistency between clinical trial consultations and reviews

- In order to ensure the consistency between clinical trial consultations and reviews, review team members are involved in all the clinical trial consultations for products falling under the category to which they are assigned. Coherence from consultations to reviews is maintained and teams are flexibly organized as necessary.

  To further secure the consistency of clinical trial consultations, etc., efforts to provide feedback information on previous clinical trial consultations were continued in FY 2018.

3.2.(1).A.(i).f. Appropriate conduct of re-examination

- When a certain period has passed since approval of new drugs, re-examinations are conducted to confirm the efficacy and safety, based on data of use-results surveys that have been conducted by marketing authorization holders (MAHs) and other data.
- The target median review time for re-examination applications filed in or after FY 2014, is 18 months (to be achieved by FY 2018). In FY 2018, re-examination result notifications were issued for 59 applications (144 products), with the median total review time being 15.0 months.

Number of Re-examinations Conducted

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Applications submitted for re-examination(Note)	34 (86)	47 (114)	49 (119)	90 (218)	63 (149)
Applications submitted in or after FY 2014	-	23 (57)	40 (101)	75 (180)	59 (144)
Median total review time (months)	-	16.7	17.1	17.8	15.0

Note: The figures represent the number of applications for which a notification of re-examination results was issued in the respective fiscal year, while those in parentheses represent the number of products.
Including applications submitted before FY 2014.

3.2.(1).A.(i).g. Development of the Japanese Pharmacopoeia draft

1) Development of the Japanese Pharmacopoeia draft

- In FY 2018, the Japanese Pharmacopoeia (JP) Draft Committee held 74 meetings. Subsequently, PMDA published on its website a draft of the Japanese Pharmacopoeia 18th edition to seek public comments: 54 official monographs (3 new articles, 51 amendments), 2 general tests and general information (2 amendments), 1 ultraviolet-visible reference spectrum (1 new test), and 1 infrared reference spectrum (1 new test). The Japanese Pharmacopoeia 18th edition will be announced in the spring of 2021.

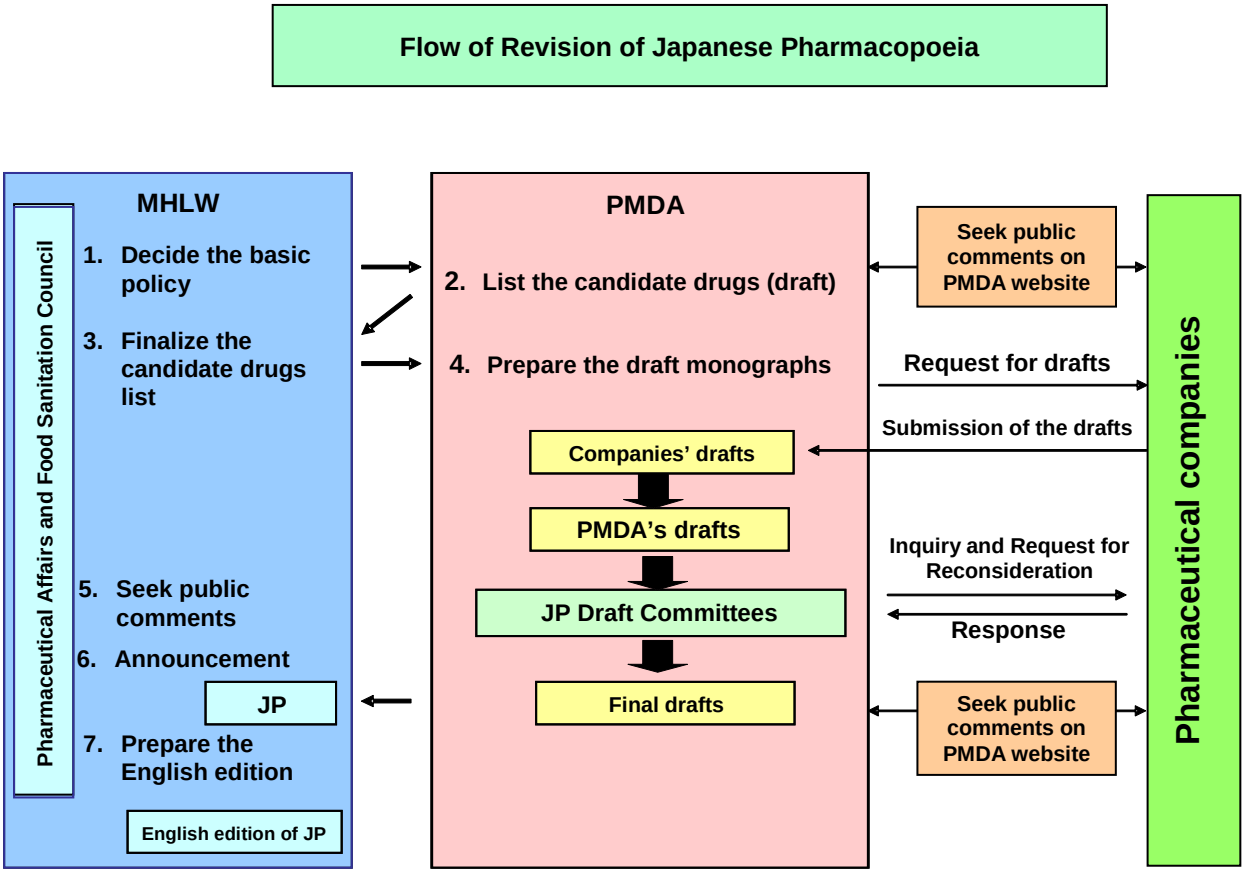
  The table below shows the number of drafts of official monographs reported to MHLW.

Month and year reported	Aug. 2010	Mar. 2012	Jan. 2013	Sep. 2013	Jul. 2015	Mar. 2017	Dec. 2018
New monographs	106	77	0	60	76	32	34
Revised monographs	330	176	1	172	471	114	77

Note: In addition to drafts of the official monographs shown in this table, PMDA prepares drafts of General Notices, General Rules for Preparations, General Rules for Crude Drugs, General Tests, Processes and Apparatus, and General Information. PMDA usually provides those drafts to MHLW 6 months before the announcement of new JP.

Announcement of the Japanese Pharmacopoeia by MHLW

	16th edition	Supplement 1 to 16th edition	Partial revision	Supplement 2 to 16th edition	17th edition	Supplement 1 to 17th edition
Month and year announced	March 2011	September 2012	May 2014	February 2014	March 2016	December 2017
New monographs	106	77	0	60	76	32
Revised monographs	330	176	1	173	471	114
Deleted monographs	15	4	0	1	10	17
Total number of monographs	1,764	1,837	1,837	1,896	1,962	1,977



- PMDA published a draft of the 18th edition of the Japanese Pharmacopoeia to seek public comments in English on all of new monographs for drug substances (that had been subjected to public comments in Japanese) on the Japanese Pharmacopoeia page on the PMDA website. The 18th edition of Japanese Pharmacopoeia will be announced in the spring of 2021.

2) Issuance of notifications, etc.

- PMDA cooperated with MHLW in publication of an English edition of Supplement 1 to the Japanese Pharmacopoeia 17th edition (September 2018).

3) Provision of information on the Japanese Pharmacopoeia page of the PMDA website

- PMDA provided information such as the status of seeking public comments on the Pharmacopoeia and information related to the international harmonization of the Pharmacopoeia.
- The PDG harmonized document (cover sheet) was posted on the website of the international harmonization of the Pharmacopoeia to disclose the handling status of the PDG harmonized document in the Japanese Pharmacopoeia.

4) Approaches to increased efficiency of operations

- The secretariat of the JP Draft Committee prepared JP drafts and proposed issues to be discussed before the meetings of the Chemicals Subcommittee and other subcommittees. In this way, the secretariat led and streamlined operations of the JP Draft Committee.
- The Office of Generic Drugs in PMDA and the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW held monthly meetings to share

information before developing the drafts of the Japanese Pharmacopoeia, in order to ensure the appropriate use of the Japanese Pharmacopoeia.

5) Japanese Accepted Names for Pharmaceuticals (JAN)

- PMDA held 6 meetings of Expert Discussion on drug names, thereby contributing to the establishment of 49 new Japanese Accepted Names for Pharmaceuticals (JAN).
- PMDA held 2 document-based Expert Discussions on drug names, thereby revising the chemical names of already existing JANs.

Number of Applications and Notifications for new JANs and Number of new JANs listed

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
(a) No. of applications and notifications for new JANs or for revisions to existing JANs	62	62	51	60	60
(b) No. of new JANs listed	67	60	67	58	49
(c) No. of revisions to existing JANs	5	0	0	0	6
(d) No. of applications and notifications withdrawn	-	-	8	4	1

Note: (b), (c), and (d) include applications and notifications submitted, but not processed, in the previous fiscal years. The procedure for withdrawal (d) is based on the "Q&A for Handling of Non-proprietary Names of Drugs" (PSEHB/ELD Administrative Notice dated March 31, 2016, by the Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW).

3.2.(1).A.(i).h. Implementation of the drug master file workshop

- A workshop on the drug master file system was held for drug substance manufacturers, in-country representatives, MAHs, etc. The purpose of the workshop was to encourage manufactures etc. to use the system, thereby reducing delays in product reviews and minimizing inadequacies in post-approval management. The participants were informed of recent guidance by PMDA regarding the system. PMDA also offered consultations via FAX at the request of drug substance manufacturers, in-country representatives, MAHs, etc., and published representative cases on the PMDA website for reference purposes.
- In January 2019, PMDA started to post information on the in-country representative (name and address) of the foreign drug substance manufacturer/drug master file holder of a particular drug substance on the PMDA website, at the request of the foreign drug substance manufacturer/drug master file holder.

3.2.(1).A.(ii) Introduction of new review systems

3.2.(1).A.(ii).a. Implementation of prior assessment consultations

- To evaluate the quality, efficacy, and safety of drugs from the pre-application stage, PMDA has offered prior assessment consultations, as a pilot program from FY 2009 to 2010, and as a formal program since FY 2011. In FY 2018, PMDA received consultation request forms in October, and implemented consultations as follows.

  Review category 3-1: 1 product (2 consultation categories)

3.2.(1).A.(ii).b. Consideration toward the development of the Advanced Review and Consultation with Electronic Data

- PMDA began to accept the electronic submission of clinical study data (hereinafter referred to as “electronic study data”) through the Electronic Data Submission System on October 1, 2016, and received data for 33 products in FY 2018. The system has functions to receive electronic data submission from companies, archive submitted electronic data at PMDA, and conduct statistical data analysis. PMDA has updated configurations to solve problems associated with the operation of the system, and has revised the system manual for applicant companies on a regular basis.
- PMDA continued to exchange opinions with related industries regarding various issues on electronic submission of data for product application. PMDA also collaborated with MHLW to issue the following notifications before the end of the transitional period: “Revision of Basic Principles on Electronic Submission of Study Data for New Drug Applications” (PSEHB/PED Notification No. 0124-1 dated January 24, 2019, issued by Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW); “Revision of Notification on Practical Operations of Electronic Study Data Submissions” (PSEHB/PED Notification No. 0124-4 dated January 24, 2019, issued by Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW); “Question and Answer Guide Regarding ‘Basic Principles on Electronic Submission of Study Data for New Drug Applications’” (PSEHB/PED Administrative Notice, dated January 24, 2019, issued by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW); and “Question and Answer Guide Regarding ‘Notification on Practical Operations of Electronic Study Data Submissions’” (PSEHB/PED Administrative Notice, dated May 17, 2018 and January 24, 2019, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW). Furthermore, PMDA made partial revisions to “Technical Conformance Guide on Electronic Study Data Submissions” (Notification No. 0427001 dated April 27, 2015, by Director of the Advanced Review with Electronic Data Promotion Group [predecessor of the Office of Advanced Evaluation with Electronic Data], PMDA) on May 17, 2018 and January 24, 2019. In addition, PMDA periodically revises “FAQ about Electronic Application Data” posted on its website.
- On October 15 and 16, 2018, PMDA co-hosted workshops with the Japan Pharmaceutical Manufacturers Association and the Japan CRO Association to provide detailed technical information on the Electronic Data Submission System for persons who actually use the system in related industries. On May 10, 2018 and February 12, 2019, PMDA held briefing sessions regarding details of revised notifications as well as experiences and points to consider obtained after the start of acceptance of electronic submission of study data.
- PMDA began to offer “Consultations for electronic study data submission” on May 15, 2015. The purpose of this consultation is to discuss issues associated with electronic submission before each individual product is filed for approval, to streamline the preparation of data for submission, and to accelerate the review process after submission. In addition, PMDA had discussions with the industry to ensure that consultations for each individual product are offered based on the revision of the basic notification (“Basic Principles on Electronic Submission of Study Data for New Drug Applications”). Accordingly, addition of new consultations to be launched in April 2019 was decided.

Number of consultations for electronic study data submission

	FY 2015	FY 2016	FY 2017	FY 2018
Number of requests	13	62	65	100
Conducted	11	55	70	90

- At the Regulatory Science Center (hereinafter referred to as “RSC”) established in April 2018, PMDA analyzed the electronic study data submitted for approval to promote utilization thereof in the review of each individual product. PMDA also held case study meetings about modeling and simulation. In the meetings, PMDA reviewers seek advice for mutual sharing on how to examine data (submitted for approval or consultations) that have been organized using advanced analytical methods such as modeling & simulation.
- Relevant PMDA staff members were encouraged to participate in both internal and external workshops so that they can broaden their knowledge of CDISC standards adopted for acceptance of electronic study data and improve their skills in analytical methods used for CDISC-compliant data and in the field of clinical pharmacology.

3.2.(1).A.(iii) Approaches to achieving “zero” review lag for drugs

- The targets for the total review time (from the date of submission to the date of approval) for drugs approved in each fiscal year (including drugs whose applications were submitted on or after April 1, 2004) are 9 months for priority review products and 12 months for standard review products. The target total review time was set by gradually increasing the percentiles. PMDA aimed to achieve the total review times at the 80th percentile by FY 2018. The regulatory authorities have been making efforts to achieve these targets while asking applicants for their cooperation.
- New drug applications (for drugs that are clearly different from approved drugs in terms of active ingredients, contents, dosage and administration, indications, etc.) were reviewed by PMDA review teams consisting of experts in the fields of pharmaceutical science, veterinary medicine, medicine, biostatistics, etc.
- In order to ensure appropriate, consistent, and prompt reviews of new drugs, PMDA’s review teams adhered to the “Procedures for Reviews of New Drugs” regarding reviews and related procedures, as well as the SOPs for various related operations.
- The following tables describe the status of reviews of new drugs in FY 2017 (excluding applications of drug products* that are reviewed by PMDA and approved only through the administrative process at MHLW):

  * Drugs that are identical to approved drugs in terms of active ingredients, dosage and administration, and indications or drugs that are within the scope of approved drugs in terms of dosage and administration, and indications.

3.2.(1).A.(iii).a. Review times for new drugs (priority review products, as designated by the Minister of Health, Labour and Welfare)

Targets

Fiscal year	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Total review time [months]	9	9	9	9	9
Percentile	60th	60th	70th	70th	80th

Results

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Percentile	60th	60th	70th	70th	80th
Total review time [months] (Reference, 80th percentile) [months]	8.8 (9.2)	8.7 (9.5)	8.8 (9.2)	8.9 (9.0)	8.6
Number of approved applications	44	37	38	38	47

Reference

Regulatory review time [months]	4.0	4.0	4.0	4.9	5.1
Applicant's time [months]	5.0	4.9	5.3	5.4	4.3

Note 1: Products submitted in or after April 2004 are covered. The number of approved applications is based on active ingredients. For details, refer to the list of approved products included in "III SUPPLEMENTARY INFORMATION."

Note 2: Public knowledge-based application for products selected by the Study Group on Unapproved and Off-label Drugs of High Medical Need are included in the priority review products.

Note 3: The figures in "regulatory review time" and "applicant's time" represent their respective percentile values. The sum of regulatory review time and applicant's time may not equal the total review time for each fiscal year.

Reference: Review times for new drugs (priority review products) excluding public knowledge-based applications for unapproved drugs

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Percentile	60th	60th	70th	70th	80th
Total review time [months] (Reference, 80th percentile) [months]	8.9 (9.2)	8.8 (9.8)	8.8 (9.3)	8.9 (9.0)	8.8
Regulatory review time [months]	3.8	4.0	3.9	4.8	5.1
Applicant's time [months]	5.2	5.2	5.5	5.5	4.7
Number of approved applications	37	33	32	33	36

- Priority reviews are conducted for applications for orphan drugs and other drugs that are regarded as having particularly high medical need (drugs for serious diseases and with distinctly superior efficacy or safety as compared to existing drugs or therapies). In FY 2018, 47 priority review products (including 11 public knowledge-based applications for products selected by the Study Group on Unapproved and Off-label Drugs of High Medical Need) were approved.
- In FY 2018, PMDA received 4 applications for priority reviews for drugs regarded to have particularly high medical needs. During the fiscal year, 4 applications were judged to be eligible for priority review (1 application filed in FY 2017 and examined for eligibility for priority review in FY 2018 was judged to be eligible). In FY 2018, PMDA received no applications for conditional early approvals (2 applications filed in FY 2017 and examined for eligibility for conditional early approval in FY 2018 were judged to be eligible).
- The priority review products accounted for 42% of products approved in FY 2018, showing an increase from 37% in FY 2017.

3.2.(1).A.(iii).b. Review times for new drugs (standard review products)

Targets

Fiscal year	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Total review time [months]	12	12	12	12	12
Percentile	60th	70th	70th	80th	80th

Results

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Percentile	60th	70th	70th	80th	80th
Total review time [months] (Reference, 80th percentile) [months]	11.9 (12.3)	11.3 (11.7)	11.6 (12.0)	11.8	11.9
Number of approved applications	73	79	74	66	66

Reference

Regulatory review time [months]	6.8	7.3	7.3	7.7	6.8
Applicant's time [months]	5.4	5.8	6.0	7.0	7.6

Note 1: Products submitted in or after April 2004 are covered. The number of approved applications is based on active ingredients. For details, refer to the list of approved products included in "III SUPPLEMENTARY INFORMATION." Five applications for drugs approved for the pre-treatment of regenerative medical products are excluded.

Note 2: The figures in "regulatory review time" and "applicant's time" represent their respective percentile values. The sum of regulatory review time and applicant's time may not equal the total review time for each fiscal year.

- In total, 112 applications were under review at the end of FY 2018 (including 23 applications for orphan drugs and 1 public knowledge-based application for unapproved drugs).

Review Status of New Drugs by Fiscal Year of Application

New drugs (FY of submission)	Applied	Approved	Not approved	Withdrawn	Under review
In or before Mar. 31, 2004	140	109	0	30 (1)	1 [-1]
FY 2004	87	78	0	9	0
FY 2005	57	50	0	7	0
FY 2006	102	93	0	9	0
FY 2007	92	78	0	14	0
FY 2008	81	77	0	4	0
FY 2009	106	87	1	18	0
FY 2010	116	105	0	11	0
FY 2011	130	128	0	2	0
FY 2012	140	135	0	5	0
FY 2013	123	119	0	4	0
FY 2014	128	118	0	10 (1)	0 [-1]
FY 2015	125	119	0	5	1
FY 2016	101	96 (2)	0	3	2 [-2]
FY 2017	113	100 (71)	0	12 (8)	1 [-79]
FY 2018	149	40 (40)	0	2 (2)	107
Total	1,790	1,532 (113)	1	145 (12)	112 [27]

Note 1: The figures in parentheses in "Approved" and "Withdrawn" represent the number of applications processed in FY 2018 (included in figures to the left).

Note 2: The figures in brackets represent differences from the status reported in FY 2017.

Note 3: The number of applications may vary depending on the counting rule applicable when new drug applications submitted are approved.

3.2.(1).A.(iv) Promotion of multi-regional clinical trials

- In order to mitigate drug lag, PMDA has promoted multi-regional clinical trials and has conducted consultations and reviews based on the following documents: "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007, issued by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW), "Basic Principles on Global Clinical Trials (Reference Cases)" (PFSB/ELD Administrative Notice, dated September 5, 2012), and "Basic Principles for Conducting Phase I Trials in the Japanese Population Prior to Global Clinical Trials" (PFSB/ELD Administrative Notice, dated October 27, 2014). These documents clarify basic principles and best practices when conducting multi-regional clinical trials.

Number of Clinical Trial Notifications of Multi-regional Clinical Trials

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Number of notifications	181	276	240	323	389

- PMDA intends to take an active approach to multi-regional clinical trials. In FY 2018, PMDA received requests for consultation on multi-regional clinical trials of drugs with new active ingredients, and conducted consultations for all the requests.

Number of Consultations on Multi-regional Clinical Trials with New Active Ingredients

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Number of consultations	67	66	73	74	89

- To promote multi-regional clinical trials in the Asian region, PMDA acted as a leader (Champion) in the area of multi-regional clinical trials/GCP inspections of the APEC Life Sciences Innovation Forum (LSIF) Regulatory Harmonization Steering Committee (RHSC), which was established as a sectoral association to harmonize regulatory affairs. PMDA also held the PMDA-ATC MRCT Seminar 2019 (January 2019) as an APEC Training Center of Excellence (CoE) for Regulatory Science. PMDA reported this achievement at the APEC-LSIF-RHSC meeting in Chile (February 2019), which was internationally highly appreciated.

3.2.(1).A.(v) Efficient conduct of clinical trial consultations

3.2.(1).A.(v).a. Conduct of priority consultations

- In accordance with the start of the SAKIGAKE designation system, in FY 2015 priority consultation service began to cover SAKIGAKE designation drugs, in addition to orphan drugs. In FY 2018, PMDA handled those drugs in a similar manner (6 priority face-to-face consultations for SAKIGAKE designation drugs were conducted in FY 2018).

3.2.(1).A.(v).b. Acceleration of the procedure for clinical trial consultations

- To expedite clinical trial consultations, PMDA streamlined the procedure by which applicants request consultations and PMDA receives such requests. The revised procedures apply to consultation requests submitted during or after October 2010. PMDA has consistently maintained its target period from request submission to consultation of approximately 2 months.

3.2.(1).A.(v).c. Implementation of clinical trial consultations and improvement of the consultation service

Number of Consultations

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Conducted	411	371	422	395	436
Withdrawn	38	33	61	34	42

Number of Prior Assessment Consultations for Drugs

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Conducted	32	1	7	0	2
Withdrawn	0	0	0	0	0

Number of Consultations on Drug Product Eligibility for Priority Review

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Conducted	6	7	5	4	3
Withdrawn	0	0	0	0	0

Number of Consultations on Drug Product Eligibility for Conditional Early Approval

	FY 2017	FY 2018
Conducted (face-to-face)	2	0
Withdrawn	0	0

Note 1: Prior assessment consultations for drugs have been conducted since FY 2009. Consultations on drug product eligibility for priority review have been conducted since FY 2011. Consultations on drug product eligibility for conditional early approval have been conducted since FY 2017. The numbers of all types of consultations were counted on the basis of the dates of delivery of consultation documents to PMDA.

Note 2: Prior assessment consultations for drugs were counted on the basis of number of consultation categories (quality; non-clinical toxicity; non-clinical pharmacology; non-clinical pharmacokinetics; phase I study; phase II study; and phase II/III study).

- To respond to all requests for clinical trial consultations (excluding prior assessment consultations, consultations on pharmacogenomics/biomarkers, consultations on drug product eligibility for priority review, and consultations on drug product eligibility for conditional early approval), as a general rule, consultations are scheduled according to requests for scheduling. When a consultation cannot be scheduled for a desired month, the consultation is scheduled within one month before or after that month. In FY 2018, PMDA provided 430 consultations (42 withdrawals), responding to all requests for clinical trial consultation.
- PMDA aimed to complete the process from conduct of clinical trial consultation to finalizing consultation records within 30 business days for 80% of products subjected to consultation. In FY 2018, the target was achieved in 402 of 418 consultations (96.2%).
- In order to improve the quality of consultations, in January 2007, PMDA introduced a system for all clinical trial consultations in which PMDA's opinions for content to be addressed in the consultations are presented to the applicants beforehand (preliminary opinion disclosure system).

Number of Consultations for Drugs by Review Category in FY 2018

Review category	Results												Total
	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	
Category 1 (Gastrointestinal drugs etc.)	5	6	7	6	5	5	6	6	2	2	4	6	60
Category 6-2 (Hormone drugs)	5	4	4	1	4	5	4	2	4	2	4	1	40
Category 2 (Cardiovascular drugs)	2	3	5	4	4	2	2	4	7	1	3	0	37
Category 5 (Drugs for the urogenital system etc.)	1	1	2	1	1	1	1	0	2	0	0	0	10
Radiopharmaceuticals	0	1	0	0	0	0	0	0	0	0	1	0	2
In vivo diagnostics	0	0	0	0	0	1	0	0	0	0	1	0	2
Category 3-1 (Central nervous system drugs etc.)	2	0	1	4	4	2	1	3	8	1	5	3	34
Category 3-2 (Anesthetic drugs etc.)	3	1	2	2	2	2	2	1	0	0	2	1	18
Category 4 (Antibacterial agents etc.)	0	2	2	1	1	1	0	2	1	1	0	5	16
Category 6-1 (Respiratory tract drugs etc.)	4	3	0	4	3	6	7	0	7	4	8	3	49
AIDS drugs	0	0	1	0	0	0	0	0	0	0	0	0	1
Oncology drugs	6	9	4	5	7	4	11	13	17	5	6	10	97
Bio-CMC	6	1	3	1	2	4	1	2	1	2	6	2	31
Vaccines	0	0	1	2	1	1	2	1	0	0	3	3	14
Blood products	1	1	1	1	0	2	2	1	3	1	3	3	19
Generic drugs	0	0	0	0	0	1	0	1	0	1	2	0	5
[Re-listed] Prior assessment	0	0	0	0	0	0	0	0	2	0	0	0	2
[Re-listed] Drug product eligibility for priority review	0	1	0	0	0	1	0	0	0	0	0	1	3
[Re-listed] Drug product eligibility for conditional early approval	0	0	0	0	0	0	0	0	0	0	0	0	0
Pharmacogenomics/biomarkers	1	0	0	0	0	0	0	0	0	0	0	0	1
GLP/GCP/GPSP compliance inspection	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	36	32	33	32	34	37	39	36	52	20	48	37	436
Withdrawn	8	4	1	5	3	4	2	5	1	5	1	3	42
Total	44	36	34	37	37	41	41	41	53	25	49	40	478

Note 1: A consultation covering several categories was counted in terms of its main category.

Note 2: Prior assessment consultations are conducted for the following categories: Quality; non-clinical, toxicity; non-clinical, pharmacology; non-clinical, pharmacokinetics; phase I study; phase II study; and phase II/III study.

Note 3: The numbers of prior assessment consultations, consultations on pharmacogenomics/biomarkers, consultations on drug product eligibility for priority review, and consultations on drug product eligibility for conditional early approval were counted on the basis of on the date of delivery of consultation documents to PMDA.

Note 4: Consultations on pharmacogenomics/biomarkers were conducted by the Omics Project Team.

Note 5: Consultations on GLP/GCP/GPSP compliance assessment were all conducted by Office of Non-clinical and Clinical Compliance or Office of Manufacturing Quality for Drugs, regardless of category.

3.2.(1).A.(v).d. Reclassification of consultation categories and their uses

- PMDA exchanged opinions with MHLW and related industries on clinical trial consultation services. As a result, in April 2018, PMDA began to offer Post-Approval Change Management Protocol (PACMP) consultation, which provides guidance and advice on making changes to approved product information using PACMP.

  PMDA also decided to launch the following consultations in April 2019:

  (a) Consultations concerning electronic study data submission for drugs
  This consultation is conducted to discuss issues associated with electronic submission of clinical data for new drug applications (including biosimilars and excluding OTC drugs) before the application for each individual product is submitted, to streamline the preparation of study data for submission, and to accelerate the review process after submission.

  (b) Consultations concerning Cartagena Act
  This consultation is conducted prior to submission of application for Type 1 Use of genetically modified living organisms, or submission of application for confirmation of Type 2 Use of modified living organisms, under the Cartagena Act. The consultation intends to provide guidance and advice regarding sufficiency of data for submission and the appropriateness of description for each individual genetically modified living organism and for matters specified in Type 1 Use regulation or location for Type 2 Use, etc., thereby reducing the time to submission.

  (c) Consultations on registry use plan
  This consultation intends to provide applicants (who wish to utilize patient/disease registries for evaluation of the efficacy and safety of individual products in filing applications for regulatory approval or re-examination) with opportunities for seeking advice on plans for use of the relevant registry, particularly focusing on appropriateness of use, adequacy of outcome measures, etc., according to the purpose of utilization.

  (d) Consultations on registry utilization
  This consultation intends to provide advice for patient/disease registry operators regarding the plans developed assuming utilization of the registries in filing applications for regulatory approval or re-examination of products, as well as general concepts for improvement of the quality of the registries to be used and the assurance of data integrity.

  (e) Consultations and additional consultations on compliance assessment of registries to be used for regulatory submission for drugs, etc.
  This consultation is conducted for individual products such as drugs for which application for regulatory approval or re-examination is planned to be filed utilizing data from patient/disease registries. The consultation intends to provide verification and advice on the data integrity of the registries to be used, before the relevant applicant files the application or initiates post-marketing surveillance.

3.2.(1).A.(vi) Promotion of evaluation of new technologies

3.2.(1).A.(vi).a. Utilization of external experts

- PMDA is required to enhance the expertise at its disposal in connection with its consultation and review activities, particularly in the fields of the latest technologies such as biotechnology and genomics. PMDA has therefore continued to commission external experts to serve as advisors to PMDA who provide expert input to scientifically important matters at Expert Discussions in connection with product reviews and safety measures.

(As of March 31, 2019, the number of commissioned experts was 1,200 including external experts commissioned for issues relating to safety measures)

- In FY 2018, 254 Expert Discussions were conducted (212 through document-based discussions; 42 through meetings).
- PMDA utilized external experts in Expert Discussions for regulatory reviews and clinical trial consultations for biologics and regenerative medical products. PMDA also continued to exchange information regarding both biosimilars and regenerative medical products with overseas regulatory authorities including the US FDA and the EMA via teleconference or by other means
- In anticipation of the development of advanced drug products using new scientific technologies such as induced pluripotent stem cells (iPS cells), PMDA has accumulated the latest knowledge by joining the following research groups:

  (a) As a study collaborator, PMDA staff joined a research group that conducted "Research on Development of Cardiotoxicity Evaluation Method for Drugs Using Human iPS Cell Differentiation Technology and International Standardization." This research is part of a project called "Research on Regulatory Science of Pharmaceuticals and Medical Devices" implemented by the Japan Agency for Medical Research and Development (AMED).

  (b) As an external collaborator, PMDA staff joined research groups that conducted "Research on Development of *in vitro* Test System for Prediction/Evaluation of Hepatotoxicity of Drugs Using Human iPS Cell-derived Hepatocytes" and "Research on Development of an *in vitro* Safety Pharmacology Evaluation System Using Human iPS Cell-derived Neurons to Predict the Risk of Drug-Induced Seizures in Humans." These researches are part of a project called "Research on Practical Application of Regenerative Medical Products" implemented by AMED.

  In addition, PMDA gathered information concerning overseas studies of safety evaluation systems using iPS cells and other technologies by participating in the Steering Team of the Comprehensive *In Vitro* Proarrhythmia Assay (CiPA) Initiative and other meetings and teleconferences. Furthermore, PMDA participated in the discussions on preparation of Addendum to E14/S7B guidelines initiated by the Expert Working Group of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) to discuss cardiac safety assessment using iPS cells and collect information thereof.

3.2.(1).A.(vi).b. Support for the development of national guidelines

- PMDA supported the development of evaluation guidelines through the activities of working groups (WG) involved in the Projects Across Multi-offices to Develop Standards (hereinafter referred to as "Projects Across Multi-offices"). In FY 2018, individual working groups collaborated with MHLW in preparing the following notifications:

  (a) Companion Diagnostics WG
  "Questions and answers (Q&A) on 'Technical Guidance on Development of In Vitro Companion Diagnostics and Corresponding Therapeutic Products'" (PSEHB/PED/MDED Administrative Notice, dated July 3, 2018, issued by the Pharmaceutical Evaluation Division and the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW);
  "Questions and answers (Q&A) on Companion Diagnostics and Corresponding Therapeutic Products (Part 2)" (PSEHB/PED/MDED Administrative Notice, dated July 20, 2018, issued by the Pharmaceutical Evaluation Division and the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW); and

"Questions and answers (Q&A) on 'Legislation Notice to Applicants for Marketing Authorization of DNA Sequencers and Related Products Utilized for Genetic Testing Systems (Part 2)'" (PSEHB/MDED/CND Administrative Notice, dated September 12, 2018, issued by the Medical Device Evaluation Division and the Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW).

(b) Global Clinical Study WG
"Guidelines on General Principles for Planning and Design of Multi-regional Clinical Trials" (PSEHB/PED Notification No. 0612-1, dated June 12, 2018, issued by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW).

(c) Clinical Innovation Network WG
"Points to Consider for Reliability Assurance of Post-marketing Database Surveys of Medical Devices" (PSEHB/MDED Notification No. 1219-4, dated December 19, 2018, issued by the Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW).

- In addition to the above, MHLW issued 4 notifications etc. in FY 2018 with the cooperation of relevant review categories or offices in PMDA.

3.2.(1).A.(vi).c. Preliminary reviews under Cartagena Act

- Preliminary reviews are conducted in relation to reviews of Type 1 Use of genetically modified living organisms and in confirmations of Type 2 Use of genetically modified living organisms under the Cartagena Act. The target regulatory review times were 6 months for approval of Type 1 Use and 2 months for confirmation of Type 2 Use, with the goal of achieving 50% (median) of applications for each type.

Review under the Cartagena Act (Median Regulatory Review Time)

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
No. of preliminary reviews for Type 1 Use	3	2	3	1	7
Median review time [months]	0.8	0.9	2.9	2.9	6.0
No. of preliminary reviews for Type 2 Use	25	21	23	17	30
Median review time [months]	1.3	1.0	1.3	1.3	1.1

Note 1: "Type 1 Use" refers to cases where no measures are taken to prevent the release to the environment.
"Type 2 Use" refers to cases where such measures are taken.
Note 2: The review time in FY 2014 through FY 2016 represents the time spent for review at PMDA, while that in FY 2017 and FY 2018 represents the sum of times spent for review at PMDA and MHLW.

3.2.(1).A.(vi).d. Implementation of Regulatory Science Strategy Consultations (R&D)

- PMDA has been offering Regulatory Science (RS) Strategy Consultations (R&D) and RS General Consultations since July 2011 mainly to universities, research institutions, and venture companies that have promising seed-stage resources to provide guidance and advice concerning studies and clinical trials that are necessary at the initial stage of clinical development. These consultations intend to facilitate the development of innovative pharmaceuticals, medical devices, and regenerative medical products in Japan. The programs were carried out as "Pharmaceutical Affairs Consultations on R&D Strategy" until March 2017. The number of consultations PMDA provided in FY 2018 is shown in the table below (Number of RS Strategy Consultations (R&D) and RS General Consultations).

- In FY 2018, PMDA provided 40 on-site consultations (all as RS General Consultation) in various prefectures throughout Japan, including Hokkaido, Fukushima, Tokyo, Aichi, and Fukuoka prefectures.
- PMDA contributed to the promotion of healthcare-related innovation by making use of the Kansai Branch Office, established in October 2013, which provided 62 RS General Consultations (including Kobe) and RS Strategy Consultations (R&D) (53 pre-consultation meetings [which also included pre-consultation meetings for medical devices in special zones] and 20 full-scale consultations [through video conference system]) in FY 2018.
- Starting in November 2014, PMDA has conducted pilot consultations concerning the product development process (roadmap) and investigator-initiated confirmatory clinical trial protocols. The purpose of the consultations is to promote the practical application of seed-stage research products originating in Japan.
- In response to the “Japan Revitalization Strategy” revised in 2015 (approved by the Cabinet on June 30, 2015), PMDA launched RS Strategy Consultation (R&D) for Medical Devices in Special Zones (carried out as “Pharmaceutical Affairs Consultation on R&D Strategy for Medical Devices in Special Zones” until March 2017) in October 2015. The PMDA consultation service offers advice on the development of innovative medical devices in core hospitals for clinical research in national strategic special zones. The consultation service includes “Pre-consultation meeting in Special Zones” and “Follow-up consultation in Special Zones,” in which PMDA staff members (acting as concierges) provide advice on development progress management. In FY 2018, PMDA conducted 4 Pre-consultation meetings in Special Zones.
- In July 2016, MHLW issued a report entitled “Advisory Panel on Promotion of Venture Companies that Lead Medical Innovation.” Based on the recommendations in this report, PMDA began to offer Collaborative Consultations on Practical Application of Innovation in April 2018, and conducted 5 consultations of this type (carried out as a part of RS General Consultations).

Number of RS Strategy Consultations (R&D) and RS General Consultations

Consultation Category	Up to FY 2013[1]	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018	Total
RS General Consultation[2] (Number of consultations conducted at the Kansai branch[4])	657 (20)	271 (63)	221 (56)	190 (63)	231 (57)	202 (62)	1,772 (321)
RS Strategy Consultation (R&D): Pre-consultation meetings[3] (Number of consultations conducted at the Kansai branch[4])	753 (26)	325 (57)	411 (60)	388 (52)	336 (61)	326 (52)	2,539 (308)
RS Strategy Consultation (R&D): Pre-consultation meetings for medical devices in special zones[5] (Number of consultations conducted at the Kansai branch)	-	-	1 (0)	9 (1)	5 (1)	4 (1)	19 (3)

RS Strategy Consultation (R&D): Full-scale consultations on[3]:	Up to FY 2013[1]	FY 2014	FY 2015	FY 2016	FY 2017	FY2018	Total
Drugs	114	48	58	40	61	49	370
Medical devices	49	16	16	20	24	26	151
Regenerative medical products[6]	-	2	11	14	13	5	45
Quality and safety of regenerative medical products[7]	31 [52]	18 [44]	29 [55]	26 [64]	29 [71]	25 [54]	158 [340]
Development planning[8]	-	1	0	0	0	0	1
Total	194 [215]	85 [111]	114 [140]	100 [138]	127 [169]	105 [134]	725 [907]

Note 1: The service for RS Strategy Consultations (R&D) (former Pharmaceutical Affairs Consultations on R&D Strategy) was launched on July 1, 2011.

Note 2: These consultations were provided as introductory consultations of Pharmaceutical Affairs Consultations on R&D Strategy until March 31, 2017.

Note 3: These consultations were provided as Pharmaceutical Affairs Consultations on R&D Strategy until March 31, 2017.

Note 4: This consultation category was introduced on October 1, 2013.

Note 5: This consultation category was introduced on November 20, 2015.

Note 6: This consultation category was introduced on November 25, 2014 (before then, consultations on regenerative medical products had been included in consultations on drugs or medical devices).

Note 7: This consultation category includes consultations conducted as Pharmaceutical Affairs Consultations on R&D Strategy for drugs on and before November 24, 2014. Some consultations were divided into multiple sessions over several days to confirm the quality and safety of the relevant products before submission of clinical trial notifications. The figures in brackets indicate the total number of these sessions.

Note 8: This consultation category was introduced on November 25, 2014. (It was provided as a Pharmaceutical Affairs Consultation on R&D Strategy for pharmaceutical development plans until March 31, 2017.)

3.2.(1).A.(vii) Handling of changes to approved product information pertaining to the quality of drugs

- MHLW issued a notification, “Strict Compliance with the Marketing Approval Documents of Drugs” on June 1, 2016 (PSEHB/ELD Notification No. 0601-3 and PSEHB/CND Notification No. 0601-2 dated June 1, 2016, jointly issued by the Director of the Evaluation and Licensing Division and the Director of the Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW). In response to the notification, PMDA exchanged opinions with MHLW and related industries, to ensure that approved product information is revised appropriately for a post-approval change made to the manufacturing process for a drug, and that manufacturing processes can be changed efficiently. For the announcement of detailed procedures for trial operation of the post-approval product information change system that is based on the Post-Approval Change Management Protocol (PACMP), MHLW issued a notification, “Handling of

Changes to Approved Product Information Pertaining to the Quality of Drugs" (PSEHB/ELD Notification No. 0309-1 and PSEHB/CND Notification No. 0309-1, dated March 9, 2018, jointly issued by the Director of the Evaluation and Licensing Division and the Director of Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW). Based on this notification, PMDA strived to proceed with the PACMP-based system in FY 2018.

3.2.(1).A.(viii) Cooperation in the development of guidelines for proper use of drugs

- PMDA provided assistance to MHLW in developing the Optimal Clinical Use Guidelines of innovative drugs, which was published by MHLW on a trial basis.

FY 2018

Drug name	Indication	Date of issue
Opdivo Intravenous Infusion 20 mg Opdivo Intravenous Infusion 100 mg	Unresectable malignant melanoma (additional dosage and administration)	May 25, 2018
Opdivo Intravenous Infusion 20 mg Opdivo Intravenous Infusion 100 mg	• Unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy • Malignant melanoma (changes in "Indications" and "Dosage and Administration") • Other indications (change in dosage)	Aug. 21, 2018
Imfinzi Injection 120 mg Imfinzi Injection 500 mg	Maintenance therapy after radical chemoradiotherapy for locally advanced, unresectable non-small-cell lung cancer	Aug. 28, 2018
Praluent 75 mg Solution for Injection in Pre-filled Pen Praluent 150 mg Solution for Injection in Pre-filled Pen Praluent 75 mg Solution for Injection in Pre-filled Syringe Praluent 150 mg Solution for Injection in Pre-filled Syringe	Familial hypercholesteremia, hypercholesteremia. The product should be used only in patients meeting both of the following conditions: • Who are at high cardiovascular risk • Who have had an inadequate response to HMG-CoA reductase inhibitors or for whom HMG-CoA reductase inhibitors are not indicated. (underlines in "Indications" denote additions)	Nov. 21, 2018
Opdivo Intravenous Infusion 240 mg	(additional volume specification)	Nov. 28, 2018
Keytruda Injection 20 mg Keytruda Injection 100 mg	• Advanced or recurrent, high microsatellite instability (MSI-High) solid tumors that has progressed after cancer chemotherapy (the product should be used only in cases refractory to standard therapies) • Malignant melanoma (changes in "Indications" and "Dosage and Administration") • Unresectable, advanced or recurrent non-small-cell lung cancer (change in "Indications")	Dec. 21, 2018
Tecentriq Intravenous Infusion 1200 mg	Unresectable, advanced or recurrent non-small-cell lung cancer (additional dosage and administration)	Dec. 21, 2018
Dupixent 300 mg Syringe for S.C. Injection	Bronchial asthma (the product should be used only in patients with severe or refractory bronchial asthma whose asthmatic responses are uncontrollable with conventional therapies)	Mar. 26, 2019

FY 2017

Drug name	Indication	Date of issue
Opdivo Intravenous Infusion 20 mg Opdivo Intravenous Infusion 100 mg	Unresectable advanced or recurrent gastric cancer that has progressed after cancer chemotherapy	Sep. 22, 2017
Bavencio Injection 200 mg	Unresectable Merkel cell carcinoma	Nov. 21, 2017
Keytruda Injection 20 mg Keytruda Injection 100 mg	Relapsed or refractory classical Hodgkin lymphoma	Nov. 30, 2017
	Unresectable urothelial carcinoma that has progressed after cancer chemotherapy	Dec. 25, 2017
Repatha SC Injection 140 mg Syringe Repatha SC Injection 140 mg Pen Repatha SC Injection 420 mg Auto mini-doser	Familial hypercholesteremia, hypercholesteremia. The product should be used only in patients with high cardiovascular risk who have had an inadequate response to HMG-CoA reductase inhibitors.	Dec. 15, 2017 (revised)
Tecentriq Intravenous Infusion 1200 mg	Unresectable advanced or recurrent non-small cell lung cancer	Apr. 17, 2018
Dupixent 300 mg Syringe for S.C. Injection	Atopic dermatitis in patients who have not responded sufficiently to conventional treatments	Apr. 17, 2018

FY 2016

Drug name	Indication	Date of issue
Opdivo Intravenous Infusion 20 mg Opdivo Intravenous Infusion 100 mg	Unresectable, advanced or recurrent non-small cell lung cancer	Feb. 14, 2017
	Unresectable malignant melanoma	Feb. 14, 2017
	Recurrent or distant metastatic head and neck cancer	Mar. 28, 2017
	Unresectable or metastatic renal cell carcinoma	Apr. 18, 2017
	Relapsed or refractory classical Hodgkin lymphoma	Apr. 18, 2017
Keytruda Injection 20 mg Keytruda Injection 100 mg	PD-L1-positive, unresectable, advanced or recurrent non-small cell lung cancer	Feb. 14, 2017
	Unresectable melanoma	Feb. 14, 2017
Repatha SC Injection 140 mg Syringe Repatha SC Injection 140 mg Pen	Familial hypercholesteremia, hypercholesteremia The product should be used only in patients with high cardiovascular risk who have had an inadequate response to HMG-CoA reductase inhibitors.	Mar. 31, 2017
Praluent 75 mg Solution for Injection in Pre-filled Syringe Praluent 75 mg Solution for Injection in Pre-filled Pen Praluent 150 mg Solution for Injection in Pre-filled Syringe Praluent 150 mg Solution for Injection in Pre-filled Pen	Familial hypercholesteremia, hypercholesteremia The product should be used only in patients with high cardiovascular risk who have had an inadequate response to HMG-CoA reductase inhibitors.	Mar. 31, 2017

3.2.(1).A.(ix) Establishment and operation of the Conditional Early Approval System

- MHLW had been planning to introduce the conditional early approval system. PMDA assisted MHLW in launching the system by joining discussions between MHLW and related industries, and by introducing a new consultation category (i.e., consultation on drug product eligibility for conditional early approval, which determines eligibility for conditional early approval prior to submission). Two applications for drug products were approved under the conditional early approval system in FY 2018.

3.2.(1).B. Generic drugs, etc.

- PMDA implemented or considered the following measures to accelerate reviews of generic drug products, etc.

3.2.(1).B.(i) Appropriate and prompt reviews

- PMDA established its Office of Generic Drugs in November 2014, and has since made efforts to further accelerate its reviews of products in this category through increased efficiency of operations.

3.2.(1).B.(i).a. Consultations and reviews based on medical care needs

- Members of PMDA's staff have participated in academic conferences and symposia held both in Japan and overseas, and have also exchanged opinions with healthcare professionals in order to better understand their needs. PMDA has also held consultations and conducted reviews while taking into account the information obtained through these methods.

3.2.(1).B.(i).b. Development of the Japanese Pharmacopoeia draft

- See Section 3.2.(1).A.(i).g.

3.2.(1).B.(i).c. Implementation of the master file workshop

- See Section 3.2.(1).A.(i).h.

3.2.(1).B.(i).d. Ensuring more efficient and transparent reviews

- PMDA prepared and released a draft of a mock-up CTD in collaboration with various industry associations to encourage the use of CTD/eCTD for marketing applications and thereby to increase the efficiency of reviews. In FY 2016, PMDA began to accept a pilot version of the CTD for new applications from companies able to prepare CTD. PMDA provided companies submitting the pilot version with individual feedback on areas for improvement in CTD preparation. MHLW issued a notification titled "Handling of Materials That Should be Attached to Application Dossiers for Prescription Drugs" (PSEHB/ELD Notification No. 0311-3, dated March 11, 2016, issued by the Director of the Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW). In accordance with the notification, applicants have, in principle, been required to submit data compiled in CTD format for new generic drug products submitted starting on March 1, 2017. In collaboration with various industry associations, PMDA prepared a Q & A document that contains answers to questions about CTD preparation and published it in FY 2017. This approach was continued in FY 2016 and 2017. PMDA also held a lecture featuring points to consider in CTD preparation in October 2018, in order to promote submission of CTD for new generic drug applications.
- PMDA started to publish the pilot version of review reports prepared for new generic drugs. Review reports for 2 generic drugs registered by one MAH were published in FY 2017. Discussion on publication of review reports for other generic drugs is ongoing, and preparation for publication has been focused on products particularly attracting social attention.
- PMDA discussed the development of a guidance concerning bioequivalence studies for drugs that cannot be evaluated based on the existing guidelines for bioequivalence studies. Accordingly, PMDA developed guidance materials concerning 2 basic concepts pertaining to bioequivalence studies of aqueous ophthalmic solutions and dry powder inhalers. As a result, MHLW issued the

following administrative notices: “Basic Principles on Bioequivalence Evaluation of Generic Dry Powder Inhalers” (PSEHB/ELD Administrative Notice, dated March 11, 2016, issued by the Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW) and “Basic Principles concerning Bioequivalence Evaluation of Generic Aqueous Ophthalmic Solutions” (PSEHB/ELD Administrative Notice, dated March 11, 2016, issued by the Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW).

Furthermore, based on discussion of bioequivalence evaluation applicable to overall ophthalmic solutions, MHLW issued an administrative notice entitled “Basic Principles for Bioequivalence Studies of Generic Ophthalmic Solutions” (PSEHB/ELD Administrative Notice, dated November 29, 2018, issued by the Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW) as a new guidance document concerning ophthalmic solutions. With the issuance of this administrative notice, the administrative notice containing the previous guidance on bioequivalence of aqueous ophthalmic solutions was abolished.

3.2.(1).B.(ii) Approaches to shorten review times

- PMDA established the following target regulatory review times for applications submitted on or after April 1, 2004 (and approved thereafter), and has made efforts to achieve these targets while asking for the cooperation of applicants.

  MHLW and PMDA discussed the handling of approval applications and the total review period to increase the predictability of approval of generic drugs etc. As a result, MHLW issued a notification, “Policy for Handling Approval Applications and Total Review Period to Increase the Predictability of Approval of Generic Drugs etc.” (PSEHB/PED Notification No. 0223-1, dated February 23, 2018, issued by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW).

- In order to carry out prompt and accurate reviews of generic drugs, PMDA performed its operations in accordance with its SOPs and its Procedures for the Review of Generic Prescription Drugs.

  Data detailing the rate of realization of the target review times were periodically collected and provided to reviewers in PMDA. The progress of operations was assessed at joint meetings of the Progress Management Committee for Reviews and Related Services and the Review Segment Committee for Progress Management.

- The approval status of generic drugs in FY 2018 is as follows:

3.2.(1).B.(ii).a. Review time for new application for generic drugs

Targets

PMDA aims to achieve the following target review time for the 50th percentile (median) of applications by FY 2018.

Type of application	Regulatory review time [months]
New generic drugs	10

Results

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Approved products	1,325	635	731	805	620
Median regulatory review time [months]	6.1	8.2	8.2	8.9	6.0

Note: Products submitted for approval in or after April 2004 are covered.

3.2.(1).B.(ii).b. Review time for partial change application for generic drugs, etc. (standard review products)

Targets

PMDA aims to achieve the following target review times for the 50th percentile (median) of applications by FY 2018.

Fiscal year	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Total review time [months]	15	14	13	12	10

Results

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Approved products	586	701	537	559	336
Median total review time [months]	15.5	13.0	11.7	11.7	8.1

Note: Products submitted for approval in or after April 2004 are covered.

3.2.(1).B.(ii).c. Review time for partial change applications for generic drugs, etc. (excluding the products that fall under "b" above)

Targets

PMDA aims to achieve the following target review time for the 50th percentile (median) of applications by FY 2018.

Type of application	Total review time [months]
Partial change (change of test methods etc.)	6
Partial change (expedited review)	3

Results

		FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Change of test methods, etc.	Approved products	1,367	1,594	1,676	1,495	1,087
	Median total review time [months]	7.3	6.9	7.0	7.3	4.6
Expedited review	Approved products	168	305	248	237	221
	Median total review time [months]	4.0	4.8	4.3	3.3	2.8

Note: Products submitted for approval in or after April 2004 are covered.

Reviews and Related Services Conducted for Generic Drugs, etc. by Fiscal Year

Fiscal Year	Applied	Approved	Withdrawn, etc.	Under review
FY 2014	3,452	3,447	214	3,396
FY 2015	3,502	3,235	281	3,382
FY 2016	3,163	3,192	254	3,099
FY 2017	2,154	3,096	311	1,846
FY 2018	2,483	2,264	163	1,902

Note: The figures provided in the "Withdrawn, etc." column do not include the number of products that were switched to other review categories during the review.

Document-based Compliance Assessments for Generic Drugs by Fiscal Year

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Generic drugs	1,080	1,045	870	883	572

- PMDA conducted compliance assessment for 572 generic drug applications to examine whether the data submitted comply with standards for data integrity. In the course of assessment, the submitted data were checked against raw data such as test records, laboratory notebook, and case report forms.

3.2.(1).B.(iii) Efficient implementation of clinical trial consultations

- In January 2012, PMDA began providing the following clinical trial consultations for generic drugs on a pilot basis: “Quality consultation for generic drugs” and “Consultation concerning generic drug bioequivalence.” The requests for these consultation types have been increasing alongside growing awareness of the usefulness of clinical trial consultations in the development of generic drugs. PMDA adapted to this increase in consultation requests by improving its operations.

Number of Consultations for Generic Drugs

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Conducted	24	48	56	79	90
Withdrawn	1	8	4	12	2

Note: PMDA began providing consultations focusing on generic drug products in FY 2011.

Number of Consultations for Generic Drugs by Consultation Category in FY 2018

Consultation category	Conducted	Withdrawn
Consultations on bioequivalence of generic drugs	70	2
Quality consultations for generic drugs	20	0
Total	90	2

3.2.(1).B.(iv) Handling of changes to approved product information pertaining to the quality of drugs

- See Section 3.2.(1).A.(vii)

3.2.(1).C. Behind-the-counter (BTC) drugs, over-the-counter (OTC) drugs, and quasi-drugs

- PMDA took the following measures to promote public self-medication.

3.2.(1).C.(i) Appropriate and prompt reviews

3.2.(1).C.(i).a. Enhancement of the review system for BTC drugs and OTC drugs

- Staff members with experience in pharmacovigilance or compliance assessment provided advice and guidance to other staff in accordance with the degree and nature of their expertise. In FY 2016, PMDA issued a notification entitled “Procedures for Conducting Document-based Compliance Assessment Related to Application for Behind-the-counter (BTC) Drugs and Over-the-counter (OTC) Drugs” (PMDA Notification No. 0306053, dated March 6, 2017, issued by the Chief Executive of the Pharmaceuticals and Medical Devices Agency). The Office of OTC/Quasi-drugs appropriately took the lead in handling document-based compliance assessments based on this notification, and made efforts to promote post-marketing surveillance in response to the establishment of BTC drugs category.

The Office of OTC/Quasi-drugs performed toxicological and clinical reviews of new BTC/OTC drugs in close collaboration with other offices in PMDA by, for example, seeking advice from expert staff in different offices, as necessary.

- Reviewers participated in academic conferences held in Japan, and exchanged opinions with healthcare professionals. The Agency conducted reviews and consultations, taking into account the information obtained in this manner.
- For details concerning the development of the draft Japanese Pharmacopoeia, see Section 3.2.(1).A.(i).g.
- PMDA made efforts to improve the quality of its reviews by having reviewers participate in the Japanese Pharmacopoeia Crude Drug Committee to exchange opinions with experts in the field of Kampo medicine (traditional herbal medicines)/crude drugs.
- PMDA assisted MHLW in (a) developing and revising approval standards and (b) preparing notifications related to standards of crude products. As a result, MHLW issued the following notification in FY 2018.
- "The Japanese Standards for Non-Pharmacopoeial Crude Drugs 2018" (PSEHB/PED Notification No. 1214-4, dated December 14, 2018, issued by Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW)

3.2.(1).C.(i).b. Reinforcement of the review system for quasi-drugs

- To improve the efficiency of review, PMDA made efforts to familiarize applicants with the "Checklist for Data Submitted for Marketing Approval of Quasi-drugs, etc.," and encouraged them to use the checklist for product applications submitted in FY 2018 as well, via lectures, etc.
- PMDA supported the holding of meetings of the "Quasi-drugs Guidance Review Committee," to encourage the use of alternative methods for animal experiments, promoted by the Japanese Center for the Validation of Alternative Methods (JaCVAM). In addition, MHLW issued the following notifications in FY 2018.
- "Guidance on Short Time Exposure (STE) Test Using Cell Line Derived from Rabbit Cornea as Alternative Testing Methods for Eye Irritation for Safety Evaluation of Quasi-drugs and Cosmetics" (PSEHB/PED Notification No. 1218-1, dated December 18, 2018, issued by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW)
- PMDA has made efforts to improve the quality of reviewers by having them participate in training programs, academic conferences, etc., held in Japan to exchange opinions with specialists. PMDA conducted reviews and consultations, taking into account the information obtained in this manner.

3.2.(1).C.(ii) Approaches to shorten review times

- PMDA established target review times for applications for BTC, OTC, and quasi-drugs submitted on or after April 1, 2004, and has since conducted reviews to achieve these targets.
- In order to conduct prompt and accurate reviews of products in these categories, PMDA executed operations in accordance with its SOPs: the Procedures for Review of OTC Drugs; the Procedures for Review of Insecticides/Rodenticides; and the Procedures for Review of Quasi-drugs. Each of these procedures specify the standard methods and protocols associated with each type of regulatory review.

Data describing the degree of realization of the target review times were collected periodically and provided to reviewers in PMDA. The progress of operations was assessed at joint meetings of the Progress Management Committee for Reviews and Related Services and the Review Segment Committee for Progress Management.

- PMDA clarified review schedule by presenting target times of initial inquiries, Expert Discussion, and Drug Committees, to contribute to progress management for novel BTC/OTC drugs. In addition, applicants delaying in responding to initial inquiries from PMDA were instructed to report the reason for the delay and to answer the inquiries quickly. The Expert Discussion had a discussion about 2 OTC ingredients. The BTC/OTC Drug Committee discussed 1 new active ingredient in 1 product (a BTC [OTC] drug with a new active ingredient) and 1 new active ingredient in 2 products (2 BTC [OTC] drugs with new dosage).
- Similarly to its handling of BTC and OTC drugs, PMDA clarified target processing times for applications for quasi-drugs (e.g., target times for the Cosmetics and Quasi-Drug Committees) to accelerate review process. The Expert Discussion discussed 3 new quasi-drugs. The request for inclusion of 1 new ingredient in the positive list of The Japanese Standards for Cosmetics was referred to the Cosmetics and Quasi-Drug Committee. MHLW issued MHLW Ministerial Announcement No. 77 to announce partial amendment of The Japanese Standards for Cosmetics (MHLW Ministerial Announcement No. 331 of 2000).
- The approval status of BTC drugs, OTC drugs, and quasi-drugs in FY 2018 is as follows:

3.2.(1).C.(ii).a. Review time for BTC drugs and OTC drugs

Targets

PMDA aims to achieve the following target review time for the 50th percentile (median) of applications by FY 2018.

Type of application	Regulatory review time
BTC and OTC drugs	7 months

Results

BTC and OTC drugs	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Approved products	844	752	646	537	452
Median regulatory review time [months]	6.3	5.5	4.3	4.6	4.8

Note: Products submitted for approval in or after April 2004 are covered. The calculation excluded the time between completion of reviews and notification of GMP inspection results issued by prefectural governments or other authorities.

3.2.(1).C.(ii).b. Review time for quasi-drugs

Targets

PMDA aims to achieve the following target review time for the 50th percentile (median) of applications by FY 2018.

Type of application	Regulatory review time [months]
Quasi-drugs	5.5 months

Results

Quasi-drugs	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Approved products	1,779	2,495	1,924	1,891	1,665
Median regulatory review time [months]	4.9	4.7	4.4	4.4	4.6

Note: Products submitted for approval in or after April 2004 are covered. The calculation excluded the time between completion of reviews and notification of GMP inspection results issued by prefectural governments or other authorities.

Reviews Conducted for BTC Drugs, OTC Drugs, and Quasi-drugs by Fiscal Year

Category	Fiscal Year	Applied	Approved	Withdrawn, etc.	Under review
BTC drugs OTC drugs	FY 2014	882	844	99	1,848
	FY 2015	716	752	126	1,686
	FY 2016	700	646	115	1,625
	FY 2017	624	537	115	1,597
	FY 2018	774	452	86	1,833
Quasi-drugs	FY 2014	1,828	1,779	125	2,280
	FY 2015	2,559	2,495	155	2,189
	FY 2016	2,062	1,924	137	2,190
	FY 2017	1,824	1,891	187	1,936
	FY 2018	1,779	1,665	137	1,913

Note: The figures in "Withdrawn etc." do not include the number of products that were switched to other review categories during the review.

3.2.(1).C.(iii) Efficient conduct of consultations

3.2.(1).C.(iii).a. Improvement of pre-application consultations for BTC drugs and OTC drugs

- PMDA began offering pre-development and pre-application consultations related to OTC drugs in FY 2010 based on opinions from industry associations. In FY 2011, PMDA started to offer consultations regarding the appropriateness of new OTC drug development activities. In addition, pre-application consultations for OTC Switch drugs and consultations on key points of clinical trial protocols became fully available from May 2015. PMDA has also established pre-development consultations for OTC Switch drugs and consultations on quality of OTC drugs as new consultation services related to the "Review Committee Meetings on Prescription to BTC/OTC switch" held in MHLW. These new consultations will be implemented in FY 2019 on a trial basis.

Consultations for OTC Drugs

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Conducted	21	15	23	35	29
Withdrawn	0	1	0	0	3

Number of Pre-development and Pre-application Consultations for OTC Drugs by Consultation Category in FY 2018

Consultation category	Conducted	Withdrawn
Pre-application consultation for OTC switch drugs	3	0
Consultation on key points of clinical trial protocols for OTC drugs	2	0
Consultation on appropriateness of development of new OTC drugs	24	3
Total	29	3

3.2.(1).C.(iii).b. Improvement of pre-application consultations for quasi-drugs

- In order to expand pre-application consultation services for quasi-drugs, PMDA exchanged views with concerned parties (e.g., the Japan Cosmetic Industry Association) regarding the development of new consultation services. Accordingly, in FY 2019, PMDA is planning to increase the number of consultations on the development of quasi-drugs (i.e., "human study plan confirmation consultation," "new excipient development consultations") that have been implemented starting in FY 2017 on a trial basis.

Number of Pre-application Consultations for Quasi-drugs

	FY 2017	FY 2018
Conducted (face-to-face)	2	9
Withdrawn	0	0

Number of Pre-application Consultations for Quasi-drugs by Consultation Category in FY 2018

Consultation category	Conducted
Human study plan confirmation consultation	6
New excipient development consultation	3
Total	9

3.2.(1).C.(iv) Handling of changes to approved product information pertaining to the quality of drugs

- See Section 3.2.(1).A.(vii)

3.2.(1).D. Medical devices

- Various measures were implemented or considered to accelerate reviews of new medical devices in accordance with the "Collaboration Plan to Accelerate Reviews of Medical Devices" (March 2014) (successor to the "Action Program to Accelerate Reviews of Medical Devices" [December 2008]), the "Japan Revitalization Strategy," the "Healthcare and Medical Strategy," and the "Growth Strategy Council."

3.2.(1).D.(i) Appropriate and prompt reviews

3.2.(1).D.(i).a. Clinical trial consultations and review structures

- To enhance its review system to become capable of achieving its targets, PMDA appropriately allocated reviewers to the categories receiving large numbers of medical device application filings where delays in the review process were most likely.
- Reviews of new medical devices and improved medical devices were conducted by review teams consisting of experts holding academic degrees in engineering, pharmaceutical science, physical science, clinical medicine, dentistry, veterinary medicine, statistics, etc., under the guidance of an office director and a review director.

  Review teams are typically comprised of a team leader and reviewers specializing in biological safety, physicochemical properties, electrical safety, and clinical evaluations.

Note:

New medical devices:

- *Medical devices which have a clearly different structure, usage, indications, performance, etc. compared with those for which marketing approval has been granted (medical devices that have been specified as being subject to use results assessment according to the provisions of Paragraph 1, Article 23-2-9 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (hereinafter, the "PMD Act") at the time of approval, excluding those for which the survey period has not expired; hereinafter referred to as "approved medical devices") (as defined under the PMD Act).*
- *Medical devices subject to re-examination, which have a clearly different structure, usage, indications, performance, etc., compared to existing approved medical devices or certified medical devices (as defined under the PMD Act)*

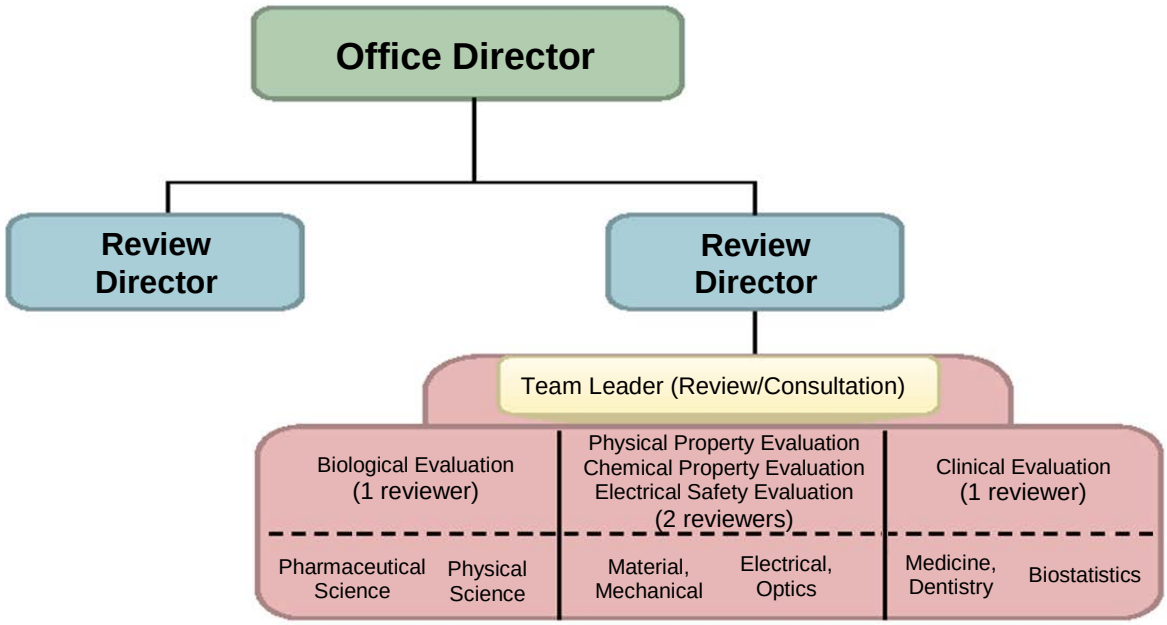
Improved medical devices:

- *Medical devices that do not fall under "new medical devices" or "generic medical devices" (definition under the PMD Act)*
- *Medical devices that do not fall under "new medical devices" or "generic medical devices," and are not so novel as to be subject to re-examination, nor are substantially equivalent to existing medical devices in terms of structure, usage, indications, performance, etc. (as defined under the PMD Act)*

Generic medical devices:

- *Medical devices that are regarded as equivalent to existing approved medical devices in terms of structure, usage, indications, and performance; that is, medical devices that are substantially equivalent to existing approved medical devices in terms of structure, usage, indications, and performance (as defined under the PMD Act)*
- *Medical devices that are regarded as substantially equivalent to existing approved medical devices in terms of structure, usage, indications, performance, etc. (as defined under the PMD Act)*

Organization for New or Improved Medical Device Reviews



- New and improved medical devices were reviewed by teams assigned based on the review categories shown below. In January 1, 2019, PMDA reorganized its device offices to allow highly specialized operation based on the characteristics of individual medical devices. This intends to reinforce cooperation and communication among medical device offices and to ensure the

increased efficiency of their operations. More specifically, four device offices (the Offices of Medical Devices I to III and the Office of In Vitro Diagnostics) were reorganized to three device offices (the Offices of Medical Devices I to II and the Office of In Vitro Diagnostics), and two additional offices (the Office of Standards and Compliance for Medical Devices and the Office of Manufacturing Quality and Vigilance for Medical Devices) were launched. These five offices constitute the Medical Device Unit.

In parallel with the organizational restructuring described above, PMDA has also restructured review categories for medical devices into new review categories (see below).

Review Categories Covered by the Offices of New/Improved Medical Devices (up to the end of December 2018)

<table>
<tr><th>Office</th><th colspan="2">Review Categories</th></tr>
<tr><td rowspan="2">Office of Medical Devices I</td><td>Robotic, ICT, and other devices</td><td>Primarily innovative medical devices utilizing robotics and advanced ICT technologies, multicategory medical devices, and other uncategorized medical devices</td></tr>
<tr><td>Orthopedic and Plastic Surgery</td><td>• Primarily medical devices targeting the hips, knees, upper extremities, hands, and digits, etc. among orthopedic devices
• Primarily plates/screws, fixation materials for intramedullary nails/spines and related appliances/machines in orthopedic surgery area, and medical devices for plastic surgery and dermatology</td></tr>
<tr><td rowspan="3">Office of Medical Devices II</td><td>Brain and Circulatory Medicine, Respiratory Medicine, Neurology, and Psychiatry</td><td>• Materials used in the fields of brain and circulatory medicine (excluding cardiology) as well as respiratory medicine, neurology, and psychiatry
• Mechanical appliances used in the fields of brain and circulatory medicine (excluding cardiology) as well as respiratory medicine, neurology, and psychiatry</td></tr>
<tr><td>Gastroenterology, Genitourinary, and Reproductive Medicine</td><td>Primarily gastrointestinal and urinary systems, obstetrics and gynecology-related products</td></tr>
<tr><td>Dentistry and Oral Medicine</td><td>Primarily dentistry-related products</td></tr>
<tr><td rowspan="2">Office of Medical Devices III</td><td>Ophthalmology and Otorhinolaryngology</td><td>Primarily ophthalmology and otorhinolaryngology-related products</td></tr>
<tr><td>Cardiopulmonary and cardiovascular areas</td><td>• Primarily cardiology-related materials used in medical devices pertaining to the circulatory system
• Primarily cardiology-related mechanical appliances pertaining to the circulatory system</td></tr>
<tr><td colspan="3">Cross-sectional teams</td></tr>
<tr><td colspan="3">(i) Clinical evaluation team
(ii) Biological safety team
(iii) Electrical safety (including laser) team
(iv) AI and software (including cyber security) team
(v) Generic team (including cooperation plan: Clarification of substantial equivalence)
(vi) International (including IMDRF) team
(vii) Regulatory science team
(viii) Biological device team, Office of Cellular and Tissue-based Products (Evaluation of virus safety of biological products)</td></tr>
</table>

Review Categories Covered by the Offices of New/Improved Medical Devices (from January 2019 onwards)

Office	Review Categories	
Office of Medical Devices I	Robotic, ICT, and other devices	Primarily innovative medical devices utilizing robotics and advanced ICT technologies, multicategory medical devices, and other uncategorized medical devices
	Ophthalmology and Otorhinolaryngology	Primarily ophthalmology and otorhinolaryngology-related products
	Cardiopulmonary and cardiovascular areas	• Primarily cardiology-related materials used in medical devices pertaining to the circulatory system • Primarily cardiology-related mechanical appliances pertaining to the circulatory system
Office of Medical Devices II	Brain and Circulatory Medicine, Respiratory Medicine, Neurology, and Psychiatry	• Materials used in the fields of brain and circulatory medicine (excluding cardiology) as well as respiratory medicine, neurology, and psychiatry • Mechanical appliances used in the fields of brain and circulatory medicine (excluding cardiology) as well as respiratory medicine, neurology, and psychiatry
	Gastroenterology, Genitourinary, and Reproductive Medicine	Primarily gastrointestinal and urinary systems, obstetrics and gynecology-related products
	Dentistry and Oral Medicine	Primarily dentistry-related products
	Orthopedic and Plastic Surgery	• Primarily medical devices targeting the hips, knees, upper extremities, hands, and digits, etc. among orthopedic devices • Primarily plates/screws, fixation materials for intramedullary nails/spines and related appliances/machines in orthopedic surgery area, and medical devices for plastic surgery and dermatology
Cross-sectional teams		
(i) Clinical evaluation team (ii) Biological safety team (iii) Electrical safety (including laser) team (iv) AI and software (including cyber security) team (v) Generic team (including cooperation plan: Clarification of substantial equivalence) (vi) International activities (including IMDRF) team (vii) Regulatory science team (viii) Biological device team, Office of Cellular and Tissue-based Products (Evaluation of virus safety of biological products) (ix) Remanufactured single-use devices (SUD) team		

- Expert Discussions were held as necessary to support reviews performed by PMDA's review teams with opinions from external experts. In addition, the decision on the approval of innovative medical devices and other products was discussed at the Committee on Medical Devices and *In-vitro* Diagnostics convened by the Pharmaceutical Affairs and Food Sanitation Council (PAFSC) at MHLW.

Review Performance for FY 2018 (medical devices and in vitro diagnostics)

(1) Number of Expert Discussions conducted: 81 (62 document-based discussions, 19 meetings)
(2) Applications deliberated at the Committee on Medical Devices and *in vitro* Diagnostics (under PAFSC): 15
Applications reported to the Committee on Medical Devices and *in vitro* Diagnostics (under PAFSC): 355 (318 medical devices, 37 *in vitro* diagnostics)

- PMDA conducted clinical trial consultations for new/improved medical devices based on the team-reviewed guidance plan drafted by three staff members consisting of a Review Director, a consultation leader, and a deputy consultation leader. Consultation leaders and deputy consultation leaders are appointed from among review team members.

- PMDA established cross-sectional review teams for generic medical devices and shared information to maintain the same quality of reviews across the review offices.

3.2.(1).D.(i).b. Introduction of the 3-track review system

- As one of the efforts to advance and accelerate reviews of medical devices, the 3-track review system (for new medical devices, improved medical devices, and generic medical devices) has been put in place in PMDA since FY 2011. In FY 2018, PMDA kept on promoting the system based on the experiences in previous fiscal years.

3.2.(1).D.(i).c. Reinforcement and improvement in the transparency of the progress management of reviews

- In joint meetings held by the “Progress Management Committee for Reviews and Related Services” and the “Review Segment Committee for Progress Management,” the committee members shared information regarding the progress of operations, and discussed how to address issues associated with new medical device reviews, by assessing relevant information comprehensively.

  At these joint meetings, necessary guidance was provided on an ongoing basis by the Director of the Center for Product Evaluation and the responsible Associate Center Director while taking into account reports from office directors of review divisions, and each review segment was notified of the results of discussions and of improvement measures for products requiring extended review.

- To accelerate review times, timelines were managed strictly in accordance with the “On the Standard Review Timeline for New Medical Device Applications” (PFSB/ELD/OMDE Notification No. 1120-1 dated November 20, 2013, by the Director of Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW), “On the Standard Review Timeline for Improved Medical Device Applications (with Clinical Data)” (PFSB/ELD/OMDE Notification No. 0328-4 dated March 28, 2014), and “On the Standard Review Timeline for Improved Medical Device (without Clinical Data) and Generic Medical Device Applications” (PFSB/ELD/OMDE Notification No. 0519-1 dated May 19, 2014).

- In accordance with the “Information Sharing about the Progress of Reviews of New Medical Devices and Improved Medical Devices” (PMDA Notification No. 0530001 dated May 30, 2014, by the Chief Executive of the Pharmaceuticals and Medical Devices Agency), the progress of the PMDA review is communicated to applicants in each review stage. The relevant office directors appropriately hold meetings with applicants upon their request to explain the progress and outlook of the review to them.

3.2.(1).D.(i).d. Standardization and transparency of review

- To clarify review standards, PMDA posted on its website 3 documents concerning basic points to consider related to its review processes: “Points to Consider in regard to Applications for New Medical Devices, etc.,” “Points to Consider in regard to Applications for Improved Medical Devices,” and “Points to Consider in regard to Applications for Generic Medical Devices.” These documents were first published in FY 2008, and were later revised in conjunction with subsequent regulatory policy changes. PMDA has also explained these points to relevant reviewers and has been using them for reviews etc.

- To promote the transparency and efficiency of reviews, PMDA posted on its website the “Guidelines for Preparation of Summary Technical Documentation (STED) Submitted in Applications for Medical Devices (new medical devices),” a revised version of the “Guidelines for

Preparation of Summary Technical Documentation (STED) Submitted in Applications for Medical Devices (new medical devices and improved medical device)" published in FY 2009. PMDA introduced the guidelines at workshops to make them widely known. PMDA posted on its website the following guidance documents: "Points to Consider in Preparing Data for Applications of Improved Medical Devices" for improved medical devices, "Points to Consider in Preparing Data for Applications of Generic Medical Devices," "Guidelines for Preparation of Summary Technical Documentation (STED) Submitted in Applications for Medical Devices in the Category of Generic Medical Devices (without approval standards, without clinical data)," and "Confirmation of Application Documents for Generic Medical Devices" for generic medical devices. PMDA also presented these guidance documents in workshops to thoroughly disseminate them.

3.2.(1).D.(i).e. Consultations and reviews based on medical care needs

- PMDA actively exchanged opinions with healthcare professionals by participating in academic conferences in and out of Japan, town hall meetings, requested lectures, etc., to comprehend their needs. The Agency has conducted consultations and reviews, taking into account the information obtained in this manner.
- In October 2006, MHLW established the "Study Group on the Early Introduction of Medical Devices with High Medical Need (currently chaired by Dr. Hiroyuki Konno, President of Hamamatsu University School of Medicine)," to encourage medical device manufacturers to develop medical devices that had already been approved in Europe and the U.S. but not in Japan. Under this Study Group, a working group was established to discuss and evaluate individual issues. The Study Group and the working group have held active discussions. In 2018, the Study Group convened once and the working group convened once. PMDA supported the operation of the Study Group. As a result of the discussions by the Study Group, PMDA conducted clinical trial consultations and product reviews, leading to the approval of 6 medical devices in FY 2018. The meeting of the working group was held at PMDA, which served as the secretariat, engaging in various activities, such as preparing documents, communicating with the working group members, and seeking the opinions of academic societies and companies.

3.2.(1).D.(i).f. Consistency between clinical trial consultations and reviews

- In order to ensure consistency between clinical trial consultations and reviews, review team members are involved in all clinical trial consultations for products falling under the category to which they are assigned. Consistency between consultations and actual review processes is maintained and teams are flexibly organized as necessary.

3.2.(1).D.(i).g. Efficient operation and implementation of the use-results evaluation system

- With the enactment of the PMD Act, a new use-results evaluation system for medical devices was introduced on November 25, 2014. PMDA strove to implement and efficiently manage the system, in accordance with the guidance document on "Basic Principles on Products Subject to Use-results Evaluation at the Time of Approval" that was deliberated and approved at the 6th meeting of the Committee on Medical Devices and In Vitro Diagnostics, the Pharmaceutical Affairs and Food Sanitation Council in MHLW in FY 2014.

  Based on the principles, 18 medical devices (including 12 medical devices selected for use-results survey) were approved in FY 2018.
- In order to implement the new system smoothly, medical devices that had been designated as products subject to re-examination before the system reform were processed with greater collaboration with the office responsible for compliance assessment (Office of Non-clinical and

Clinical Compliance). As a result, 12 medical devices subject to re-examination were processed in FY 2018.

3.2.(1).D.(ii) Introduction of new review systems

3.2.(1).D.(ii).a. Short-term review of applications for specified partial changes

- Applications for specified partial changes were reviewed in accordance with the notification entitled "Acceleration of the Procedure for Specified Changes Made to Medical Devices" (PFSB/ELD/OMDE Notification No. 1110001, dated November 10, 2008, issued by Director of the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW). In FY 2018, applications for 26 products were approved, and the total review time for 22 of the 26 products approved was not more than 3 months.

3.2.(1).D.(ii).b. Support for the development of approval standards, certification standards, and review guidelines for medical devices

- In order to support MHLW in developing approval standards etc., for medical devices, the Committee on Medical Device Approval Standards held 4 meetings in FY 2017.

  The table below shows the number of approval or certification standards reported to MHLW in FY 2017 to be established or revised.

FY (for reporting)	Up to FY 2013	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018	Total
Approval standards	41	0	3	2	8	1	55
Certification standards (designated controlled medical devices)	691	129	99	156	34	16	1125
Certification standards (designated specially controlled medical devices)	-	3	7	1	0	0	11
Review guidelines	9	0	0	1	0	0	10

The following table shows the number of standards established by MHLW in FY 2018 based on the reports from PMDA.

Numbers of Approval Standards, Certification Standards, and Review Guidelines Established for Medical Devices

FY (for establishment)	Up to FY 2013	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018	Total
Approval standards	45	0	-1[*1]	0	1	0	45
Certification standards (designated controlled medical devices)	827	109	0	-1[*2]	0	-1[*3]	934
Certification standards (designated specially controlled medical devices)	-	3	7	1	0	0	11
Review guidelines	8	0	0	0	1	0	9

**1 In FY 2015, one established approval standards was switched to certification standards, resulting in a negative number (indicated as -1).*

**2 In FY 2016, one established certification standard was integrated with certification standards for designated specially controlled medical devices, resulting in a negative number (indicated as -1).*

**3 In FY 2018, two established certification standards were repealed and one certification standard was newly established, resulting in a negative number (indicated as -1).*

List of Certification Standards for Medical Devices (FY 2018)

Established: Certification standards,1; Approval standards,0; Review guidelines, 0	
Date of issue	Name of standards
MHLW Ministerial Announcement No. 231 dated May 22, 2018	Standards for Light Therapy Carbon Arc Apparatus for Home Use

- The “Standards for Medical Devices” web page on the PMDA website provides current information on certification and approval standards for medical devices as well as links to their components, including: Japanese Industrial Standards (JIS), International Organization for Standardization (ISO)/ International Electrotechnical Commission (IEC), MHLW Notifications, Japanese Medical Device Nomenclature (JMDN), etc. The information on the web page is updated, in principle at least twice per month.

  In addition, PMDA has posted 945 certification standards with related Essential Principles Checklists, etc., in English on its website by FY 2018. Furthermore, to globally disseminate information concerning basic principles of the third-party certification system for medical devices employed in Japan as well as certification standards established by utilizing international standards such as ISO/IEC, PMDA prepared the English database of the JMDN which lists term names and definitions of individual medical devices (covering more than 4,300 devices) and posted it on the “Standards for Medical Devices” web page in FY 2018, in response to strong requests from foreign governments (including those of ASEAN member countries, European countries, and the US) and industry associations in Japan. PMDA further implemented various functions to search standards and term names on this English web page to improve its convenience.

- PMDA provided advice on each individual product through simple consultations on the scope of changes for which partial change applications are not required, or minor change notifications are required, based on the “Procedures Associated with Partial Change for Medical Devices” (PFSB/ELD/OMDE Notification No.1023001, dated October 23, 2008).

  MHLW issued a notification, “Handling of Procedures for Minor Changes Associated with Partial Changes for Medical Devices” (PSEHB/MDED Notification No. 0731-5 dated July 31, 2017, issued by Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW). In response to the notification, PMDA established a consultation category, “simple consultation prior to submission of change notifications for medical devices.” This type of consultation serves to provide advice to Marketing Authorization Holders (MAHs) who plan to submit a medical device change notification that is likely to fall under “minor change notification” but may possibly fall under “partial change application,” to determine an applicable category in advance. By encouraging MAHs to utilize this consultation service, PMDA strived to contribute to a reduction in the operational burdens of both MAHs and regulatory agencies.

- PMDA addressed procedures for changing raw materials for individual products through simple consultations based on “Regarding the Procedure for Changing Raw Materials of Medical Devices” (PFSB/ELD/OMDE Notification No. 0329-7, dated March 29, 2013), which clarifies the principle of the procedure.

- Based on the accumulated knowledge concerning irradiation sterilization, PMDA supported MHLW in preparing the following notifications that provide guidance on the handling of approval (certification) of sterile medical devices:

  “Partial Revision of ‘Points to Consider in Preparing Summary Technical Documentation (STED) for Medical Devices’” (PSEHB/MDED Notification No. 0228-7 dated February 28, 2018, by the Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW)

"Handling of Sterilization in the Application for Marketing Approval (Certification) of Sterile Medical Devices" (PSEHB/MDED Notification No. 0228-10 dated February 28, 2018, by the Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW)

"Q&A on Handling of Sterilization in the Application for Approval of Sterile Medical Devices" (PSEHB/MDED Administrative Notice dated February 28, 2018, by the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW)

PMDA appropriately conducted approval reviews and consultations for individual medical devices.

- In response to MAH inquiries concerning whether clinical study data are also necessary during consultations, PMDA provided guidance in the context of each applicable product based on notifications and similarly authoritative materials previously by MHLW.
- In order to clarify the scope of individual products, PMDA conducted simple consultations etc., by referring to the "Points to Consider in Preparing Application Forms for Marketing Certification of Medical Devices" (Notification No. 1120-4, by the Counsellor of Minister's Secretariat [for Medical Device and Regenerative Medical Product Evaluation], MHLW, dated November 20, 2014), "Handling of Applications for Dental Implants" (PFSB/ELD/OMDE Notification No. 0713-1, dated July 13, 2012).

3.2.(1).D.(ii).c. Equivalence review of generic medical devices

- PMDA conducted equivalence reviews for generic medical devices filed in FY 2018 based on a notification titled "Points to Consider in Preparing Summary Technical Documentation (STED) for Medical Devices" (Notification No. 0120-9 by the Counsellor of Minister's Secretariat (for Medical Device and Regenerative Medical Product Evaluation), MHLW, dated January 20, 2015).
- In order to clarify the definition of substantial equivalence of generic medical devices based on the "Cooperation Plan to Accelerate Reviews of Medical Devices," PMDA held 3 meetings with related industry associations and strove to identify and summarize problems that needed to be resolved.

3.2.(1).D.(iii) Efforts to realize "zero" review lag for medical devices

- The targets for the total review time for medical device approved in each fiscal year (including those whose applications were submitted on or after April 1, 2004) were determined for each category. The target total review time was set by gradually increasing the percentiles. PMDA has made every effort to achieve the targets by FY 2018 and sought the cooperation of applicants.
- PMDA worked to improve its progress management activities for products under review in any application category (new, improved, or generic medical devices). PMDA also worked to reduce the backlog of pending applications. Specifically, to promptly complete the prolonged review of applications filed years earlier, PMDA and applicants had discussions to analyze reasons for prolonged review and resolve relevant issues for each product. In addition, reminder notices were frequently sent to applicants if their responses to PMDA's inquiries were delayed. For products for which new applications have been submitted, progress management was enhanced to accelerate reviews.
- In order to eliminate review/development lag for medical devices being developed or to be developed in the near future, PMDA encouraged medical device-related industries, medical device companies, and academic institutions to take measures such as the proactive use of clinical trial consultations prior to regulatory submission, at academic conferences or periodic opinion exchange sessions with the industries. Moreover, PMDA provided specific examples of

deficiencies often seen at the time of regulatory submission, at workshops, etc., to call for improvements to be made on the applicants' side.

- PMDA organized cross-sectional review teams for generic medical devices and shared information to maintain the consistent quality of reviews across the review teams.
- In order to ensure consistency between review teams and to ensure prompt and appropriate medical device reviews, PMDA developed standard operating procedures (SOPs) relating to various operations, which describe reviews and related procedures for each type of new medical device, improved medical devices, and generic medical devices. Relevant reviewers were given an explanation of these SOPs. PMDA also collected monthly data on the achievement level of the target review times and informed the reviewers of the achievement status.
- PMDA contributed to the activities of Harmonization by Doing (HBD), which is a cooperative effort by industry, government, and academia in Japan and the US, as shown below.
  - Through HBD activities, PMDA compiled basic concepts of global clinical trial of intravascular interventional devices for the treatment of critical limb ischemia. The devices are actively developed in Japan and the US. The results were published in an academic journal.
  - As part of the HBD activities for children, PMDA participated in regular teleconferences and HBD sessions at academic conferences (PICS-AICS2018: Pediatric and Adult Interventional Cardiac Symposium, September 2018, Las Vegas; 2 other academic conferences in Japan). PMDA held face-to-face meetings with concerned persons to discuss specific measures for global development of pediatric medical devices, based on experiences of an ongoing global clinical trial of medical devices for pediatrics.
  - As part of the HBD activities, PMDA participated in scientific sessions held at the following academic conferences. At these conferences, PMDA conducted publicity activities concerning HBD activities and discussed issues and countermeasures in the development of individual new medical devices, the utilization of post-marketing data, etc. with representatives of industry, government, and academia.

    Major academic conferences:

    - CVIT (Cardiovascular Intervention and Therapeutics, July 2018, Kobe)
    - TCT (Transcatheter Cardiovascular Therapeutics, September 2018, San Diego)
    - VIVA (Vascular InterVentional Advances, November 2018, Las Vegas)
    - CRT (Cardiovascular Research Technologies, March 2019, Washington, D.C.)
  - To widely disseminate achievements of HBD activities, PMDA strived to release brochures on these activities (in both Japanese and English languages) and enrich the contents of the HBD page on the PMDA website to provide information and promote participation of Japanese stakeholders in these activities.
- PMDA worked to achieve its target total review times through these measures. The performance of reviews for medical devices in FY 2018 is shown in the sections below.

3.2.(1).D.(iii).a. Review times for new medical devices (priority review products)

Targets

Fiscal year	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Total review time [months]	10	10	10	10	10
Percentile	60th	60th	70th	70th	80th

Results

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Percentile	60th	60th	70th	70th	80th
Total review time [months] (Reference, 80th percentile) [months]	8.8 (8.9)	7.9 (8.2)	8.0 (8.0)	8.3[Note] (9.6)	8.3
Number of approved applications	5	8	1	3	2

Note: In FY 2017, the total review time of 10 months was achieved for 2 of 3 products, with an achievement rate of 66.7%; the target for the total review time was achieved from the standpoint of the percentiles of products, but was not achieved from the standpoint of the achievement rate.

Reference

Regulatory review time [months]	4.0	4.2	3.2	5.5	4.2
Applicant's time [months]	3.3	3.8	4.8	3.0	4.8

Note 1: Applications submitted for approval in or after April 2004 are covered.

Note 2: The figures in "regulatory review time" and "applicant's time" represent their respective percentile values. The sum of regulatory review time and applicant's time may not equal the total review time for each fiscal year.

- In FY 2017, PMDA conducted priority reviews of applications for orphan medical devices and other devices with particularly high medical needs (medical devices for serious diseases; or medical devices exhibiting clearly superior efficacy or safety in comparison with existing medical devices or therapies). As a result, several priority review products were approved.
- The approval results of priority review products in FY 2018 substantially exceeded the target.

3.2.(1).D.(iii).b. Review times for new medical devices (standard review products)

Targets

Fiscal year	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Total review time [months]	14	14	14	14	14
Percentile	60th	60th	70th	70th	80th

Results

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Percentile	60th	60th	70th	70th	80th
Total review time [months] (Reference, 80th percentile) [months]	5.6 (10.6)	10.1 (11.9)	12.0 (14.0)	11.9 (12.0)	12.0
Number of approved applications	62	48	24	24	36

Reference

Regulatory review time [months]	3.5	5.0	7.8	6.0	6.6
Applicant's time [months]	2.2	4.3	4.3	6.5	6.1

Note 1: Applications submitted for approval in or after April 2004 are covered.

Note 2: The results in FY 2016 and FY 2017 exclude applications for standalone medical device software that meet both of the following criteria: (1) the software was newly categorized as a medical device on or after November 25, 2014, under the PMD Act; and (2) The application for the software was submitted for approval during the transitional period between November 25, 2014 and February 24, 2015.

Note 3: The figures in "regulatory review time" and "applicant's time" represent their respective percentile values. The sum of regulatory review time and applicant's time may not equal the total review time for each fiscal year.

- The approval results of new medical devices (standard review products) in FY 2018 exceeded the target.

Review Status of New Medical Devices by Fiscal Year of Submission

New medical devices (FY of submission)	Applied	Approved	Withdrawn	Under review
Up to FY 2003 (i.e., until Mar. 31, 2004)	132	54	78	0
FY 2004	56	35	21	0
FY 2005	7	7	0	0
FY 2006	23	19	4	0
FY 2007	37	31	6	0
FY 2008	32	30	2	0
FY 2009	24	20	4	0
FY 2010	28	26	2	0
FY 2011	42	40	2	0
FY 2012	64	63	1	0
FY 2013	72	72	0	0
FY 2014	99	95	4	0
FY 2015	30	29 (1)	1 (1)	0 [-2]
FY 2016	30	28	1	1
FY 2017	37	35 (24)	1	1 [-24]
FY 2018	39	16 (16)	0	23
Total	752	600 (41)	127 (1)	25 [-3]

Note 1: The figures in "Applied" represent the number of applications for new medical devices.
Note 2: The figures in "Approved" include the number of approved improved medical devices.
Note 3: The figures in parentheses indicate applications processed in FY 2018 (included in values to the left).
Note 4: The figures in brackets indicate differences from FY 2017.

3.2.(1).D.(iii).c. Review times for improved medical devices (with clinical data)

Targets

Fiscal year	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Total review time [months]	10	10	10	10	10
Percentile	52th	54th	56th	58th	60th

Results

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Percentile	52th	54th	56th	58th	60th
Total review time [months] (Reference, 60th percentile) [months]	9.9 (10.5)	11.0 (11.6)	10.0 (11.6)	8.8 (8.8)	8.8
Number of approved applications	35	53	43	42	52

Reference

Regulatory review time [months]	5.0	5.3	6.3	4.7	5.2
Applicant's time [months]	5.0	4.8	4.7	4.0	3.4

Note 1: Applications submitted for approval in or after April 2004 are covered.
Note 2: Applications filed in or before FY 2008 have been re-categorized in this table according to the new categorization implemented in FY 2009.
Note 3: The results in FY 2016 and FY 2017 exclude devices to be used in combination with "new medical devices" that were submitted for approval around the same time.
Note 4: The figures in "regulatory review time" and "applicant's time" represent their respective percentile values. The sum of "regulatory review time" and "applicant's time" may not equal "total review time."
Note 5: The number of applications was counted by initial review category selected on the receipt date of submission data.

- The approval results of improved medical devices (with clinical data) in FY 2018 substantially exceeded the target. The number of approvals in FY 2018 was nearly equal to that in previous fiscal years.

Review Status of Improved Medical Devices (with Clinical Data) by Fiscal Year of Submission

Improved medical devices (with clinical data) (FY of submission)	Applied	Approved	Withdrawn	Under review
FY 2009	34	33	1	0
FY 2010	34	33	1	0
FY 2011	26	21	5	0
FY 2012	42	39	3	0
FY 2013	46	42	4	0
FY 2014	45	41	4	0
FY 2015	27	24	3	0
FY 2016	50	48 (4)	2	0 [-4]
FY 2017	58	54 (40)	2 (1)	2 [-43]
FY 2018	38	11 (11)	0	27
Total	400	346 (55)	25 (1)	29 [-20]

Note 1: The figures in "Approved" include the number of approved products includes those approved under other application categories for medical devices.

Note 2: The figures in parentheses indicate applications processed in FY 2018 (included in values to the left).

Note 3: The figures in brackets indicate differences from FY 2017.

Note 4: Applications submitted in FY 2017 include those for new and re-manufactured single-use medical devices (based on the fee categories [Article 33, Paragraph 1, Item 1 (a)] of the Cabinet Order on User Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics).

Note 5: The number of applications may change due to a change in the initial application categories or withdrawal of applications.

3.2.(1).D.(iii).d. Review times for improved medical devices (without clinical data)

Targets

Fiscal year	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Total review time [months]	6	6	6	6	6
Percentile	52th	54th	56th	58th	60th

Results

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Percentile	52th	54th	56th	58th	60th
Total review time [months] (Reference, 60th percentile) [months]	6.0 (7.4)	6.0 (7.0)	5.8 (5.9)	5.8 (5.8)	5.7
Number of approved applications	213	233	218	205	209

Reference

Regulatory review time [months]	3.3	3.9	3.4	3.4	3.3
Applicant's time [months]	3.4	2.6	2.6	2.1	2.4

Note 1: Applications submitted for approval in or after April 2004 are covered.

Note 2: Applications filed in or before FY 2008 have been re-categorized in this table according to the new categorization implemented in FY 2009.

Note 3: The results in FY 2015 to FY 2017 exclude applications for standalone medical device software that meet both of the following criteria: (1) the software was newly categorized as a medical device on or after November 25, 2014, under the PMD Act; and (2) The application for the software was submitted for approval during the transitional period between November 25, 2014 and February 24, 2015.

Note 4: The results in FY 2018 exclude applications for medical devices to be used in combination with "new medical devices" for which application was submitted around the same time.

Note 5: The figures in "regulatory review time" and "applicant's time" represent their respective percentile values. The sum of regulatory review time and applicant's time may not equal the total review time for each fiscal year.

Note 6: The number of applications was counted by initial review category selected on the receipt date of submission data.

- The approval results of improved medical devices (without clinical data) in FY 2018 achieved the target. The number of approved applications in FY 2018 was nearly equal to that in previous fiscal years.

Review Status of Improved Medical Devices (without Clinical Data) by Fiscal Year of Submission

Improved medical devices (without clinical data) (FY of submission)	Applied	Approved	Withdrawn	Under review
FY 2009	137	122	15	0
FY 2010	165	141	24	0
FY 2011	176	160	16	0
FY 2012	210	198	12	0
FY 2013	190	177	13 (1)	0 [-1]
FY 2014	247	232 (6)	4	11 [-14]
FY 2015	219	203 (1)	13 (2)	3 [-3]
FY 2016	216	206 (5)	8	2 [-5]
FY 2017	165	157 (69)	2	6 [-70]
FY 2018	207	112 (112)	1 (1)	94
Total	1,932	1,708 (193)	108 (4)	116 [1]

Note 1: The figures in "Approved" include the number of applications approved under other medical device categories.

Note 2: The figures in parentheses indicate applications processed in FY 2018 (included in values to the left).

Note 3: The figures in brackets indicate differences from FY 2017.

Note 4: The number of applications may change due to a change in the initial application categories or withdrawal of applications.

3.2.(1).D.(iii).e. Review times for generic medical devices

Targets

Fiscal year	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Total review time [months]	4	4	4	4	4
Percentile	52th	54th	56th	58th	60th

Results

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Percentile	52th	54th	56th	58th	60th
Total review time [months] (Reference, 60th percentile) [months]	3.9 (4.5)	4.4 (5.0)	3.5 (3.6)	3.6 (3.7)	3.5
Number of approved applications	920	868	825	869	799

Reference

Regulatory review time [months]	1.9	2.0	1.9	2.2	2.1
Applicant's time [months]	1.8	2.3	1.4	1.4	1.2

Note 1: Applications submitted for approval in or after April 2004 are covered.

Note 2: Applications filed in or before FY 2008 have been re-categorized in this table according to the new categorization implemented in FY 2009.

Note 3: The figures in "regulatory review time" and "applicant's time" represent their respective percentile values. The sum of "regulatory review time" and "applicant's time" may not equal "total review time."

Note 4: The number of applications was counted by initial review category selected on the receipt date of submission data.

- The approval results of generic medical devices in FY 2018 exceeded the target.

Review Status of Generic Medical Devices by Fiscal Year of Submission

Generic medical devices (FY of submission)	Applied	Approved	Withdrawn	Under review
FY 2009	1,126	1,038	88	0
FY 2010	1,020	919	100	1
FY 2011	995	931	64	0
FY 2012	1,075	1,031	43	1
FY 2013	921	889	29	3
FY 2014	946	897	47	2
FY 2015	785	763 (1)	21	1 [-1]
FY 2016	925	907 (13)	16	2 [-13]
FY 2017	859	831 (244)	12 (8)	16 [-258]
FY 2018	810	558 (558)	5 (5)	247
Total	9,462	8,764 (816)	425 (13)	273 [-25]

Note 1: The figures in "Approved" include the number of applications approved under other medical device categories.

Note 2: The figures in parentheses indicate applications processed in FY 2018 (included in values to the left).

Note 3: The figures in brackets indicate differences from FY 2017.

Note 4: The number of applications could change due to a change in the initial application categories or withdrawal of applications.

3.2.(1).D.(iv) Efficient conduct of clinical trial consultations

3.2.(1).D.(iv).a. Conduct of priority consultations

- During FY 2018, there were no requests for priority consultation designation or consultations related to GLP/GCP compliance for priority medical device products.

3.2.(1).D.(iv).b. Implementation of clinical trial consultations and improvements to consultation service offerings

Number of Consultations

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Conducted	196	203	276	263	301
Withdrawn	11	4	7	16	14

Number of Prior Assessment Consultations for Medical Devices

	FY 2012	FY 2013	FY 2014
Conducted	3	1	3
Withdrawn	0	0	0

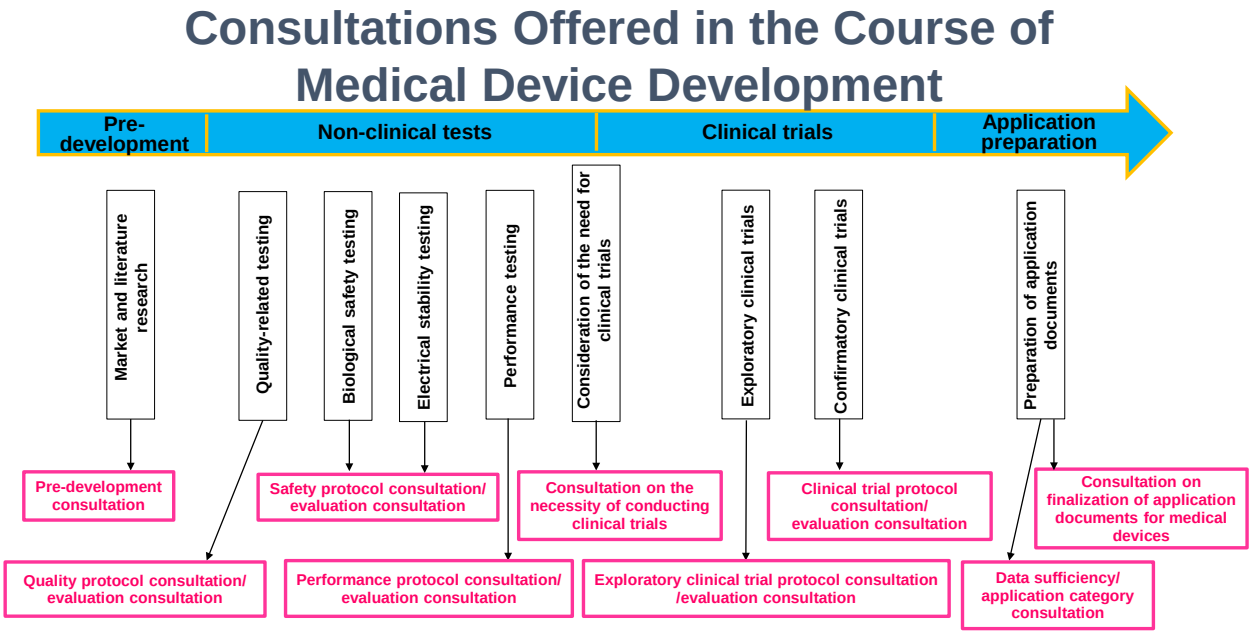
Note 1: Prior assessment consultations for medical devices were abolished in association with the revision of the consultation framework as of November 25, 2014.

Note 2: The number of prior assessment consultations for medical devices was counted on the basis of delivery dates of consultation documents to PMDA.

Note 3: Prior assessment consultations for medical devices are conducted for the categories of quality, non-clinical, and clinical.

3.2.(1).D.(iv).c. Review of consultation categories

- To eliminate review/development lag for medical devices currently in development or to be developed in the near future, PMDA encouraged medical device industry associations, medical device companies, academic institutions, etc., to take measures such as the proactive use of clinical trial consultations prior to regulatory submission, at academic conferences or through periodic exchanges of opinions with industry (reposted).
- PMDA decided to offer the following consultations starting in April 2019: “Consultations on data sufficiency/category of application for medical devices (additional consultations),” “consultations on compliance assessment of data for use-results evaluation for medical devices,” “consultations on use-result evaluation for medical devices,” “consultations on registry utilization for medical devices,” “consultations on compliance assessment of registries to be used for regulatory submission for medical devices;” and “simple consultations on applicability of certification standards to medical devices and in vitro diagnostics.”



* *In addition to the consultation menu in the above diagram, other categories such as additional consultation are also available.*

3.2.(1).D.(v) Promotion of evaluation of new technologies

3.2.(1).D.(v).a. Utilization of external experts

- PMDA is required to increase the degree of scientific sophistication of its guidance and review activities, particularly with regard to emerging technologies such as AI, ICT, IoT, and robotics. PMDA has therefore continued to commission highly knowledgeable external experts to serve as advisors to PMDA who provide expert input to scientifically-important matters at Expert Discussions in connection with product reviews and post-marketing safety measures (reposted). (As of March 31, 2019, there were 7 commissioned experts for issues relating to safety measures.)
- The number of Expert Discussions conducted in FY 2018 was 81 (62 document-based discussions, 19 meetings).
- PMDA utilized the Science Board in discussion of evaluation methodologies, etc., and promoted evaluation by external experts with advanced expertise. Basic principles presented in “Issues and Proposals Concerning Medical Diagnostic Systems and Medical Devices Utilizing AI” reported by a subcommittee of the Science Board “Subcommittee on Artificial Intelligence” on December 27, 2017 were utilized in RS Strategy Consultations (R&D), etc.

3.2.(1).D.(v).b. Support for the development of national guidelines

- PMDA supported the project for development of guidance for the approval process of new-generation medical products and regenerative medicine products to accelerate development and facilitate regulatory review of next-generation medical devices utilizing new technologies. More specifically, PMDA participated in the working groups that prepare guidance documents for “boron neutron capture therapy (BNCT)” and for “artificial intelligence areas,” for which substantial discussions are under way, and discussed the guidance contents.

3.2.(1).D.(v).c. Preliminary reviews under Cartagena Act

- See Section 3.2.(1).A.(vi).c.

3.2.(1).D.(v).d. Implementation of RS Strategy Consultations (R&D)

- See Section 3.2.(1).A.(vi).d.

3.2.(1).D.(v).e. Support project for promoting consultations/applications for innovative medical devices

- PMDA advanced the “support project to promote consultations/applications for innovative medical devices etc.,” to prevent delays in practical application of innovative medical devices or regenerative medical products (hereinafter, “medical devices etc.”) due to financial difficulties at small and medium-sized enterprises (SMEs) and venture companies that discovered promising seed-stage technologies. The purpose of the project is to provide a subsidy to SMEs and venture companies that meet certain requirements for the purpose of reducing their financial burdens for consultations/applications for regulatory approval. This scheme reimburses 50% of the user fee for the consultation or application for innovative medical devices etc. after the user fee is paid by the relevant company. In FY 2018, PMDA received applications for fee subsidies to 2 consultations but provided subsidies to none of them due to failure to meet the requirements.
- PMDA has set up a dedicated web page for the above-mentioned program on its website and uploaded operating procedures, etc. on this page to familiarize SMEs and venture companies with it.

3.2.(1).E. *In vitro* diagnostics

3.2.(1).E.(i) Appropriate and prompt reviews

- PMDA launched its Office of *In vitro* Diagnostics on April 1, 2015, in accordance with the Collaborative Plan to Accelerate Reviews of *In vitro* Diagnostics (March 2014). PMDA also allocated the increased number of reviewers to the office to strengthen the review system to achieve future targets.
- On the backdrop of recent advancements in personalized medicine, PMDA has been promoting review of companion diagnostics and diagnostic agents used in tests recommended by the optimal use guidelines. In FY 2018, PMDA received 7 applications for diagnostics, including partial change applications for addition of cancer or specimen types. The Office of *In vitro* Diagnostics contributed to the review of 1 companion diagnostic system approved as a medical device.
- Under the leadership of the Consortium on Promotion of Cancer Genome Medicine, a medical system that allows the public to have access to state-of-the-art cancer genome medicine has been established and gene panel tests to be used for comprehensive genomic profiling (tests that provide comprehensive analysis of oncogene mutation data from the patient’s tissue) have been developed. In FY 2018, The Office of *In vitro* Diagnostics contributed to the review of 2 gene panel tests approved as medical devices for the first time (including 1 SAKIGAKE designation product).

Review Status of In Vitro Diagnostics

In vitro diagnostics (FY of submission)	Applied	Approved	Withdrawn	Under review
Up to FY 2003 (i.e., until Mar. 31, 2004)	327	223	76	28
FY 2004	615	596	19	0
FY 2005	69	65	4	0
FY 2006	180	173	7	0
FY 2007	197	189	8	0
FY 2008	170	160	10	0
FY 2009	183	173	10	0
FY 2010	164	157	7	0
FY 2011	177	170	7	0
FY 2012	165	155	10	0
FY 2013	136	123	13	0
FY 2014	163	154 (1)	9	0 [-1]
FY 2015	196	189 (4)	6	1 [-4]
FY 2016	149	141 (4)	7	1 [-4]
FY 2017	196	185 (71)	2 (1)	9 [-72]
FY 2018	135	73 (73)	0	62
Total	3,222	2,926 (153)	195 (1)	101 [-19]

Note 1: The figures in parentheses indicate applications processed in FY 2018 (included in values to the left).

Note 2: The figures in brackets indicate differences from FY 2017.

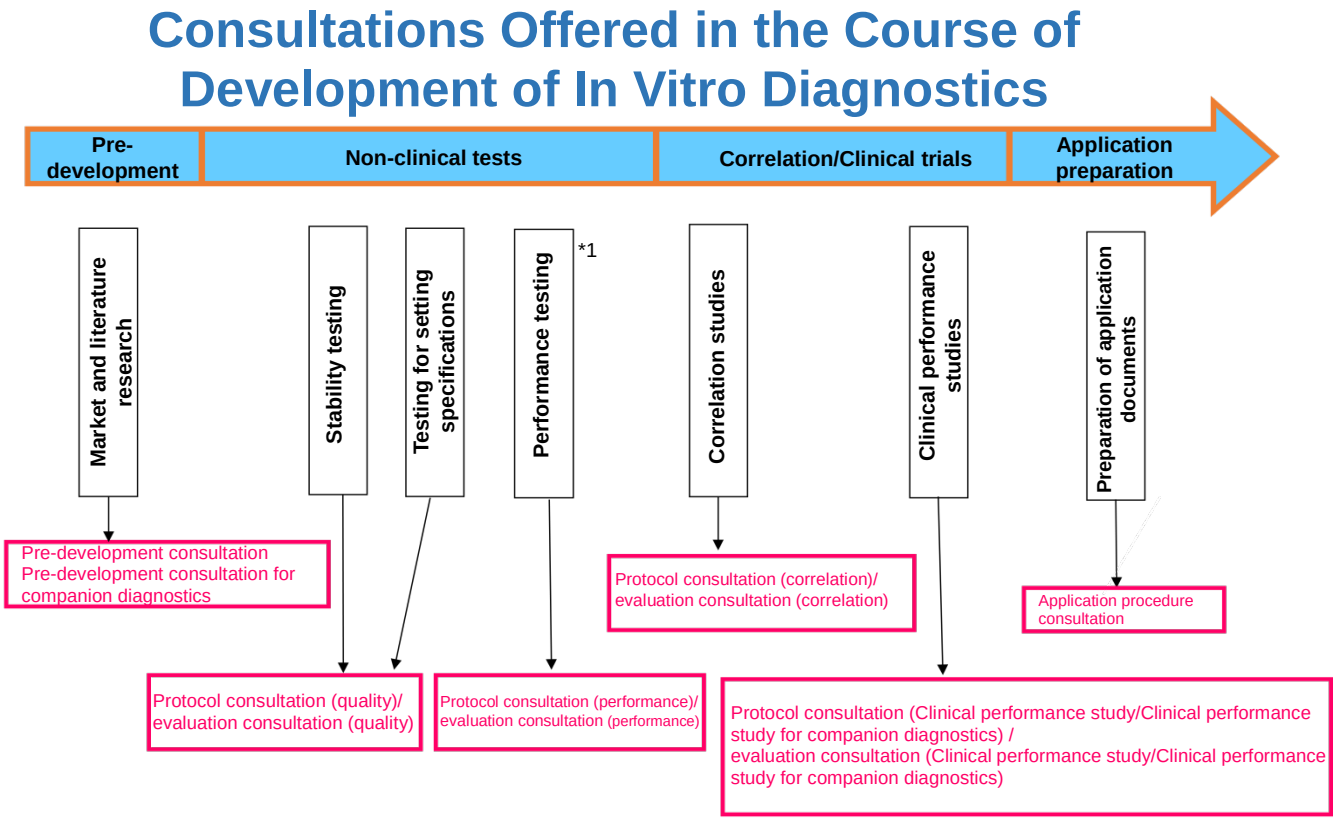
Note 3: The figures are calculated based on the applications filed in or after FY 1994, when the equivalence review system was introduced (numerical values stored in the current application management system were used).

3.2.(1).E.(ii) Expansion of consultation services

- PMDA revised its clinical trial consultation types related to *in vitro* diagnostics in 2014, in order to provide more efficient and effective consultations. In FY 2017, PMDA began to offer comments before consultation meetings in response to applicant's demand.

Number of Consultations

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Conducted	25	45	43	36	42
Withdrawn	0	0	1	1	4



**1 Refers to quality control testing and tests other than stability testing (e.g., operation and cross-reactivity testing)*

** In addition to the consultation menu displayed above, other categories such as additional consultations are also available.*

3.2.(1).F. Regenerative medical products

3.2.(1).F.(i) New review systems and appropriate and prompt reviews

- With the enactment of the PMD Act in November 2014, PMDA has conducted consistent and efficient review and consultation activities by maintaining communications between consultation teams and review teams, in order to ensure appropriate implementation of a new conditional time-limited authorization system for regenerative medical products. In FY 2018, 3 new regenerative medical products and 1 regenerative medical product with new indication were granted marketing approval. PMDA contributed to implementation of the conditional time-limited authorization of 2 of the 3 new regenerative medical products.

3.2.(1).F.(ii) Setting of target review time

- The target for standard regulatory review time (i.e., the time from initial submission to final approval) for regenerative medical products approved in FY 2018 was 9 months; the progress management of product reviews was carried out to achieve this target. One of the 4 regenerative medical products granted marketing approval in FY 2018 was a SAKIGAKE designation product. This was the first product approved within the standard regulatory review time of 6 months required for the SAKIGAKE-designated product.

- **Review times for regenerative medical products**

Targets

The following target for the standard review time should be achieved.

Type of application	Regulatory review time [months]
Regenerative medical products	9

Results

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Total review time [months]	-	11.3	8.1	-	10.3
Regulatory review time [months]	-	2.8	2.7	-	3.7
Applicant's time [months]	-	8.6	5.5	-	5.6
Number of approved applications	0	2	1	0	4

Note 1: Results for FY 2015 and FY 2018 indicate median values.

Note 2: The figures in "regulatory review time" and "applicant's time" represent their respective median values. The sum of regulatory review time and applicant's time may not equal the total review time for each fiscal year.

3.2.(1) F (iii) Cooperation in the development of optimal use guidelines

- In response to the "Basic Policy on Economic and Fiscal Management and Reform 2016" (adopted by the Cabinet on June 2, 2016) recommending the promotion of optimal use of innovative drugs, MHLW decided to develop product-specific Optimal Clinical Use Guidelines intended to offer regenerative medical products to patients who really need them. PMDA assisted MHLW in developing the Optimal Clinical Use Guidelines.

FY 2018

Product name	Indication	Date of issue
Stemirac for Injection	Improvement of neurological symptoms and functional disorders associated with spinal cord injury only in patients with traumatic spinal cord injury assessed as American Spinal Injury Association Impairment Scale (AIS) grade A, B, or C	Feb. 25, 2019

3.2.(1).F.(iv) Efficient execution of clinical trial consultations

- To conduct faster and more efficient reviews, PMDA communicated with related parties at meetings of academic societies, such as the Japanese Society for Regenerative Medicine, and industry associations, and encouraged these organizations to take advantage of consultations offered by PMDA. In consideration of the unique characteristics of regenerative medical products, PMDA provides consultation services designed to clearly explain the requirements of its review procedures with respect to the appropriateness of ingredients, product quality and safety, clinical study plans, etc., as well as the SAKIGAKE designation system.
- The pre-trial notification (confirmation) application scheme for gene therapy products was abolished and incorporated into the purview of RS Strategy Consultations (R&D) for quality and safety of regenerative medical products.
- To increase the accessibility of consultation services to academic institutions and venture companies, in November 2014, PMDA implemented a pilot consultation service to provide general advice regarding matters including the development process (roadmap), as part of RS Strategy Consultations (R&D) for Development Plan. PMDA has been implementing dedicated consultations for the quality or safety of regenerative medical products, pre-consultations on regenerative medical products, with minutes recorded, and other consultations.

Number of Consultations regarding Regenerative Medical Products

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Conducted	6	18	28	38	47
Withdrawn	0	1	2	4	6

Number of Prior Assessment Consultations regarding Regenerative Medical Products

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Conducted	0	1	0	0	0
Withdrawn	0	0	0	0	0

Note 1: The consultation categories for regenerative medical products were established on November 25, 2014. The figure is the number of consultations conducted since then (before November 25, 2014, consultations for regenerative medical products had been included in consultations for drugs or medical devices).

Note 2: PMDA started to offer prior assessment consultations for regenerative medical products on November 25, 2014. The number of the consultations was counted on the basis of delivery dates of consultation documents to PMDA.

Note 3: For prior assessment consultations for regenerative medical products, the number of consultation categories was summed. (Set categories: safety/quality/effects, exploratory trial, verification trial)

3.2.(1).F.(v) Promotion of evaluation of new technologies

3.2.(1).F.(v).a. Utilization of external experts

- PMDA took a proactive approach to the utilization of its Science Board, which retains highly knowledgeable external experts, to contribute to assessment of new evaluation methods. PMDA conducted Regulatory Science General Consultation and Regulatory Science Strategy Consultation (R&D) from the viewpoints presented in the following reports:
  - "Proposal on Basic Principle to Quality Assurance of Cell Therapy (CT) Products" dated August 14, 2015 (Cell Processing Center Subcommittee);
  - "Current Perspective on Evaluation of Tumorigenicity of Cellular and Tissue-based Products Derived from induced Pluripotent Stem Cells (iPSCs) and iPSCs as Their Starting Materials" dated August 20, 2013 (Cellular and Tissue-based Products Subcommittee).

  PMDA exchanged opinions about future international regulations on regenerative medical products and information on products under development with experts from regulatory authorities of the EU and the US at international academic conferences and through teleconferences on a regular basis.

3.2.(1).F.(v).b. Knowledge accumulation

- PMDA has dispatched staff to Japanese academic conferences held by scientific societies including the Japanese Society for Regenerative Medicines, the Japan Society of Gene and Cell Therapy, and to international academic conferences held by the International Society for Cellular Therapy (ISCT), the Asian Cellular Therapy Organization (ACTO), and other meetings. Through these dispatch activities, PMDA endeavors to deepen its understanding of the needs of medical institutions engaged in the development of regenerative medical products and to collect information regarding their practical application.

3.2.(1).F.(v).c. Support for the development of national guidelines

- PMDA collaborated with MHLW in the development of guidelines for the evaluation of products developed using state-of-the-art technologies, such as regenerative medical products.
- To proceed with the project on the development of guidance on the evaluation of next-generation medical devices and regenerative medical products, PMDA participated, as an observer, in group

meetings regarding draft guidance on the evaluation of regenerative medical products for the treatment of spinal cord injury (entrustee, Rumi Sawada; chairperson, Professor Yukihiro Matsuyama [Department of Orthopaedic Surgery, Hamamatsu University School of Medicine]) in FY 2018. PMDA thus supported the development of guidance on this matter.

- To proceed with the initiative to foster development of innovative drugs, medical devices, and regenerative medical products, PMDA supported research conducted at research institutions for the development of seed-stage resources and assisted study groups in developing guidelines for evaluation of regenerative medical products. In FY 2018, PMDA supported the handling of public comments and subsequent issuance of a notification on draft guidelines for the following evaluations.
  - Regenerative medical products: 3 topics (Kyoto University [iPS cells, platelets, etc.], Osaka University [cardiac muscle sheets, corneal epithelial sheets, cartilage regeneration, etc.], Chiba University [regenerative medicine for spinal cord injury])
  - Drug products: 2 topics (Mie University [cancer vaccines and immunotherapy], National Center for Child Health and Development [pediatric disease, gene therapy drugs])

3.2.(1).F.(vi) Promotion of the use of RS Strategy Consultations (R&D)

- PMDA has conducted preliminary reviews of regenerative medical products (including gene therapy products) prior to the initiation of clinical trials, to determine whether the quality and safety of the products conform to relevant guidance. The preliminary review process was abolished in July 2011 for regenerative medical products and medical devices and in July 2013 for gene therapy products. These preliminary reviews were replaced with RS Strategy Consultation (R&D). PMDA has promoted the use of RS Strategy Consultation (R&D) by doing the following activities: issuance of notifications to inform relevant parties of consultation services as well as the new consultation category of regenerative medical products established with the enactment of the PMD Act in November 2014; and provision of relevant information at academic conferences. As a result, PMDA received 60 initial clinical trial notifications, including those for investigator-initiated trials of regenerative medical products, between November 2014 and March 2019 (i.e., the end of FY 2018). PMDA has thus supported and promoted the execution of clinical trials [for the results of RS Strategy Consultations (R&D), see Section 3.2.(1).A.(vi).d.].
- For preliminary reviews under the Cartagena Act, see Section 3.2.(1).A.(vi).c.

3.2.(1).G. Promotion of GLP/GCP/GPSP compliance assessments and clinical trials, etc.

- PMDA took the following measures to promote the proper conduct of laboratory tests and clinical trials to obtain data used for submission of applications for marketing approval of drugs, etc. and to ensure the reliability of data submitted with applications.

3.2.(1).G.(i) Efficient GLP/GCP/GPSP inspections and data integrity assessments for new drugs, etc.

- To employ efficient and risk-based approaches to assessment and inspection, PMDA discussed the methods for selection of sites subject to on-site GCP inspections.
- PMDA's Office of Non-clinical and Clinical Compliance obtained information, at an early stage, regarding products to be submitted for regulatory approval in Japan by having its staff participate in pre-application consultations, so as to know whether applications for these products have already been submitted to regulatory authorities outside Japan. In addition, the Office of Non-clinical and Clinical Compliance strived to share information on the planned reviews/inspections with the relevant review offices in PMDA.

- With the aim of promoting more efficient GLP/GCP/GPSP inspections and data integrity assessments, PMDA participated in the EMA-US FDA GCP Initiative on a pilot basis (from June 2017 to December 2018), thereby sharing information and exchanging opinions with US FDA and EMA on plans and results of GCP inspections. Furthermore, after the end of the pilot participation period, PMDA decided to continue activities such as sharing information with these regulatory authorities under the framework mentioned above.
- PMDA discussed how to conduct inspections of clinical trials that adopt CDISC standards. As a result, PMDA began to use electronic study data, if submitted, in a complementary manner before the conduct of inspections of clinical trials.

3.2.(1).G.(ii) Efficient GLP/GCP/GPSP inspections and data integrity assessments for medical devices

- The Offices of Medical Devices and the Office of Non-clinical and Clinical Compliance held periodic joint meetings to share information on the progress of both reviews and inspections, and conducted GLP/GCP/GPSP compliance assessments in an appropriate and timely manner.

  In FY 2018, PMDA conducted on-site GCP inspections of the manufacturers of 1 new medical device and 5 improved medical devices under the proper procedures and systems.
- PMDA participated in working-level meetings on the “Collaborative Action Plan to Accelerate Reviews of Medical Devices” to exchange opinions with industry on specific requirements for compliance assessment to expedite reviews of medical devices. As a result, a working group on compliance assessment was established to discuss the above matters from a technical standpoint.
- PMDA discussed with industry the content of the “Checklist for compliance assessment of clinical trials of medical devices” and “An example of a detailed list of documents submitted for document-based compliance assessment” at meetings of the working group on compliance assessment, based on the “Collaborative Action Plan to Accelerate Reviews of Medical Devices.” These guidance documents were posted on the PMDA website and issued as an administrative notice by the Office of Non-clinical and Clinical Compliance to prefectural governments and medical device-related organizations.

3.2.(1).G.(iii) Efficient GLP/GCP/GPSP inspections and data integrity assessments for regenerative medical products

- In FY 2018, PMDA conducted inspections for regenerative medical products in accordance with the inspection procedure for drugs.

3.2.(1).G.(iv) Efficient GLP inspections and data integrity assessments

- To train Japanese GLP inspectors who meet international standards, an expert staff member of the Office of Non-clinical and Clinical Compliance (who served as the chair of the OECD GLP working group until the end of FY 2017) attended many GLP inspections conducted in Japan, and directly instructed other inspectors about the difference between GLP inspection methods employed in Japan and those employed internationally. According to the results of international assessment of GLP inspection level conducted by OECD once every decade, PMDA inspectors were highly regarded.
- PMDA participated in the GLP working group of the OECD and dispatched 1 staff member to the OECD office, thereby introducing PMDA’s knowledge and expertise into international GLP-related activities.

3.2.(1).G.(v) Efficient GLP/GCP/GPSP inspections and data integrity assessments for re-examination (including use-results evaluation)

- PMDA continued efforts to increase the efficiency of inspections/assessment for re-examination of drugs in FY 2018 as well. For example, when an applicant filed applications for several products around the same time, PMDA conducted inspections on the products simultaneously.
- To address post-marketing database surveys, PMDA issuing a notification for revision, “Partial Revision of the ‘Procedure for Document-based Compliance Assessment and On-site GPSP Inspections on Data Submitted for Re-examination/Re-evaluation of Drugs” (PMDA Notification No. 0913026 dated September 13, 2018, issued by the Chief Executive of the Pharmaceuticals and Medical Devices Agency).
- The Office of Non-clinical and Clinical Compliance and each Office of Medical Devices regularly shared information regarding the progress of the inspection for re-examination of medical devices.
- PMDA participated in working-level meetings on the “Collaborative Action Plan to Accelerate Reviews of Medical Devices.” A working group on compliance assessment was established to exchange opinions with industry on specific requirements for compliance assessment to expedite reviews of medical devices. Working group members discussed methods for compliance assessment of data submitted for use-result surveys conducted using medical information databases. Based on the results of discussion mentioned above, MHLW issued a notification entitled “Points to Consider for Assurance of Data Integrity of Post-marketing Database Surveys for Medical Devices” (PSEHB/MDED Notification No.1219-4 dated December 19, 2018, issued by Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW).
- PMDA provided 7 re-examination compliance assessment consultations for drugs.

3.2.(1).G.(vi) Proper conduct of clinical trials, etc.

- To further promote the proper execution of clinical trials, etc., PMDA held GCP/GPSP workshops in Tokyo and Osaka and presented its data regarding frequently revealed findings in document-based GLP/GCP/GPSP compliance assessments, on-site GCP inspections, and GLP/GCP/GPSP compliance assessments for re-examination. Materials used for the workshops were posted on the PMDA website. In addition, PMDA representatives gave lectures regarding GLP/GCP/GPSP compliance assessments at academic conferences attended by healthcare professionals, exchanging ideas with related parties.
- PMDA provided information regarding GLP/GCP/GPSP compliance assessments (e.g., points to consider), such as document-based compliance inspections, on-site GCP inspections, and post-marketing surveillance of medical devices, at briefing sessions hosted by the medical device industry associations in August, October, and November in 2018, and February in 2019. PMDA also held workshops on compliance assessments of medical devices in January and February 2019 to further improve the integrity of data submitted by applicants.

Number of Participants in GCP/GPSP Workshops

Venue	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Tokyo	1,189	1,242	1,140	1,043	1,122	1,004
Osaka	404	448	352	368	385	315
Total	1,593	1,690	1,492	1,411	1,507	1,319

- As a sub-investigator, PMDA participated in a study group for “Research on Regulatory Science of Pharmaceuticals and Medical Devices” funded by the AMED, and conducted research on operation of GCP, to contribute to the efficient implementation of clinical trials. To implement the ICH-E6 (R2) guidelines in Japan, PMDA prepared a draft revision of the guidance on the “Ministerial Ordinance on Good Clinical Practice for Drugs” and its draft notification.
- In FY 2014, PMDA launched new consultation categories concerning GCP/GLP/GPSP compliance assessments. PMDA provided 63 consultations for drugs, 39 for medical devices, and 3 for regenerative medical products.
- PMDA accepted any invitation to give lectures concerning GCP/GLP/GPSP, etc., to the extent scheduling and resources permitted, in order to foster greater understanding of GCP/GLP/GPSP compliance assessment procedures and requirements.

Number of GLP/GCP/GPSP Compliance Assessments by Fiscal Year

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Document-based assessments	2,396	2,332	2,066	2,118	1,703
New drugs	370	389	381	394	342
Generic drugs	1,080	1,045	870	883	572
Medical devices	946	894	812	840	782
Regenerative medical products	0	4	3	1	7
On-site GCP inspections	236	201	204	207	224
New drugs	221	191	191	192	202
Generic drugs	10	7	11	9	11
Medical devices	5	1	1	6	6
Regenerative medical products	0	2	1	0	5
Document-based assessments for re-examination	81	136	230	137	143
New drugs	74	120	176	106	115
New medical devices	7	16	54	31	28
On-site GPSP inspections for re-examination	74	120	176	107	113
New drugs	74	120	176	106	113
New medical devices	0	0	0	1	0
Document-based assessments for re-evaluation	0	19	0	0	0
On-site GPSP inspections for re-evaluation	0	19	0	0	0
GLP inspections	40	36	24	45	36
Drugs	27	22	17	22	21
Medical devices	13	9	4	14	10
Regenerative medical products	0	5	3	9	5

Note: These figures represent the respective numbers of products for which inspection/assessment was completed.

3.2.(1).H. Promotion of GMP/GCTP/QMS inspections

3.2.(1).H.(i) Efficient GMP/GCTP/QMS inspections

3.2.(1).H.(i).a. Implementation of GMP/GCTP/QMS inspections

- In accordance with the amended Pharmaceutical Affairs Act, which came into effect in 2005, both manufacturing and quality control procedures for drugs etc. implemented at manufacturing facilities of such products must comply with the requirements specified in the Ministerial Ordinance on GMP for Drugs and Quasi-drugs and/or Ministerial Ordinance on QMS for Medical Devices and *In vitro* Diagnostics, in order to satisfy regulatory requirements for approval. Therefore, in addition to the manufacturing sites already licensed by the Minister of Health, Labour and Welfare, the following manufacturing sites became subject to inspection by PMDA: (1) Foreign manufacturing sites related to all products that require regulatory approval; and (2) Japanese manufacturing sites for new drugs, new medical devices or Class IV medical devices (high-risk medical devices such as pacemakers).
- PMDA has begun to discuss a revision to the Ministerial Ordinance on GMP, revised in 2005, to harmonize the evolving GMP standards which are accepted globally.
- With the enactment of the PMD Act in November 2014, manufacturing of medical devices and *in vitro* diagnostics was changed from a license-based system to a registration-based system.
- In 2015, an MAH was found to have manufactured blood products for many years using processes diverging from those prescribed in the corresponding marketing approval documents for those products, and systematically created falsified and altered records to conceal this fact. Faced with this problem, PMDA began to conduct unannounced on-site GMP inspections as a safeguard against similar instances of fraud, in accordance with the related MHLW notification (“Thorough Implementation of For-cause Inspections of Drugs,” PSEHB/CND Notification No. 0115-3 dated January 15, 2016, by Director of the Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW). In FY 2018, PMDA conducted 36 unannounced on-site inspections.
- As a part of efforts towards a “paperless” inspection process, PMDA established a system for receiving the applicant’s responses to regulatory inquiries in document-based compliance assessments via e-mail and issued an administrative notice entitled “Submission of E-mail Responses to Inquiries Concerning Document-based GMP Compliance Assessments for Drugs, Medical Devices, and Regenerative Medical Products” (Administrative Notice dated November 1, 2018, issued by the Office of Manufacturing/Quality and Compliance, PMDA). PMDA also revised “Submission of Documents for Application for GMP Inspections for Drugs” (Administrative Notice dated September 15, 2017, issued by the Office of Manufacturing/Quality and Compliance, PMDA) on February 7, 2018, to ensure that applicants submit appropriate application documents for GMP Inspections.
- As in previous years, PMDA took part in the activities of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S), to promote international harmonization of GMP in Japan. PMDA also participated in the working group for the development of 4 PIC/S guidelines and 3 training programs.
- Based on the program to rationalize international GMP inspections of active pharmaceutical ingredients/active drug substance manufacturers, launched in FY 2016, PMDA held a meeting to exchange information such as GMP inspection plans and results, and conducted a joint inspection in FY 2018, thereby promoting international cooperation.

- The Ministerial Ordinance on QMS for Medical Devices and In Vitro Diagnostics was also revised, and MAHs were newly subjected to QMS inspections. In addition, PMDA currently undertakes QMS inspections which were previously conducted by prefectural governments.

  MHLW begun to issue QMS compliance certificates to applicants (manufacturers) if a QMS inspection has revealed conformance of their facility or system to the QMS standards. Furthermore, if the applicant has already been granted a valid QMS compliance certificate for a particular family of products manufactured at a particular manufacturing facility, application for a separate QMS inspection is not required for another product belonging to the same product family and manufactured at the same manufacturing facility.

- Since the laws and regulations for re-manufacturing single-use medical devices (SUDs) were implemented in July 2017, PMDA has begun to discuss methods for on-site QMS inspections concerning re-manufacturing of SUDs.

- In 2014, the Ministerial Ordinance on GCTP and the Regulations for Buildings and Facilities for Pharmacies and Manufacturing Establishments were established and came into effect. To promote efficient manufacturing and quality control at manufacturing sites, PMDA supported the preparation of guidelines and a document providing examples on how to deal with the regulations.

  * *Ministerial Ordinance on Good Manufacturing Practice (GMP) for Drugs and Quasi-drugs (MHLW Ministerial Ordinance No.179 of 2004)*
  * *Ministerial Ordinance on Quality Management System (QMS) for Medical Devices and In vitro Diagnostics (MHLW Ministerial Ordinance No.169 of 2004)*
  * *Ministerial Ordinance on Good Gene, Cellular, and Tissue-based Products (GCTP) (MHLW Ministerial Ordinance No.93 of 2014)*

  Note 1: GMP (Good Manufacturing Practices)
  Note 2: QMS (Quality Management System)
  Note 3: GCTP (Good Gene, Cellular, and Tissue-based Product Manufacturing Practices)

3.2.(1).H.(i).b. Establishment of the inspection system

- PMDA had 61 GMP/GCTP/QMS inspectors (including inspectors in the Kansai Branch) at the end of FY 2018.

  To reinforce mutual cooperation and communication among medical device offices and ensure the increased efficiency of their operations, the Office of Manufacturing/Quality and Compliance was reorganized as a part of PMDA's organizational restructuring implemented in January 2019: The division of QMS inspections plus division of vigilance for medical devices constituted the Office of Manufacturing Quality and Vigilance for Medical Devices, while the division of GMP/GCTP inspections was incorporated into Office of Manufacturing Quality for Drugs. In FY 2014, Japan joined the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S: An international framework on GMP inspections, centering on European countries). In response to this, PMDA established the "inspection quality assurance group" in the Office of Manufacturing/Quality and Compliance (name at that time), to supervise quality management of drugs and quasi-drugs. PMDA also introduced another group to supervise quality management of medical devices, thereby enhancing the overall quality supervision system in PMDA.

  The Inspection Division of the Kansai Branch conducted inspections mainly in the Western region of Japan and the Asian region.

- The processing status of GMP/GCTP/QMS inspections in FY 2018 is shown below. PMDA completed 68 QMS inspections by using the Medical Device Single Audit Program (MDSAP) in FY 2018.

GMP/GCTP/QMS Inspections Conducted under the PMD Act

	FY 2013			FY 2014		
	Applied	Completed	Withdrawn	Applied	Completed	Withdrawn
Drugs*	1,508	1,415 (168)	75	1,877	1,672 (163)	51
In vitro diagnostics	52	67 (1)	0	65	38 (1)	0
Quasi-drugs	3	3 (1)	0	5	6 (0)	0
Medical devices	988	883 (61)	11	755	512 (42)	18
Regenerative medical products	-	-	-	0	0 (0)	0
Total	2,551	2,368 (231)	86	2,702	2,228 (206)	69

	FY 2015			FY 2016		
	Applied	Completed	Withdrawn	Applied	Completed	Withdrawn
Drugs*	1,719	1,647 (165)	67	1,818	1,783 (171)	122
In vitro diagnostics	1 179	1 (0) 146 (33)	0 1	0 54	0 (0) 83 (44)	1 1
Quasi-drugs	2	2 (0)	0	1	3 (0)	0
Medical devices	70 2,333	178 (25) 1,854 (326)	7 38	0 739	1 (0) 951 (251)	10 11
Regenerative medical products	9	8 (3)	1	1	0 (0)	0
Total	4,313	3,836 (552)	114	2,613	2,821 (466)	145

	FY 2017				FY 2018			
	Applied	Completed	Withdrawn	In progress	Applied	Completed	Withdrawn	In progress
Drugs*	1,753	1,796 (237)	119	796	1,761	1,667 (265)	73	821
In vitro diagnostics	0 61	0 (0) 49 (18)	0 3	0 29 (11)	0 43	0 (0) 55 (19)	0 0	0 17 (3)
Quasi-drugs	2	1 (0)	0	1	2	2 (0)	0	1
Medical devices	0 693	0 (0) 577 (142)	0 13	0 (0) 313 (115)	0 596	0 (0) 615 (184)	0 3	0 (0) 275 (73)
Regenerative medical products	0	1 (0)	0	0	31	18 (5)	0	13
Total	2,509	2,424 (397)	135	1,139 (126)	2,433	2,357 (473)	76	1,127 (76)

**) Excluding in vitro diagnostics.*

Note: The figures in parentheses represent the numbers of on-site inspections out of completed inspections. The columns for in vitro diagnostics and medical devices in FY 2015 to FY 2018 include applications filed before the enactment of the PMD Act (revised Pharmaceutical Affiars Act) in 2014 (upper) and those filed after the enactment of the PMD Act in 2014 (lower). Inspections are conducted fort an average of three manufacturing sites per application after the enactment of the PMD Act; this precludes a simple comparison of figures between before and after the enactment of the PMD Act, or between drugs, quasi-drugs, and regenerative medical products.

- The processing times of GMP/GCTP/QMS inspections in FY 2018 are shown below:

Median Processing Time of GMP/GCTP/QMS Inspections

	FY 2013		FY 2014		FY 2015	
	Median total processing time (days)	Median PMDA processing time (days)	Median total processing time (days)	Median PMDA processing time (days)	Median total processing time (days)	Median PMDA processing time (days)
Drugs*	118	71	172	76	172	81
In vitro diagnostics	106	66	147	102	160/120	38/72
Quasi-drugs	272	71	166	96	422	158
Medical devices	106	56	118	74	114/140	60/85
Regenerative medical products	-	-	-	-	84	54
	FY 2016		FY 2017		FY 2018	
	Median total processing time (days)	Median PMDA processing time (days)	Median total processing time (days)	Median PMDA processing time (days)	Median total processing time (days)	Median PMDA processing time (days)
Drugs*	163	84	149	59	133	44
In vitro diagnostics	772/128	30/57	- /118	- /70	- /155	- /94
Quasi-drugs	141	74	100	63	167	55
Medical devices	601/105	35/49	- /112	- /72	- /134	- /93
Regenerative medical products	-	-	128	47	275	62

** Excluding in vitro diagnostics.*

The figures in "In vitro diagnostics" and "Medical devices" in FY 2015 and FY 2018 represent processing times for applications filed before the enactment of the PMD Act (left) and those filed after the enactment of the PMD Act (right).

- The table below shows the number of building and facility inspections conducted in FY 2018 at Japanese manufacturing sites licensed by the Minister of Health, Labour and Welfare, in accordance with the Regulations for Buildings and Facilities for Pharmacies, etc. No manufacturing sites for medical devices or *in vitro* diagnostics were subject to inspection because of the change from the license-based system to the registration-based system in accordance with the PMD Act.

Number of Inspections of Buildings and Facilities at Manufacturing Sites in Japan

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Drugs*	25 (11)	26 (18)	19 (11)	16 (6)	18 (9)
In vitro diagnostics	0 (0)	-	-	-	-
Medical devices	2 (2)	-	-	-	-
Regenerative medical products	1 (1)	1 (1)	-	3 (2)	6 (5)
Total	28 (14)	27 (19)	19 (11)	19 (8)	24 (14)

** Excluding in vitro diagnostics.*

Note: These figures include withdrawn applications. The figures in parentheses represent the numbers of on-site inspections out of completed inspections.

- PMDA conducts for-cause inspections, questioning, and sampling at manufacturing facilities and other locations in Japan, at the direction of MHLW. The number of for-cause inspections conducted in FY 2018 is shown below:

Number of For-cause Inspections (Manufacturers in Japan)

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Drugs*	5	7	15	31	30
In vitro diagnostics	0	0	0	0	0
Medical devices	0	0	0	0	1
Regenerative medical products	0	0	3	0	0
Total	5	7	18	31	31

** Excluding in vitro diagnostics.*

- PMDA conducts simple consultations concerning GMP/GCTP/QMS inspections. The number of such consultations conducted in FY 2018 is shown below.

Number of Simple Consultations Conducted for GMP/QMS Inspections

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Drugs*	32	33	36	26	30
In vitro diagnostics	0	4	0	0	0
Quasi-drugs	0	0	0	0	0
Medical devices	51	64	34	11	5
Regenerative medical products	-	3	0	0	0
Total	83	104	70	37	35

** Excluding in vitro diagnostics.*

3.2.(1).H.(i).c. Promotion of on-site inspections of foreign manufacturing sites

- The following tables show the number of on-site inspections of foreign manufacturing sites, launched in FY 2005:

On-site Inspections of Foreign Drug Manufacturing Sites by Region

	Europe	North, Central, and South America	Asia/Oceania	Africa	Total
FY 2008	31	19	32	0	82
FY 2009	39	20	47	0	106
FY 2010	12	24	29	0	65
FY 2011	9	7	45	0	61
FY 2012	14	14	38	0	66
FY 2013	12	10	42	0	64
FY 2014	20	3	51	0	74
FY 2015	0	2	61	0	63
FY 2016	6	6	67	0	79
FY 2017	9	7	89	0	105
FY 2018	3	11	108	0	122

Note: Breakdown of FY 2018:
Europe: Italy, Hungary, and the United Kingdom
North, Central, and South America: the United States, Canada, and Argentina
Asia/Oceania: China, India, South Korea, Taiwan, Singapore, Vietnam, Indonesia, and Thailand

On-site Inspections of Foreign Manufacturing Sites for Regenerative Medical Products by Region

	Europe	North, Central, and South America	Asia/Oceania	Africa	Total
FY 2018	2	7	0	0	9

Note: Breakdown of FY 2018:
Europe: Austria and the United Kingdom,
North, Central, and South America: the United States

On-site Inspections of Foreign Medical Device Manufacturing Sites by Region

	Europe	North, Central, and South America	Asia/Oceania	Africa	Total
FY 2008	13	17	0	0	30
FY 2009	3	28	5	0	36
FY 2010	8	19	1	0	28
FY 2011	4	15	1	0	20
FY 2012	11	22	4	0	37
FY 2013	4	12	10	0	26
FY 2014	4	5	20 (2)	0	29 (2)
FY 2015	0	0	12	0	12
FY 2016	0	0	3	0	3
FY 2017	6	15	10	0	31
FY 2018	15	11	14	0	40

Note 1) Breakdown of FY 2018:
Europe: Ireland, Netherlands, France, Denmark, Belgium, and Germany
North, Central, and South America: the United States, Mexico, Brazil, and Costa Rica
Asia, Oceania: China, South Korea, Thailand, Philippines, and Indonesia

- The table below shows the number of inspections of buildings and facilities in foreign manufacturing sites conducted in FY 2018 in accordance with the Regulations for Buildings and Facilities for Pharmacies, etc. No manufacturing sites for medical devices or *in vitro* diagnostics were subject to inspection because of the change from the license-based system to the registration-based system in accordance with the PMD Act.

Number of Inspections of Buildings and Facilities at Foreign Manufacturing Sites

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Drugs*	384	356	686	510	427
In vitro diagnostics	23	-	-	-	-
Quasi-drugs	58	33	69	54	43
Medical devices	722	-	-	-	-
Regenerative medical products	0	0	0	2	10 (2)
Total	1,187	389	755	566	480 (2)

** Excluding in vitro diagnostics.*
Note: These figures include withdrawn applications. The figures in parentheses represent the numbers of on-site inspections.

- PMDA conducts for-cause inspections, questioning, and sampling at foreign manufacturers etc., at the direction of MHLW. The number of for-cause inspections conducted in FY 2018 is shown below:

Number of For-cause Inspections at Foreign Manufacturing Sites

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Drugs*	1	0	0	9	6
In vitro diagnostics	0	0	0	0	0
Medical devices	0	0	0	0	0
Regenerative medical products	0	0	0	0	0
Total	1	0	0	9	6

** Excluding in vitro diagnostics.*

Number of On-site GMP Inspections of Foreign Drug Manufacturing Sites by Country

Region	Country	FY 2010	FY 2011	FY 2012	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Europe	France	1	3	2	1	3	0	1	0	0
	Denmark	0	0	0	2	0	0	0	0	0
	Ireland	2	0	1	1	0	0	0	0	0
	UK	0	0	1	1	0	0	0	0	1
	Netherlands	0	0	2	0	0	0	0	0	0
	Spain	0	0	0	0	1	0	0	2	0
	Italy	2	0	1	2	3	0	1	3	1
	Belgium	3	1	0	2	3	0	1	0	0
	Austria	0	1	2	0	1	0	2	2	0
	Finland	0	0	1	0	0	0	0	1	0
	Germany	0	3	1	0	1	0	0	0	0
	Sweden	0	0	0	1	0	0	0	0	0
	Romania	0	0	0	1	0	0	0	1	0
	Czech Rep.	0	0	1	0	0	0	0	0	0
	Ukraine	0	0	1	0	0	0	0	0	0
	Lithuania	0	0	1	0	0	0	0	0	0
	Portugal	3	0	0	0	0	0	0	0	0
	Greece	0	1	0	0	0	0	0	0	0
	Turkey	1	0	0	0	1	0	0	0	0
	Iceland	0	0	0	1	0	0	0	0	0
	Hungary	0	0	0	0	3	0	1	0	1
	Cyprus	0	0	0	0	1	0	0	0	0
	Latvia	0	0	0	0	2	0	0	0	0
	Slovakia	0	0	0	0	1	0	0	0	0
	Subtotal	12	9	14	12	20	0	6	9	3
North, Central, and South America	USA	23	6	14	8	3	2	6	2	9
	Canada	1	0	0	1	0	0	0	0	1
	Mexico	0	1	0	0	0	0	0	2	0
	Argentina	0	0	0	0	0	0	0	3	1
	Brazil	0	0	0	1	0	0	0	0	0
	Subtotal	24	7	14	10	3	2	6	7	11
Asia/ Oceania	China	10	20	16	18	23	27	30	28	43
	India	7	4	4	3	4	19	18	30	30
	Singapore	0	0	0	2	0	0	1	1	1
	South Korea	10	18	14	11	13	10	11	19	19
	Indonesia	0	0	1	0	0	3	0	0	1
	Taiwan	1	1	2	6	6	2	6	8	9
	Thailand	0	1	0	2	1	0	1	0	2
	Vietnam	1	1	0	0	3	0	0	1	3
	Israel	0	0	1	0	0	0	0	0	0
	Malaysia	0	0	0	0	1	0	0	1	0
	Macau	0	0	0	0	0	0	0	1	0
	Subtotal	29	45	38	42	51	61	67	89	108
Grand Total		65	61	66	64	74	63	79	105	122

Note 1: For-cause inspections at foreign manufacturing sites under Article 75-4 of the PMD Act are excluded.
Note 2: Puerto Rico was included in the USA.

Number of On-site GCTP Inspections of Foreign Manufacturing Sites for Regenerative Medical Products by Country

Region	Country	FY 2018
Europe	UK	1
	Austria	1
	Subtotal	2
North, Central, and South America	USA	7
	Subtotal	7
Total		9

Note 1: No GCTP inspections conducted in or before FY 2017.

Note 2: For-cause inspections at foreign manufacturing sites under Article 75-4 of the PMD Act are excluded.

Note 3: Puerto Rico was included in the USA.

Number of On-site QMS Inspections of Foreign Medical Device Manufacturing Sites by Country

Region	Country	FY 2010	FY 2011	FY 2012	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Europe	Ireland	4	1	3	0	1	0	0	0	1
	UK	0	1	0	1	2	0	0	2	0
	Italy	2	1	1	0	1	0	0	0	0
	Netherlands	1	0	0	0	0	0	0	0	1
	Switzerland	0	0	0	1	0	0	0	0	0
	Spain	0	0	1	0	0	0	0	1	0
	France	1	1	4	0	0	0	0	0	6
	Denmark	0	0	0	0	0	0	0	0	1
	Austria	0	0	1	0	0	0	0	0	0
	Belgium	0	0	1	0	0	0	0	0	2
	Turkey	0	0	0	1	0	0	0	0	0
	Germany	0	0	0	0	0	0	0	3	4
	Subtotal	8	4	11	3	4	0	0	6	15
North, Central, and South America	USA	19	12	21	8	4	0	0	12	7
	Mexico	0	1	0	0	1	0	0	3	1
	Brazil	0	0	0	0	0	0	0	0	2
	Canada	0	1	1	4	0	0	0	0	0
	Costa Rica	0	1	0	0	0	0	0	0	1
	Subtotal	19	15	22	12	5	0	0	15	11
Asia	China	0	0	1	1	6	0	0	2	6
	South Korea	1	0	0	5	8	7	2	6	4
	Thailand	0	0	1	0	0	0	0	1	2
	Singapore	0	0	0	2	1	1	1	0	0
	Philippines	0	0	2	0	0	0	0	0	1
	Israel	0	1	0	1	0	0	0	0	0
	Taiwan	0	0	0	1	3	3	0	1	0
	UAE	0	0	0	1	0	0	0	0	0
	Malaysia	0	0	0	0	1	1	0	0	1
	India	0	0	0	0	1	0	0	0	0
	Subtotal	1	1	4	11	20	12	3	10	14
Grand Total		28	20	37	26	29	12	3	31	40

Note 1: For-cause inspections at foreign manufacturing sites under Article 75-4 of the PMD Act are excluded.

Note 2: Puerto Rico was included in the USA.

Note 3: Only the manufacturing sites as defined under the new Act are included in the totals from FY 2015 onward.

3.2.(1).H.(i).d. Coordination between GMP/GCTP/QMS inspections and reviews

- During the review process for drugs, quasi-drugs, and regenerative medical products, the Office of Manufacturing/Quality and Compliance holds monthly meetings with the review division (Offices of New Drugs) to exchange information on the progress of reviews and the quality of reviews related to manufacturing control and quality control, and thereby ensures that inspections are conducted in a timely manner in the review process.
- In July 2015, MHLW issued a notification directing medical device manufacturers to file applications for QMS inspections within 10 days of submitting applications for marketing approval of "generic medical devices" and "improved medical devices (without clinical data)." This enabled PMDA to confirm whether an application for a QMS inspection has been submitted after submission for marketing approval.

3.2.(1).H.(i).e. For-cause inspections of registered certification bodies

Outline of the System

- To market a specially-controlled/controlled medical device and an in-vitro diagnostic reagent for which certification standards are defined, a certification granted to the product by a certification body registered by MHLW (hereinafter referred to as "registered certification body") is required. The Division of Registered Certification Bodies Assessment conducts inspections of registered certification bodies: (1) inspections at registration or registration renewal (once every 3 years); and (2) periodic inspections (annual).

Results

- In FY 2018, PMDA conducted the following inspections of Japanese certification bodies: 3 inspections for registration renewal and 11 periodic inspections.

3.2.(1).H.(i).f. Inspection of MDSAP-recognized auditing organizations

- In June 2015, Japan announced that it would formally participate in MDSAP.[Note] PMDA therefore began the inspection of MDSAP-recognized auditing organizations (11 inspections conducted in FY 2018).

Note: The Medical Device Single Audit Program (MDSAP) permits auditing organizations jointly certified by participating regulatory authorities (Japan, USA, Canada, Australia, and Brazil) to conduct a single QMS inspection of a medical device manufacturer. The inspection results are shared and utilized by the regulatory authorities within the framework of each country's regulations.

3.2.(1).H.(ii) Development of the inspection system based on the Act on Safety of Regenerative Medicine

3.2.(1).H.(ii).a. Establishment of the inspection system

- In accordance with the Act on Safety of Regenerative Medicine (enforced in 2014), PMDA conducts compliance assessments of buildings and facilities specified under Article 42 of the Act of Safety of Regenerative Medicine required for obtaining manufacturer's license / accreditation for manufacturing at cell processing facilities. These compliance assessments are carried out at the request of the Health Policy Bureau in MHLW or Regional Bureau of Health and Welfare.

  As in previous years, PMDA provided training on inspection methods to inspectors in the Office of Manufacturing Quality for Drugs, to enhance their inspection proficiency. PMDA is also making efforts to secure the necessary number of inspectors to handle all applications submitted.

Number of Applications for Manufacturer License/Accreditation under the Act on Safety of Regenerative Medicine

	FY 2014			FY 2015			FY 2016		
	Application	Completed	Withdrawn	Application	Completed	Withdrawn	Application	Completed	Withdrawn
Applications for manufacturer license (in Japan)	19	0	0	43	37 (36)	2	13	7 (7)	1
Applications for manufacturer accreditation (outside Japan)	0	0	0	4	1 (1)	1	2	1 (1)	0
For-cause Inspections	0	0 (0)	0	0	0 (0)	0	0	0 (0)	0
Total	19	0	0	47	38 (37)	3	15	8 (8)	1

	FY 2017				FY 2018			
	Application	Completed	Withdrawn	In progress	Application	Completed	Withdrawn	In progress
Applications for manufacturer license (in Japan)	9	7 (7)	0	2	13	4 (4)	0	9
Applications for manufacturer accreditation (outside Japan)	1	0 (0)	0	1	0	0 (0)	0	0
For-cause Inspections	0	1 (1)	0	0	0	0 (0)	0	0
Total	10	8 (8)	0	3	13	4 (4)	0	9

Note: The figures in parentheses represent the number of on-site inspections.

Administrative Processing Time for Inspection related to Manufacturer Licensing/Accreditation

	FY 2014		FY 2015		FY 2016		FY 2017		FY 2018	
	Median total processing time (days)	Median PMDA processing time (days)	Median total processing time (days)	Median PMDA processing time (days)	Median total processing time (days)	Median PMDA processing time (days)	Median total processing time (days)	Median PMDA processing time (days)	Median total processing time (days)	Median PMDA processing time (days)
Applications for manufacturer license (in Japan)	-	-	134	83	142	64	127	80	162	90
Applications for manufacturer accreditation (outside Japan)	-	-	166	136	133	114	-	-	191	45

Number of For-cause Inspections Conducted by PMDA

Region	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Japan	0	0	0	1	0
Outside Japan	0	0	0	0	0
Total	0	0	0	1	0

Number of On-site Inspections of Foreign Cell Processing Facilities by Region

	Europe	North, Central, and South America	Asia/Oceania	Africa	Total
FY 2014	-	-	-	-	-
FY 2015	0	0	2	0	2
FY 2016	0	0	2	0	2
FY 2017	0	0	1	0	1
FY 2018	0	0	0	0	0

Number of On-Site Inspections of Foreign Cell Processing Facilities by Region

Region	Country	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018	Total
Europe	-	-	-	-	-	-	-
	Subtotal	-	0	0	0	0	0
North, Central, and South America	-	-	-	-	-	-	-
	Subtotal	-	0	0	0	0	0
Asia	South Korea	-	2	2	0	-	4
	Taiwan	-	0	0	1	-	1
	Subtotal	-	2	2	1	0	5
Grand Total		-	2	2	1	0	5

3.2.(2) Initiatives to facilitate practical application of innovative drugs, medical devices, and regenerative medical products

3.2.(2).(i) Development and revision of review standards for innovative products

- The Science Board was established in May 2012 as a forum where PMDA reviewers exchange opinions with leading researchers in Japan regarding methods of evaluating new and advanced technologies. Activities of the Science Board for the fourth term started in April 2018. For details regarding the “Use of the Science Board” during its fourth term, see Section 3.4(1).
- The initiatives to facilitate the practical application of innovative drugs, medical devices, and regenerative medical products, were completed in FY 2016. In FY 2018, the MHLW issued the following 7 notifications to announce the guidelines developed based on the outcomes of the initiatives: “Points to Consider for Assurance and Evaluation of the Quality of Oligonucleotide Therapeutics” (PSEHB/PED Notification No. 0927-3 dated September 27, 2018, issued by Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW); “Publication of Considerations Developed Based on the Results of Initiatives to Facilitate Practical Application of Innovative Drugs, Medical Devices, and Regenerative Medical Products” (PSEHB/MDED Notification No. 1106-1, dated November 6, 2018, issued by Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW); “Publication of Testing Methods Developed Based on the Results of Initiatives to Facilitate Practical Application of Innovative Drugs, Medical Devices, and Regenerative Medical Products” (PSEHB/MDED Notification No. 1115-1, dated November 15, 2018, issued by Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW); “Publication of Testing Methods Developed Based on the Results of Initiatives to Facilitate Practical Application of Innovative Drugs, Medical Devices, and Regenerative Medical Products (Guidelines for Review of Non-invasive Vagus Nerve Stimulation Devices for Treatment of Acute Coronary Syndrome)” (PSEHB/MDED Notification No. 1221-2, dated December 21, 2018, issued by Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW); “Publication of Considerations Developed Based on the Results of Initiatives to Facilitate Practical Application of Innovative Drugs, Medical Devices, and Regenerative Medical Products (Guidelines for Image-guided

High-intensity Focused Ultrasound Systems)" (PSEHB/MDED Notification No. 1228-1, dated December 28, 2018, issued by Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW); "Guidance on Cancer Immunotherapy Development" (PSEHB/PED Notification No. 0308-1 and PSEHB/MDED Notification No. 0308-1, dated March 8, 2019, issued jointly by the Director of the Pharmaceutical Evaluation Division, and the Director of Medical Device Evaluation Division, of Pharmaceutical Safety and Environmental Health Bureau, MHLW); "Publication of Testing Methods Developed Based on the Results of Initiative to Facilitate Practical Application of Innovative Drugs, Medical Devices, and Regenerative Medical Products (Guidelines for the Review of Combination Products as Medical Devices [Implantable Device/Equipment Combined with Antimicrobials or Tissue Regeneration Agents] Used in the Field of Dentistry and Orthopedic Surgery)" (PSEHB/MDED Notification No. 0313-2, dated March 13, 2019, issued by Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW).

- To ensure the proper execution of product reviews, safety measures, and relief services for adverse health effects, and to enhance the quality of these operations, PMDA is striving to promote regulatory science research on topics contributing to the development of standards, guidelines, and guidance and on how to conduct scientific prediction, evaluation, and judgment. Some regulatory science research activities conducted by PMDA are designated as within the scope of PMDA's official operations. This designation is dependent on the research purpose, how the research is related to PMDA's operations, and on comments from the Regulatory Science Research Selection Committee and the Regulatory Science Research Evaluation Committee. In FY 2018, 6 projects (4 new projects and 2 ongoing projects) were underway as designated research projects, and the results of 8 projects were published in academic journals or presented in conference sessions (2 published in papers, 6 presented in sessions).
- PMDA supported the development of evaluation guidelines through the activities of 11 working groups (WG) (Companion Diagnostics WG, Omics WG, Pediatric Drugs WG, Orphan Drugs WG, ICH Q12 WG, Nanomedicine Initiative WG, Global Clinical Study WG, Cardiovascular Risk Evaluation WG, Clinical Innovation Network WG, Innovative Manufacturing Technology WG, and Induced Pluripotent Stem Cells (iPSC) WG) in the Projects Across Multi-offices in PMDA to Develop Standards etc. (hereinafter, "Projects Across Multi-offices"). The Projects aim to promote product development, facilitate international collaborations for review standards etc., and accelerate reviews by making clear scientific principles for reviews of drugs and medical devices.

  In FY 2018, individual working groups collaborated with MHLW to issue the following notifications:

  (a) Companion Diagnostics WG

  "Questions and answers (Q&A) on 'Technical Guidance on Development of In Vitro Companion Diagnostics and Corresponding Therapeutic Products'" (PSEHB/PED/MDED Administrative Notice, dated July 3, 2018, issued jointly by the Pharmaceutical Evaluation Division and the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW)

  "Questions and answers (Q&A) on Companion Diagnostics and Corresponding Therapeutic Products (Part 2)" (PSEHB/PED/MDED Administrative Notice, dated July 20, 2018, issued jointly by the Pharmaceutical Evaluation Division and the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW),

  "Questions and answers (Q&A) on 'Legislation Notice to Applicants for Marketing Authorization of DNA Sequencers and Related Products Utilized for Genetic Testing Systems' (Part 2)" (PSEHB/PED/CND Administrative Notice, dated September 12, 2018, issued jointly

by the Pharmaceutical Evaluation Division and the Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW)

(b) Global Clinical Study WG
"Guidelines on General Principles on Planning and Design of Global Clinical Trials" (PSEHB/PED Notification No.0612-1, dated June 12, 2018, issued by Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW)

(c) Clinical Innovation Network WG
"Points to Consider for Assurance of Data Integrity of Post-marketing Database Surveys for Medical Devices" (PSEHB/MDED Notification No.1219-4, dated December 19, 2018, issued by Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW) (reposted).

- The Companion Diagnostics WG for Projects Across Multi-Offices prepared "List of Approved Companion Diagnostics" and posted it on the PMDA website.
- The Pediatric Drugs WG, ICH Q12 WG, Global Clinical Study WG, and Innovative Manufacturing Technology WG for Projects Across Multi-Offices supported the activities of ICH Expert Working Groups to develop draft guidelines for ICH E11A, ICH S11, ICH Q12, ICH E17, and ICH Q13, respectively.
- The Pediatric Drugs WG, ICH Q12 WG, Nanomedicine Initiative WG, Cardiovascular Risk Evaluation WG, and Innovative Manufacturing Technology WG for Projects Across Multi-Offices exchanged opinions with US FDA, EMA, and other foreign regulatory authorities.
- The Pediatric Drugs WG, ICH Q12 WG, Cardiovascular Risk Evaluation WG, Clinical Innovation Network WG, Innovative Manufacturing Technology WG, and Induced Pluripotent Stem Cells (iPSC) WG for Projects Across Multi-Offices facilitated the exchange of opinions between the industry, government, and academia by participating in the AMED Research Project.
- The Clinical Innovation Network WG for Projects Across Multi-Offices exchanged and coordinated opinions with industry to launch a new consultation category concerning registries.

3.2.(2).(ii) Expansion of RS Strategy Consultations (R&D)

- Since November 2014, PMDA has provided, on a trial basis, general advice related to the product development process (roadmap) and confirmatory clinical trial protocols to applicants including pharmaceutical companies. Further, PMDA offered on-site consultations and distributed brochures to relevant academic conferences for publicity purposes. Through collaboration between relevant PMDA offices, activities were carried out promptly and appropriately.
- In July 2016, MHLW issued a report titled "Advisory Panel on Promotion of Venture Companies that Facilitate Medical Innovation." In response to the report, PMDA took the following actions in April 2017 as measures to facilitate the practical application of innovative drugs, medical devices, and regenerative medical products:

  (a) The Division of Pharmaceutical Affairs Consultation was renamed the Division of Innovation Support and Consultations on R&D Strategy.

  (b) Pharmaceutical Affairs Consultation on R&D Strategy (introductory consultation, pre-consultation meeting, and full-scale consultation) was reorganized into RS General Consultation (introductory consultations) and RS Strategy Consultation (R&D) (pre-consultation meeting and full-scale consultation).

  Furthermore, PMDA launched the following consultation category in April 2018:

(c) Consultation on Cooperation for Practical Application of Innovation Advancements.

PMDA also had monthly meetings with the Economic Affairs Division, Health Policy Bureau, MHLW to share information concerning the practical application of seed-stage resources that may lead to innovative drugs, medical devices, etc., possessed by academic institutions or venture companies. Furthermore, PMDA assisted the activities of the "Total Support Program for Healthcare Ventures (also known as Medical Innovation Support Office, MEDISO)" provided by MHLW, for example, by giving lectures to "MEDISO supporters" who serve as advisors.

- To promote the use of PMDA's Kansai Branch Office, PMDA strived to familiarize potential service users with a video conference system, which is a system available for consultation services such as face-to-face consultations, in a telecommunication format and allows service users to hold video conference for RS General Consultations, RS Strategy Consultations (R&D), and other consultations without visiting the PMDA head office in Tokyo. The Kansai Branch Office organized lecture activities and observational tours for academic institutions, etc. based in the Kansai region. A total of 105 consultations (vs. 59 in FY 2017), including 20 RS Strategy Consultations (R&D) (vs. 11 in FY 2017), used the video conference system in FY 2018.
- On August 19, 2015, PMDA and AMED concluded the "Agreement on Collaboration between the Pharmaceuticals and Medical Devices Agency and the Japan Agency for Medical Research and Development" to facilitate the early creation and practical application of innovative drugs and medical devices. As a collaborative effort based on the Agreement, PMDA and AMED agreed that research projects adopted by AMED should in principle undergo RS Strategy Consultation (R&D) before advancing to the stage of practical application. PMDA held discussions, as appropriate, with AMED about the timing and content of RS Strategy Consultations (R&D) for research projects.

3.2.(2).(iii) Implementation of approval system based on characteristics of regenerative medical products

- To address the introduction of the conditional limited-time authorization system for regenerative medical products, the relevant PMDA offices collaborated in offering RS Strategy Consultations (R&D), and provided information on this system at academic conferences and similar events, and thus promoted the use of the system.

3.2.(2).(iv) Implementation of the SAKIGAKE product designation system

- In FY 2015, the "SAKIGAKE designation system" was launched on a trial basis for drugs, medical devices, *in vitro* diagnostics, and regenerative medical products. To manage this system, PMDA has improved its organizational setup through methods including the introduction of "review partners (concierges)" and the "SAKIGAKE comprehensive assessment consultation" service intended for pre-evaluation of designated products.
- At the request of MHLW, PMDA's review offices conducted pre-evaluations of products submitted to be considered for SAKIGAKE designation. Based on the results of the pre-evaluations, MHLW designated 17 drugs, 7 medical devices, 1 *in vitro* diagnostic product, and 9 regenerative medical products as SAKIGAKE-designated products in FY 2018. The progress of regulatory review process for these designation products was managed by review partners on a per product basis. (Designation for 1 drug and 1 medical device was cancelled by the end of FY 2018). In FY 2018, 2 drugs, 1 in vitro diagnostic product (since this was a combination product comprised of a medical device software program and an *in vitro* diagnostic product, the whole product was approved as a medical device), and 1 regenerative medical product were approved under the SAKIGAKE

designation system. A current list of SAKIGAKE-designated products and a summary of their characteristics are both available on the PMDA website.

3.3 Safety Measure Services

3.3.(i) Proper assessment of adverse drug reaction and medical device malfunction reports

- PMDA aims to ensure that the safety of marketed drugs, medical devices, and regenerative medical products is improved and that patients and healthcare professionals use these products as properly as possible. To this end, PMDA makes efforts to efficiently collect and examine product safety information, process this information, plan appropriate and adequate safety measures, and rapidly disseminate the details of these measures with easy-to-understand safety information, thereby integrating the risk management aspects of both pre-market reviews and post-market vigilance activities at PMDA.
- PMDA implemented organizational restructuring in January 2019. To reinforce its systems concerning safety measures for drugs and medical devices and to address the advancement and specialization of drug safety measures/pharmacovigilance, PMDA reorganized its two offices responsible for safety (the Office of Safety I and Office of Safety II) into three offices (the Office of Informatics and Management for Safety, Office of Pharmacovigilance I, and Office of Pharmacovigilance II).

  Furthermore, defects in the design and manufacturing control of medical devices may often cause device malfunction. Considering such aspects of medical devices, PMDA established the Office of Manufacturing Quality and Vigilance for Medical Devices, which is responsible for medical device malfunction reporting program and QMS inspections.
- Every year, PMDA receives various types of case reports from industry: approximately 553,000 reports on serious adverse reactions and infections attributable to drugs (from Japanese and foreign companies); approximately 53,000 reports on medical device malfunctions and infections attributable to medical devices (from Japanese and foreign companies); approximately 163 reports on regenerative medical product malfunctions and infections attributable to such products; approximately 4,200 case reports on suspected malfunctions, etc. of equipment components from combination products (from Japanese and foreign companies); and 186 reports on adverse reactions attributable to quasi-drugs/cosmetics. PMDA records the information obtained from these reports into a database that is shared with MHLW. PMDA also monitors information regarding new measures implemented by foreign regulatory agencies such as US FDA and EMA with respect to drugs, medical devices, and other products. The purpose of these monitoring activities is to help PMDA to conduct daily assessment of its responses to safety issues concerning products marketed in Japan. PMDA also reviews academic literature in conjunction with these activities for analyzing and sharing information on adverse drug reactions and device malfunctions. In addition, PMDA is working to implement comprehensive safety measures for drugs, medical devices, and regenerative medical products in the post-marketing stage by enhancing cooperation between product review offices and safety offices, and between the relief office and safety offices.
- Reports on adverse drug reactions, medical device malfunctions, etc. are analyzed by PMDA's product safety teams every day. PMDA assesses and reviews such reports, based on the analysis results, with MHLW every week, seeks opinions from external experts and companies, and proposes necessary safety measures, such as revision to precautions in package inserts, to MHLW. If any urgent issue arises, PMDA responds to it immediately in cooperation with MHLW.
- The following table displays the numbers of reports (in terms of the number of active pharmaceutical ingredients, and the number of term names for medical devices) submitted to MHLW for products for which safety measures such as revisions to package inserts were determined to be necessary. PMDA analyzes near-incident case reports collected by the Japan

Council for Quality Health Care while seeking opinions from experts. The number of near-incident case reports submitted to MHLW was categorized under “Medical Safety.”

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Drugs	100	87[*2]	152	219[*3]	97
Medical devices	4	28	6	0	1
Regenerative medical products	0[*1]	0	0	0	0
Medical safety	6	6	6	6	5

**1 Number of reports after enactment of the PMD Act on November 25, 2014*
**2 A total of 84 reports concerning drugs and 3 reports concerning in vitro diagnostics.*
**3 A total of 218 reports concerning drugs and 1 report concerning quasi-drugs*

- Actions taken by MHLW based on reports from PMDA, such as revisions of precautions, were as follows (includes duplicated measures). Initially, 97 reports submitted to MHLW for products for which safety measures such as revision of package inserts were determined to be necessary, but MHLW determined that no revision of package inserts is required for 3 reports (concerning oxytocin, dinoprost, and dinoprostone). The 94 reports leading to revisions of precautions in package inserts included 6 reports based on information from the relief office and 6 reports submitted from medical institutions.

		FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Drugs	Directions for revision to precautions in package insert	100	87[*1]	152	219[*2]	94
	Releasing PMDSI reports	29	28[*3]	32	32	23
Medical devices	Directions for revision to precautions in package insert or issuance of self-check notifications[*4]	4 (2)	28 (3)	6 (1)	0 (0)	1 (1)
	Releasing PMDSI reports	1	1	0	0	0
Regenerative medical products	Directions for revision to precautions in package insert or issuance of self-check notifications	0[*5]	0	0	0	0
	Releasing PMDSI reports	0[*5]	0	0	0	0

**1 A total of 84 reports concerning drugs and 3 reports concerning in vitro diagnostics.*
**2 A total of 218 reports concerning drugs and 1 report concerning quasi-drugs*
**3 A total of 27 reports concerning drugs and 1 report concerning in vitro diagnostics.*
**4 Figures in parentheses indicate the number of notifications, etc.*
**5 Number of cases after the enactment of the PMD Act on November 25, 2014*
PMDSI: Pharmaceuticals and Medical Devices Safety Information

- The 94 reports for products for which actions such as revisions of precautions in package inserts were taken include cases with difficulties (e.g., world-first implementation of safety measures in Japan, briefing sessions targeting multiple marketing authorization holders (MAHs) to ensure implementation of safety measures for drugs in the same class without delay). Major revisions of precautions in package inserts are as follows:
  - The Clinically Significant Adverse Reactions section in the package inserts for pembrolizumab (genetical recombination) were revised to add “sclerosing cholangitis,” “hemophagocytic syndrome,” and “agranulocytosis.”

- The Clinically Significant Adverse Reactions section in the package inserts for lenvatinib mesilate were revised to add “pneumothorax.”
- The Clinically Significant Adverse Reactions section in the package inserts for axitinib were revised to add “interstitial lung disease.”
- The Clinically Significant Adverse Reactions section in the package inserts for nivolumab (genetical recombination) were revised to add “hemophagocytic syndrome,” “hemolytic anemia,” and “agranulocytosis.”
- The Careful Administration section in the package inserts for intravenous injections containing sorbitol or fructose as an excipient were revised to add “patients with hereditary fructose intolerance.”

- Collaborative activities between offices responsible for pre-market review of products and offices responsible for monitoring post-marketing safety (e.g., Office of Pharmacovigilance I and II) at PMDA include the evaluation of adverse drug reactions reported in accordance with early post-marketing phase vigilance (EPPV) requirements together with review staff. Product safety staff also participate in the review process (in clinical trial consultations, assessments of post-marketing surveillance plans, reviews of draft package inserts, Expert Discussions, etc.) for new drugs, new medical devices, and new regenerative medical products. In accordance with the PMD Act, product safety staff have organized information and conducted research on claims for relief benefits in collaboration with Office of the Relief Fund. In addition, after approval or rejection has been judged for claims for relief benefits, relevant information such as the names of drugs and adverse drug reactions in question is provided to the safety offices and is reflected in safety measures implemented.
- PMDA evaluated post-marketing safety data regarding drugs approved on the condition that MAHs conduct post-marketing surveillance covering all patients treated. PMDA also held consultations with such MAHs and provided instruction as necessary to distribute information materials to patients and healthcare professionals who use the drugs.
- When the approval conditions of a drug were lifted, PMDA notified the public and medical information-related parties by releasing the risk management plan (RMP) and package inserts.
- Concerning cases with difficulties in determining the necessity of safety measures based solely on adverse reaction reports, PMDA started efforts to improve the quality of safety measures by utilizing pharmacoepidemiological methods, e.g., the initiation of surveys using the MID-NET® System.
- As for collaboration with overseas regulatory authorities, PMDA continued participating as an observer in the US FDA-EMA pharmacovigilance cluster in FY 2018 and participated in 6 conferences. Through these activities, PMDA endeavors to participate in the global exchange and early stage consideration of safety information.
- PMDA has made efforts to adequately collect, organize, and examine reports on adverse drug reactions, case reports on medical device malfunctions, etc., that have been submitted by MAHs and medical institutions. For example, PMDA holds periodical liaison meetings with MHLW, promotes the participation of employees in academic conferences, and collects relevant information. In addition to these activities, in FY 2018 PMDA carried out the following actions:

  a. In accordance with the ICH-E2B (R3) guideline, the electronic transmission of Individual Case Safety Reports from MAHs is scheduled to be implemented in April 2019. PMDA raised the industry’s awareness of this system replacement by holding workshops and other activities to ensure smooth implementation of the system.

b. PMDA started to receive reports on diseases etc. that are suspected to be attributable to the conduct of clinical research, in response to the enforcement of the Clinical Research Act in April 2018.

c. PMDA continued to deliver lectures to healthcare professionals, in order to familiarize them with adverse reaction reporting, thereby increasing adverse reaction reports from medical institutions. PMDA also supported the project (regulatory harmonization research initiative) implemented by the AMED to promote reporting of adverse drug reactions.

d. To enable device malfunction reports to be submitted directly at the PMDA website rather than via the e-Gov website (the official web portal of the Japanese government), PMDA discussed the construction and management of a new system for submission of device malfunction reports, with stakeholders including the industry sector, and developed specifications for the new system.

Collection of adverse reaction reports etc.

1-1) Number of reports relating to drugs

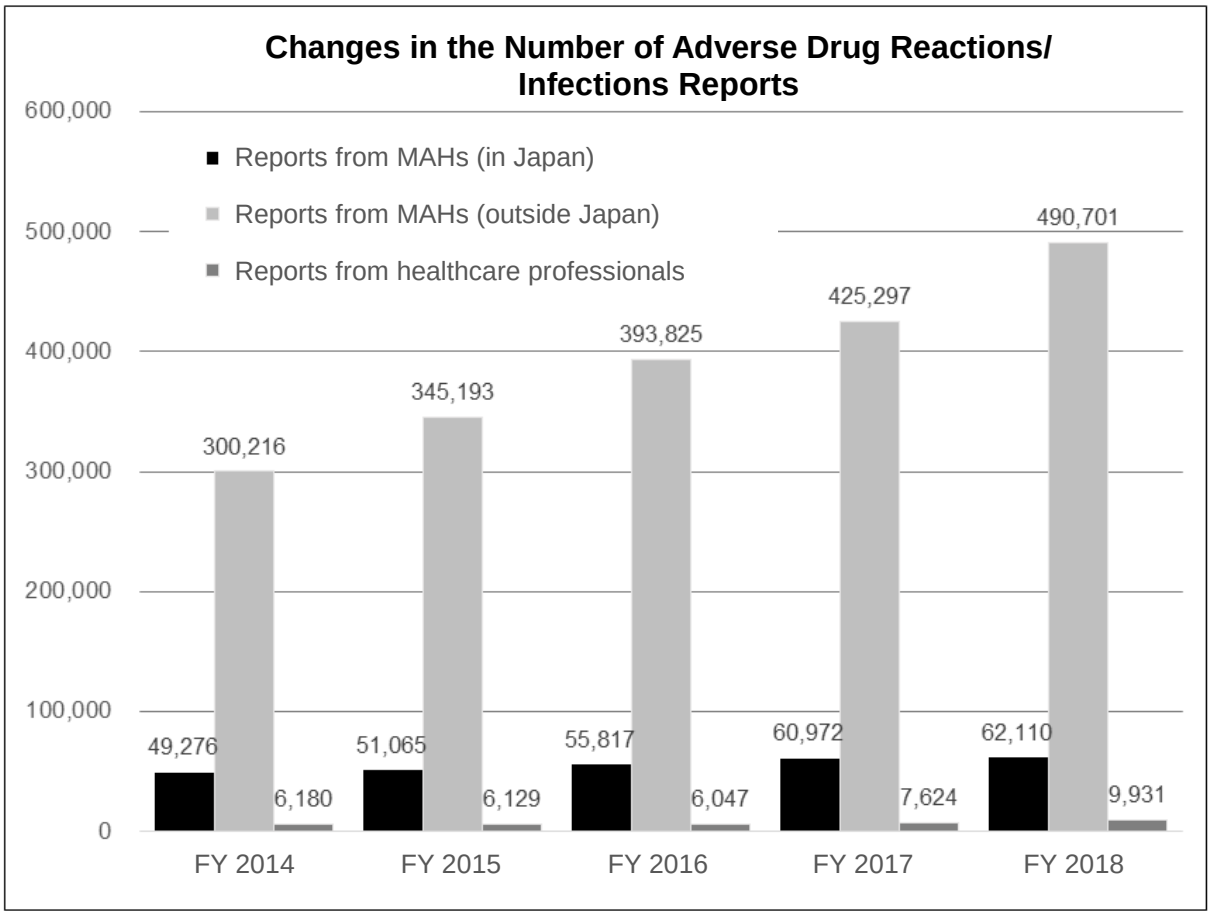
	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Reports from MAHs	352,908	399,852	453,296	490,019	556,424
(Adverse drug reactions, in Japan)	(49,198)	(50,977)	(55,728)	(60,872)	(62,037)
(Infections caused by drugs, in Japan)	(78)	(88)	(89)	(100)	(73)
(Adverse drug reactions, outside Japan)	(300,191)	(345,161)	(393,767)	(425,251)	(490,674)
(Infections caused by drugs, outside Japan)	(25)	(32)	(58)	(46)	(27)
(Research reports)	(1,099)	(1,219)	(1,117)	(1,206)	(1,078)
(Foreign safety measure reports)	(1,219)	(1,273)	(1,397)	(1,492)	(1,451)
(Periodic infection reports)	(1,098)	(1,102)	(1,140)	(1,052)	(1,084)
Reports from healthcare professionals	6,180	6,129	6,047	7,624	9,931
([1] Safety information reporting system)	(4,782)	(4,891)	(4,956)	(6,606)	(9,065)
([2] Vaccines)	(1,398)	(1,238)	(1,091)	(1,018)	(863)
([3] Disease reports)[*1]	(-)	(-)	(-)	(-)	(3)
Total	359,088	405,981	459,343	497,643	566,355

[*1] *Number of reports after the enactment of the Clinical Research Act on April 1, 2018 (1 report related to unapproved drug use, 2 reports related to off-label drug use)*

		FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Cases of malfunctions of combination drugs (in Japan)	Reports from MAHs	0	38	661	1,120	1,653
	Reports from healthcare professionals	-	-	4	12	19
Cases of malfunctions of combination drugs (outside Japan)	Reports from MAHs	0	60	1,126	2,951	2,542

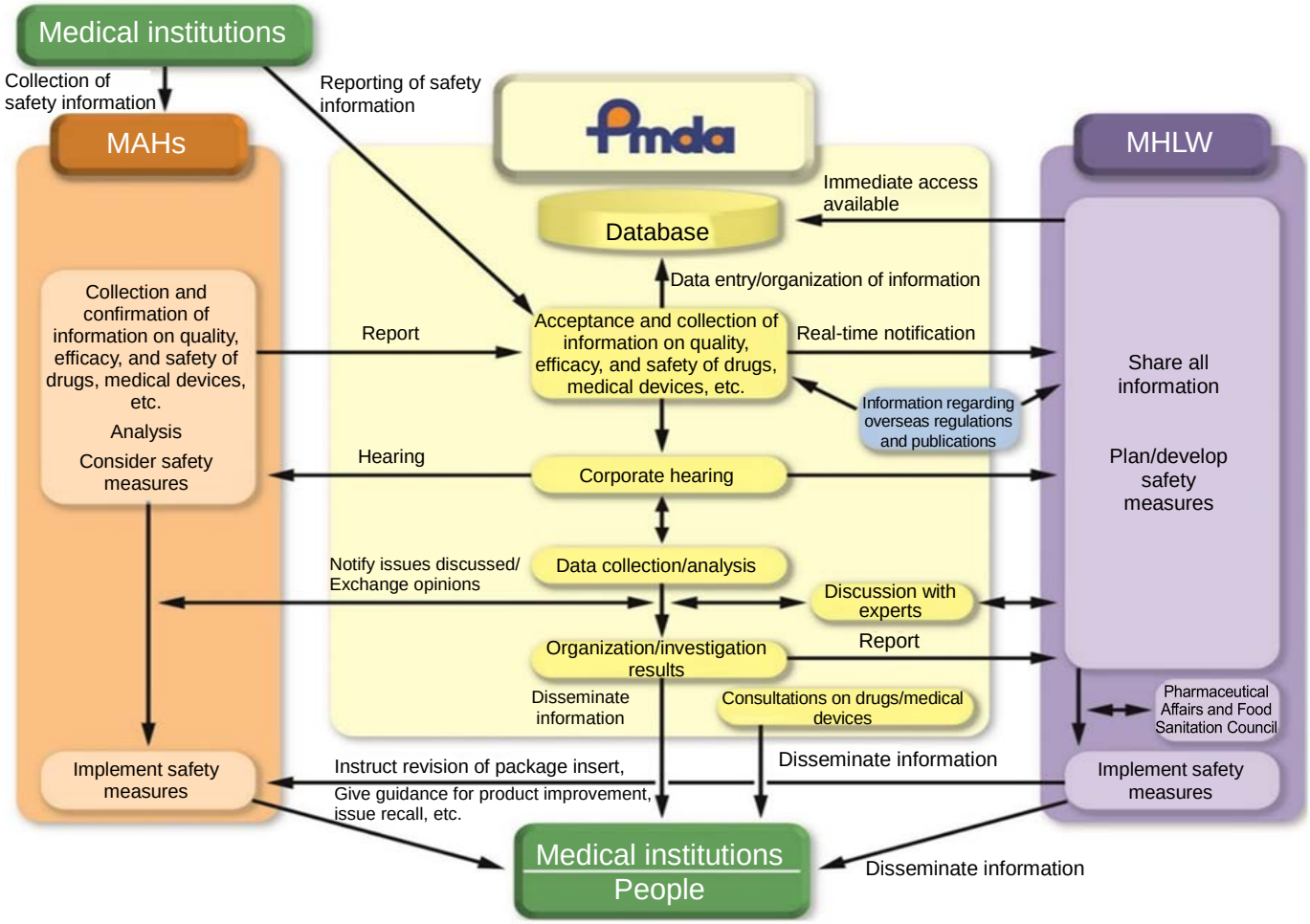
Note: The transitional period (during which reporting was not mandatory) was from November 25, 2014 to November 24, 2016. Reporting was made mandatory on November 25, 2016. The number of reports in FY 2014 is the number of reports after enactment of the PMD Act on November 25, 2014.

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Quasi-drugs	561	323	146	119	103
Cosmetics	116	114	71	97	83



- MAHs submit to PMDA adverse drug reaction/infectious disease reports originally made by healthcare professionals and other sources. Among the reports submitted by MAHs in Japan in FY 2018, 89.3% had been collected from healthcare professionals (physicians, 66.1%; pharmacists, 14.2%; other healthcare professionals, 9.0%) and 10.7% from non-healthcare professionals (consumers or other non-healthcare professionals, 6.6%; unknown, 4.1%).
- In total, 98.8% of adverse drug reaction/infection reports from MAHs in Japan in FY 2018 were submitted electronically (online reporting),[1] and 35.7% of adverse drug reaction reports from healthcare professionals were submitted electronically (by email).[2]

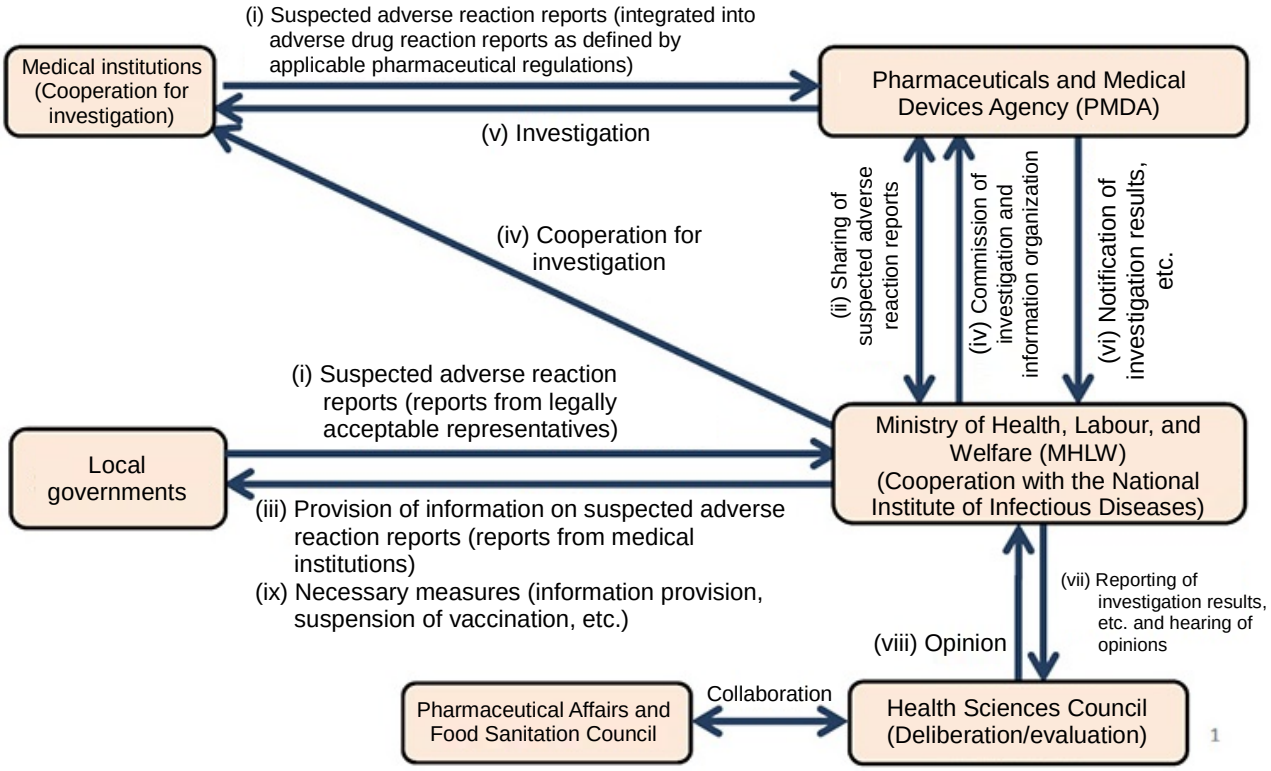
[1, 2] Including additional reports and reports exempted from reporting requirements after reporting


Medical institutions
Collection of safety information
Reporting of safety information
MAHs
Pmda
MHLW
Immediate access available
Database
Data entry/organization of information
Collection and confirmation of information on quality, efficacy, and safety of drugs, medical devices, etc.
Analysis
Consider safety measures
Report
Acceptance and collection of information on quality, efficacy, and safety of drugs, medical devices, etc.
Real-time notification
Information regarding overseas regulations and publications
Share all information
Hearing
Corporate hearing
Plan/develop safety measures
Notify issues discussed/ Exchange opinions
Data collection/analysis
Discussion with experts
Organization/investigation results
Report
Disseminate information
Consultations on drugs/medical devices
Pharmaceutical Affairs and Food Sanitation Council
Implement safety measures
Instruct revision of package insert,
Give guidance for product improvement, issue recall, etc.
Disseminate information
Implement safety measures
Medical institutions
People
Disseminate information

1-2) Reports on suspected adverse reactions following vaccination based on the Preventive Vaccination Act

Pursuant to the provisions of Article 14 of the Preventive Vaccination Act (Act No. 68 of 1948), PMDA has been conducting projects for investigating and organizing “suspected adverse reaction reports.” As of November 25, 2014, suspected adverse reaction reports submitted to PMDA in accordance with the revised Preventive Vaccination Act and the Ministerial Ordinance for Enforcement thereof (see the diagram below). In FY 2018, PMDA received 863 suspected adverse reactions reports. After receiving suspected adverse reaction reports, PMDA provides the information to the MAHs of the suspected vaccines, and instructs the MAHs to properly handle such events in accordance with the regulations set forth in the PMD Act.

As for reported cases of suspected adverse reactions to vaccines, PMDA conducted interviews as needed with physicians who diagnosed symptoms suspected to be adverse reactions and those who administered vaccinations. In the cases of deaths and symptoms suspected to be particular serious adverse reactions (e.g., anaphylactic reaction), PMDA sought opinions from experts regarding matters such as the appropriateness of diagnosis and causal relationships with vaccines, thereby supporting vaccination initiatives by MHLW.



1-3) Reporting of disease etc. implemented in accordance with the Clinical Research Act

Pursuant to the provisions of the Clinical Research Act (Act No. 16 of 2017) enforced on April 1, 2018, the principal investigator conducting a specified clinical research program using an unapproved drug or involving off-label drug use is obliged to report to PMDA any unexpected and serious diseases, etc., suspected to be attributable to the conduct of the specified clinical research.

In FY 2018, PMDA received 3 disease reports (2 reports related to off-label drug use, 1 report related to unapproved drug use). PMDA utilized reported information for safety measures, and reported the results of analysis or review of the information to the Minister of Health, Labour and Welfare.

In addition, when PMDA receives a disease report related to a drug, etc., granted marketing authorization, etc., PMDA provides information on this report to the MAH supplying the drug, as a rule. PMDA or the MAH may conduct a detailed investigation on the medical institution submitting the report to PMDA. The reported information may also be publicly disclosed as a part of safety measures, after removal of parts related to the patient's personal information, etc.

1-4) Adverse drug reaction reports from patients

The final recommendations by the Committee for Investigation of Drug-induced Hepatitis Cases and Appropriate Regulatory Administration to Prevent Similar Sufferings at MHLW (April 2010) highlighted the need to establish a system that utilizes information from patients for safety measures. The report submitted by the Investigational Sub-committee on Revision of Pharmaceutical Regulatory Systems of the Health Science Council at MHLW (January 2012) also recommended that information on adverse drug reactions reported by patients themselves should be utilized.

PMDA set up the Direct Patient Reporting System for Adverse Drug Reactions on March 26, 2012 with reference to the outcomes of a study supported by the Health and Labour Sciences Research Grants from FY 2009 to FY 2011 ("Research on System for Receiving Adverse Drug Reaction Reports from Patients"), and conducted a project for receiving adverse drug reaction reports from patients and their family on a trial basis via the Internet.

Considering the results of this trial reporting system, PMDA started a program for directly collecting information on suspected adverse drug reactions from patients or their family on March 26, 2019. This program intends to utilize reported information in taking measures for drug safety in accordance with the Procedures for Adverse Drug Reaction Reports from Patients established by MHLW. In addition, with the start of full-scale operation of this program, PMDA begun to receive reports sent by post, in addition to reports via the Internet. This change is based the opinions of individuals who reported adverse drug reactions during the trial period.

The table below shows the number of adverse drug reaction reports from patients collected by FY 2018. PMDA has been disclosing the reported cases as they come to hand.

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018**	
					Trial period	After full-scale operation
Patient-submitted adverse drug reaction reports (total number)*	91	186	50	84	73	11

* *The figures indicate the numbers of reports at the end of each fiscal year. Reports may be withdrawn at the request of reporters. Reports concerning items not classified as patient-submitted adverse drug reaction reports (including reports concerning quasi-drugs, cosmetics, and nutraceuticals) are excluded.*

** *The figure for the trial period represents the number of reports received by March 25, 2019. The figure for the full-scale operation period represents the number of reports received between March 26, 2019 and March 31, 2019.*

1-5) PMDA's detailed investigation on reports from medical institutions

PMDA has worked to collect adverse drug reaction reports from medical institutions more comprehensively, by directing its inquiries to medical institutions on some of serious cases for the purpose of investigation.

Specifically, cases of suspected serious adverse drug reactions that reflect either of the following circumstances are subject to investigation by PMDA: no information was provided by a medical institution to a MAH; or whether information has been provided by a medical institution to a MAH is unknown. PMDA conducted detailed investigations into these cases as necessary. Cases not subject to investigation by PMDA were investigated by MAHs as necessary.

The numbers of cases investigated by PMDA in previous fiscal years are provided in the table below.

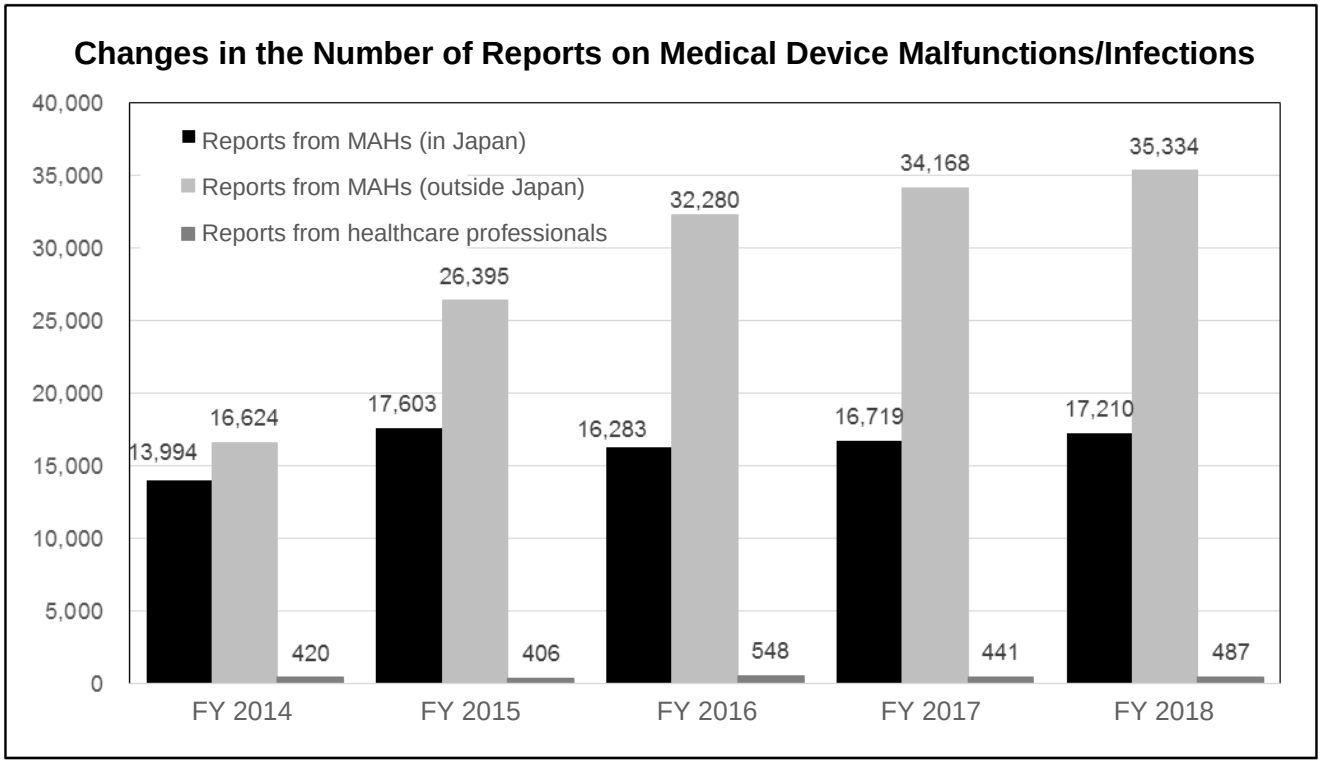
	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Number of cases investigated by PMDA	1,067	1,100	1,132	1,453	1,778

In principle, all case reports from medical institutions are provided to the MAHs of suspected drugs by fax. Concerning case reports from medical institutions investigated and analyzed by PMDA, Individual Case Safety Report (ICSR) files together with the results of detailed investigation by PMDA are provided to the MAHs of suspected drugs (i.e., drugs suspected by PMDA to be the cause), via the exclusive webpages for drug MAHs (the SKW site).

2) Number of reports relating to medical devices

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Reports from MAHs	32,490	46,406	52,063	56,081	57,439
(Medical device malfunctions, in Japan)	(13,994)	(17,603)	(16,283)	(16,719)	(17,210)
(Medical device malfunctions, outside Japan)	(16,624)	(26,394)	(32,280)	(34,168)	(35,334)
(Infections caused by medical devices, in Japan)	(0)	(0)	(0)	(0)	(0)
(Infections caused by medical devices, outside Japan)	(0)	(1)	(0)	(0)	(0)
(Research reports)	(20)	(598)	(1,289)	(2,701)	(2,314)
(Foreign safety measure reports)	(1,779)	(1,742)	(2,144)	(2,437)	(2,512)
(Periodic infection reports)	(73)	(68)	(67)	(56)	(69)
Reports from healthcare professionals	420	406	548	441	487
([1] Safety information reporting system)	(420)	(406)	(548)	(441)	(487)
([2] Disease reports)[*1]	(-)	(-)	(-)	(-)	(0)
Total	32,910	46,812	52,611	56,522	57,926

[*1] *Number of cases after the enforcement of the Clinical Research Act on April 1, 2018 (including unapproved medical device use and off-label medical device use)*



- In total, 79.9% of medical device malfunction/infection reports from MAHs in Japan, were submitted electronically (online reporting),* and 67.0% of medical device malfunction reports from healthcare professionals were submitted electronically (by email).*

* Including reports exempted from reporting requirements (e.g., follow-up reports).

3) Number of reports relating to regenerative medical products

	FY 2014*	FY 2015	FY 2016	FY 2017	FY 2018
Reports from MAHs	17	49	122	144	197
(Product malfunctions, in Japan)	(12)	(35)	(88)	(110)	(163)
(Product malfunctions, outside Japan)	(0)	(0)	(0)	(0)	(0)
(Infections caused by regenerative medical products, in Japan)	(0)	(0)	(0)	(0)	(0)
(Infections caused by regenerative medical products, outside Japan)	(0)	(0)	(0)	(0)	(0)
(Research reports)	(0)	(0)	(0)	(0)	(0)
(Foreign safety measure reports)	(0)	(0)	(0)	(0)	(0)
(Periodic infection reports)	(5)	(14)	(34)	(34)	(34)
Reports from healthcare professionals	0	0	0	0	0
Total	17	49	122	144	197

** Number of cases after the enactment of the PMD Act on November 25, 2014.*

3.3.(ii) Sophistication of safety measures

3.3.(ii).a. Introduction of the risk management system and implementation of appropriate safety measures based on the risk management plan for drugs

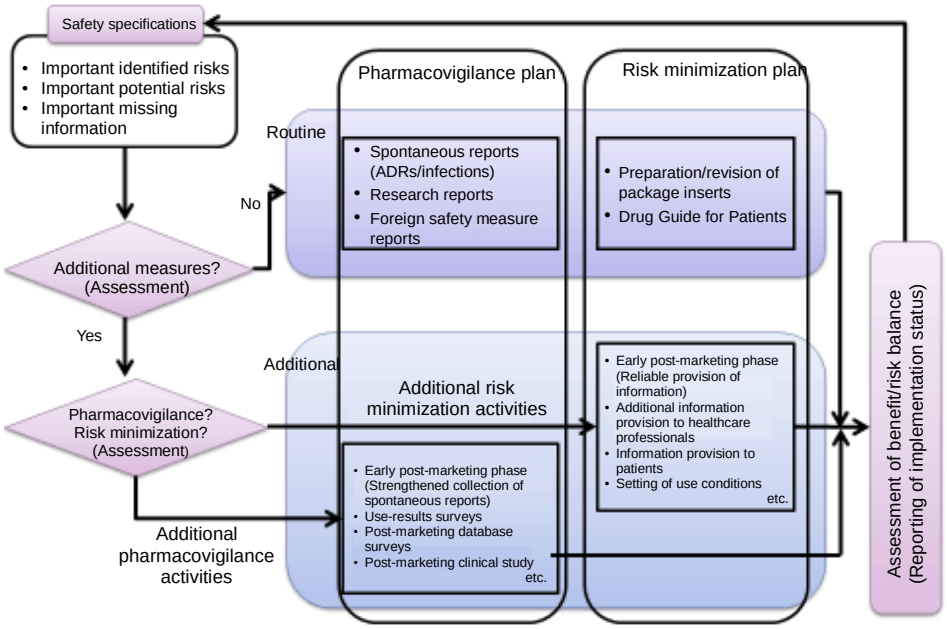
- PMDA launched a full-scale risk management system in FY 2011, and has been improving the system to consistently manage drug safety from the development phase to the post-marketing phase by having Risk Managers also work in Offices of New Drugs. As of March 2018, 14 Risk Managers were assigned to each team in Offices of New Drugs.

Risk Management Plan (RMP) is required to be developed for new products (those filed in or after April 2013), in order to evaluate benefits and risks throughout the lifecycle of medical products, from the development phase to the post-marketing phase and to implement necessary safety measures based on the evaluation. In October 2013, submitting an RMP together with submission dossier became a mandatory requirement for regulatory approval of products. PMDA's product safety and review offices cooperate to evaluate proposed RMPs for products under review by identifying safety and efficacy specifications and assessing the appropriateness of pharmacovigilance, investigations/studies for efficacy evaluation, and risk minimization activities. To ensure that these activities are appropriately conducted, PMDA directs inquiries regarding RMPs to applicants during the review process. While providing guidance and instructions through discussions with applicants, evaluation of RMPs is completed by the end of review process.

In FY 2018, new RMPs for 79 products and revised RMPs for 304 products (total) were posted on the PMDA website. In addition, RMPs for 5 products were deleted due to withdrawal of approval or completion of re-examination. The number of RMPs available on the PMDA website as of the end of FY 2018 is shown in the table entitled "Number of Information Documents Released on the PMDA's Website as of the End of FY 2018."

Furthermore, to promote the use of materials for additional risk minimization activities based on RMP, PMDA upgraded the system so that users can obtain these materials from the PMDA website.

Outline of Risk Management Plan



3.3.(ii).b. Use of electronic medical records etc.

- In accordance with the Third Mid-term Plan, PMDA plans to perform pharmacoepidemiological analysis using digitized medical information, such as a medical information database, and advance the analytical method, in order to utilize digitized information for risk-benefit assessment or safety measures for drugs. In FY 2018, PMDA took the following actions to achieve this goal.
- As a part of utilization of the Medical Information Database Network (MID-NET®) system for regulatory purposes, PMDA made investigations and requests for utilization of 33 surveys. In addition, PMDA conducted a survey on the status of prescription drugs by using the National

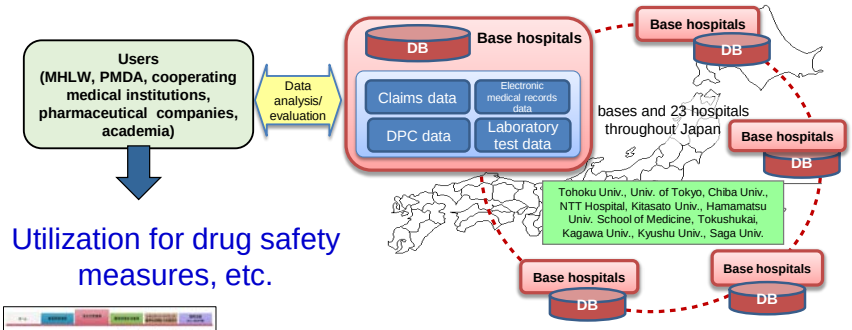
Claim Data. The survey served to investigate the feasibility of drug evaluation based on electronic medical records. Furthermore, pilot studies for utilization of MID-NET® were conducted in FY 2017 and a summary of the studies was published in a peer-reviewed, international journal (Pharmacoepidemiol Drug Saf. 2019;28:601) (submitted in November 2018; accepted in May 2019).

- PMDA's Offices of New Drugs and Offices of Pharmacovigilance worked together to promote the implementation of medical information database surveys in post-marketing pharmacovigilance plans. PMDA also conducted epidemiology consultations properly to advise MAHs on planning of post-marketing database surveys. Furthermore, PMDA issued a guidance document titled "How to Proceed with Discussions to Formulate Post-marketing Surveillance Plan" (January 2018) and published its English translation in September 2018.
- In April 2018, PMDA started full-scale operation of the MID-NET® system. Specifically, PMDA began to receive requests for utilization of the MID-NET® system (utilization by MHLW/PMDA, cooperating medical institutions, and other organizations that intend to conduct post-marketing database surveys and studies for drug safety evaluation in the scope of acceptable purposes of utilization) and started operation of the MID-NET® On-site Center for users. PMDA also strived to enrich information for MID-NET® users available on the PMDA website and offered training opportunities and other support to them (see the diagram below).
- Cases of utilization of the MID-NET® system approved after discussion at an expert committee meeting in FY 2018 include post-marketing surveillance of 2 products (IBRANCE Capsules and PRALIA Subcutaneous Injection 60 mg Syringe) as utilization for non-regulatory purposes and 2 other surveys.

* Information on approved utilization is available at: https://www.pmda.go.jp/safety/mid-net/0010.html

- Furthermore, PMDA continued operations including validation tests to control and improve the quality of stored data in the database, data standardization, and system control. Thus, PMDA steadily increased the data volume ready for utilization and realized smooth utilization to ensure the reliability of MID-NET®.

MID-NET®: a quality-controlled medical information database network



Utilization for drug safety measures, etc.

- Operation started on April 1, 2018
- Information essential for utilization, etc., is available from a dedicated webpage
  https://www.pmda.go.jp/safety/mid-net/0001.html

MID-NET On-site Center (within PMDA's Tokyo Office)

• Reception desk

On the reserved date, every user of the MID-NET On-site Center must visit the reception desk for identification. If no problem is found, then he or she can borrow an IC card required for entrance/exit control for a DB workroom/meeting room.

• DB workroom (equipped with monitoring cameras) • Meeting room for discussion

Each DB workroom has a dedicated computer terminal installed inside and an adjacent meeting room for discussion.

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3.3.(ii).c. Collection of data on medical devices (implantable ventricular-assist devices [IVADs])

- The Japanese Registry for Mechanically Assisted Circulatory Support (J-MACS) Project was operated starting in FY 2010 as a registry model project through collaboration among industries, government, and academia. The project intends to enhance a system for the collection of post-marketing product information by incorporating (in collaboration with relevant academic societies, companies, etc.) a patient registration system (registry) for confirming long-term safety. In April 2017, management of the J-MACS Project was transferred to the J-MACS Committee of the Japanese Association for Thoracic Surgery (JATS). As of June, 2018, 790 patients have been enrolled in the J-MACS at 53 medical institutions nationwide (disclosed on the JATS website).

3.3.(ii).d. Building the patient registration system (registry) for regenerative medical products

- The “Workshop on the Proper Composition of a Project for a Patient Registration System for Cellular and Tissue-based Products” held at MHLW developed a summary report, which stated that a “patient registration system” for registering information on patients using regenerative medical products should be built to enhance post-marketing safety measures for regenerative medical products. To this end, PMDA is building the patient registration system (registry) for verifying long-term safety in collaboration with relevant academic societies, companies, etc.
- In FY 2018, operation of patient registries for three approved regenerative medical products, was continued, using databases of academic societies or those developed by MAHs. To enhance understanding, the operation status of individual registries was presented at a workshop on the project for the patient registration system for regenerative medical products and meetings of product-specific working groups.
- Product-specific working groups were newly established for 2 products approved in FY 2018. One registry started its operation by using a database maintained by an academic society and the other a database developed by the MAHs of the product.

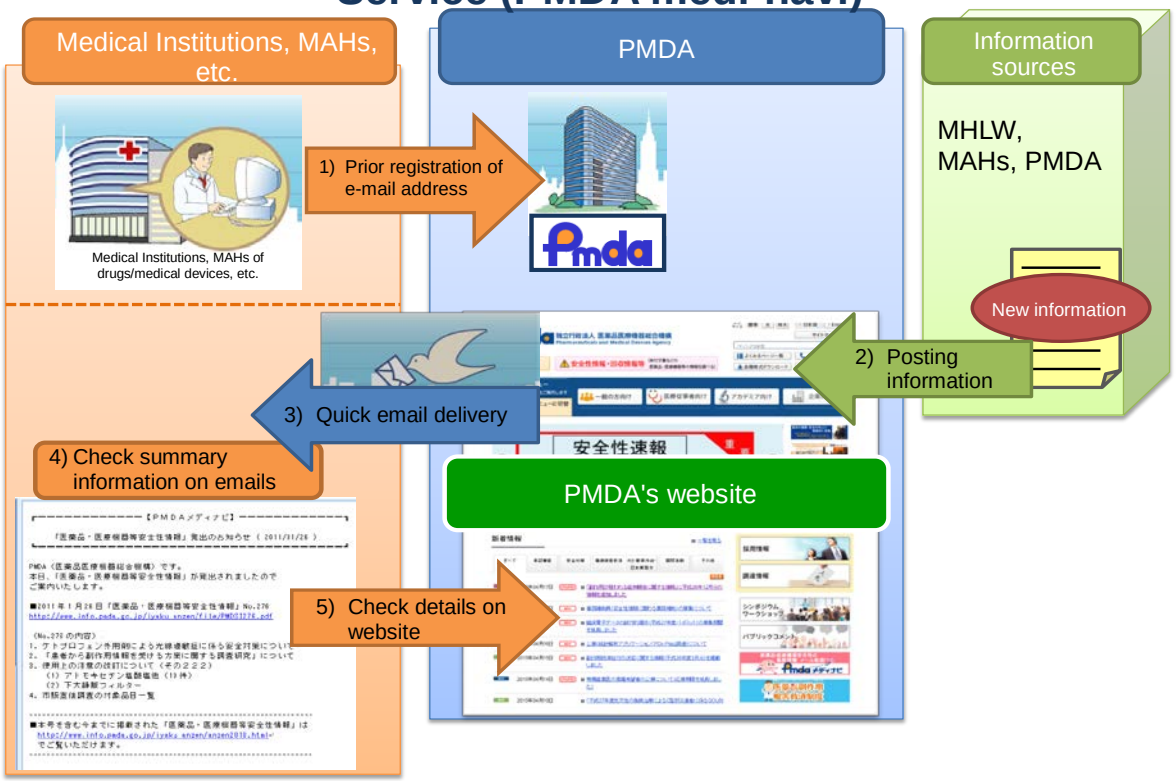
3.3.(iii) Establishment of a post-marketing safety system through information feedback

3.3.(iii).a. Provision of information via website content and e-mail distribution (use of the pharmaceuticals and medical devices information e-mail service [PMDA medi-navi])

- PMDA promptly posts important safety information including revisions to precautions in package inserts on the PMDA website on a daily basis, and distributes such information to healthcare professionals and relevant persons at companies by e-mail (PMDA medi-navi) upon issuance thereof. PMDA has also been taking steps to enhance the scale of its information provision activities by posting various safety information, including package inserts, on the PMDA website.
- The PMDA medi-navi service provides immediate notification of important safety information, such as “Yellow Letters” (Dear Healthcare Professional Letters of Emergent Safety Communications), “Blue Letters” (Dear Healthcare Professional Letters of Rapid Safety Communications), mandated revisions to precautions in product package inserts, and Class I recalls. Use of this information by healthcare professionals is both necessary and critical. In FY 2018, PMDA hosted symposiums and lectures to ensure better understanding of the information it provides. PMDA also carried out PR activities for the medi-navi service, including banner advertisements on its website and distribution of leaflets, in cooperation with the MHLW, related organizations, related academic societies, etc.
- Furthermore, PMDA started to distribute information concerning the approval of additional indications of generic prescription drugs via the PMDA medi-navi in February 2019.
- An article featuring an interview between the Executive Director of PMDA and the President of the Japan Medical Association (JMA) was published in the JMA Journal (February 2018 Issue). Since this article was intended for physicians at clinics, its reprints together with the PMDA medi-navi Registration Form were handed out to participants in a training workshop held by JMA in order to promote user registration for the PMDA medi-navi service.
- When the “Notice of a Class I Recall (drugs)” distributed via PMDA medi-navi is related to a blood product for transfusion mainly used at hospitals, a keyword “Blood Product for Transfusion” was indicated in the e-mail subject, etc., to highlight the difference from information related to other drug products used at both hospitals and pharmacies, etc., thereby enhancing users’ convenience.

- The “My Drug List for Safety Updates” is an additional service offered by the PMDA medi-navi. It allows users to register selected drugs, list package insert information, RMPs, and safety information issued for these drugs, and view related websites and PDF files linked to the list. In order to familiarize users with the service, a leaflet describing its functions was distributed at academic conferences.
- As a result of the efforts described above, the number of subscribers to the PMDA medi-navi service was 174,803 at the end of FY 2018, showing an increase of 9,982 compared with the figure at the end of FY 2017. The breakdown of subscribers is as follows:
  Approximately 51,300 hospitals or clinics (with an increase of approx. 2,600);
  Approximately 62,500 pharmacies (with an increase of approx. 3,500);
  Approximately 9,800 dental clinics or other medical facilities (with an increase of approx. 400);
  Approximately 23,300 MAHs or distributors (with an increase of approx. 1,400)
- As of the end of FY 2018, there were 15,661 subscribers to the “My Drug List for Safety Update,” which was an increase of 10% (1,403) from FY 2017.
- MAHs are required to post their product information (e.g., package inserts, Drug Guide for Patients) on the PMDA website via the exclusive webpages for MAHs, to ensure that product information is widely disseminated through the website. PMDA upgraded the safety information distribution system in response to implementation of the “Revision of Format and Content of Package Inserts of Prescription Drugs, etc.” On this occasion, the exclusive webpages for MAHs was changed to add a new webpage featuring system upgrade and consultation for revision of package inserts made in accordance with the above guidance document, so that MAHs could properly and efficiently update their product information on the PMDA website. PMDA also prepared and posted manuals and other documents for the new system.
- PDF files of the Drug Safety Update (DSU) created by using a new system launched by the Federation of Pharmaceutical Manufacturers’ Associations of Japan in June 2018 became available on the PMDA website. A click on the product name for each DSU enabled direct jumping to the corresponding notice of revision of precautions created by the MAH. The smartphone version of DSUs was also posted on the PMDA website for users’ convenience.
- In July 2018, the DSUs for individual OTC drugs (that have been uploaded on the PMDA website since FY 2017) were linked to the corresponding labeling information subjected to revision of precautions, to improve users’ convenience.

Pharmaceuticals and Medical Devices Information E-mail Service (PMDA medi-navi)



Breakdown of Content Distributed through the PMDA medi-navi during FY 2018*

Content of e-mails	Number of e-mails	Content of e-mails	Number of e-mails
Dear Healthcare Professional Letters of Rapid Safety Communications (Blue Letters)	0	Approval information (medical devices)	12
Product Recalls (Class I)	31	Approval information (prescription drugs)	28
Product Recalls (Class II)	329	Approval information (regenerative medical products)	2
Pharmaceuticals and Medical Devices Safety Information	10	Approval information (generic drugs)	2
Drug Safety Update (DSU)	10	Notifications on drugs Notifications on medical devices	43
DSU (OTC version)	0	Information on proper use of drugs	6
Revision of PRECAUTIONS (drugs)	14	Information on drug risk under evaluation	9
Revision of PRECAUTIONS (medical devices)	1	Information on products submitted for public knowledge-based applications, covered by national health insurance	3
Revision of PRECAUTIONS (quasi-drugs and cosmetics)	0	Notice of decision on payment/non-payment of adverse reaction relief benefits	12
Revision of PRECAUTIONS (regenerative medical products)	0	Risk Management Plan (RMP)	37
Notification on self-check (medical devices)	0	Information on generic drugs	4
PMDA Medical Safety Information	5	Others	29

** The number of e-mails distributed by medi-navi differs from the figures in the table because one distributed issue of medi-navi e-mail covers several items in its contents.*

Number of Information Documents Released on the PMDA's Website as of the End of FY 2018[*1]

		FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Package insert (labeling) information						
	Prescription drugs	14,912	14,843	14,639	14,812	14,789
	Medical devices [*2]	20,504	22,001	23,754	26,815	29,669
	Class I	-[*3]	-[*3]	-[*3]	10,290	12,233
	Class II	-[*3]	-[*3]	-[*3]	9,069	9,529
	Class III	-[*3]	-[*3]	-[*3]	4,524	4,953
	Class IV	-[*3]	-[*3]	-[*3]	2,931	2,954
	Regenerative medical products	2	3	4	4	5
	OTC drugs	11,127	11,360	11,385	11,425	11,444
	BTC drugs	20	15	16	16	15
	In vitro diagnostics	4,247	4,238	4,178	4,390	4,668
Drug Guide for Patients		2,701	3,213	3,366	3,873	4,139
Guidance for persons receiving vaccination		72	73	72	74	73
Safety information issued by MHLW						
	Directions for revision of package inserts (drugs)	272	284	297	309	325
	Notification of safety measures (drugs)	-[*3]	40	56	74	85
	Directions for revision of package inserts (medical devices)	50	53	54	55	56
	Notification of safety measures (medical devices)	-[*3]	83	88	95	99
	Notification concerning self-check	52	52	52	52	52
	Pharmaceuticals and Medical Devices Safety Information	178	188	198	208	218
	MHLW Press release	69	73[*4]	87[*4]	97[*4]	103[*4]
Dear Healthcare Professional Letters of Emergent Safety Communications (Yellow Letters)		30	24	24	24	24
Dear Healthcare Professional Letters of Rapid Safety Communications (Blue Letters)			15[*5]	15[*5]	15[*5]	15[*5]
Risk Management Plan (RMP)		117*[6]	180	270	333	407
Drug Safety Update (by Federation of Pharmaceutical Manufacturers' Associations of Japan [FPMAJ])		111	121	132	142	152
DSU (OTC version [JFSMI])		-	-	-	4	4
Information about case reports						
	Information about case reports on suspected ADR	338,224	387,162	440,485	498,809	561,122
	Information about case reports on suspected malfunction	98,407	116,182	133,159	149,696	166,427
	Information about case reports on suspected malfunction of regenerative medical products	-	35	91	191	340
	Information about case reports on suspected malfunction in the mechanical part of combination drugs	-	6	339	1,459	2,909
Notification related to medical safety measures		108	119	130	147	161
PMDA Medical Safety Information		45	48	50	53	57
Manuals for management of individual serious adverse drug reactions		75	75	75	75	77
Information on recalls[*8]						
	Drugs (including *in vitro* diagnostics)	1,817	375	351	375	405
	Quasi-drugs		49	42	42	44
	Cosmetics		229	242	242	254
	Medical devices		1,223	1,224	1,259[*7]	1,214
Pharmaceuticals and Medical Devices Information E-mail Service (PMDA medi-navi)						
	E-mails issued	234	223	557	556	574
	Subscribed	112,079	135,487	153,596	164,821	174,803

**1 Because of the change in the number of pages posted due to the renewal of the PMDA website in March 2015, some figures do not represent the additional posted pages as the difference between the total pages until FY 2014 and those posted during and after FY 2015.*

**2 Including one medical device labeling showing no term name. (The term name of a medical device is determined according to the medical device classification defined by the MHLW ministerial announcement No. 298 dated July 20, 2004.)*

**3 Not totaled.*

**4 The total number of "MHLW press release (drug-related)," "MHLW press release (medical devices)," and "MHLW press release (quasi-drugs and cosmetics)" pages posted.*

**5 The number of Yellow and Blue Letter pages posted. (This figure also includes documents released as the same position of the Letters of Rapid Safety Communications in and before September 2011.)*

**6 The total number of files posted, including the number of revised files.*

**7 The figure was modified due to one Class II recall in FY 2017 submitted on September 18, 2018.*

3.3.(iii).b. Provision of information on package inserts

- The number of package inserts available on the PMDA website as of the end of FY 2018 is shown in the table entitled “Number of Information Documents Released on the PMDA’s Website as of the End of FY 2018.”
- When a notification requiring revisions of package inserts for drugs is issued, PMDA releases the information on its website and distributes a PMDA medi-navi e-mail within 2 business days of issuance.
- Upon the issuance of MHLW notifications requiring the revision of package inserts of drugs, PMDA releases these notifications on its website and provides a link to the corresponding package inserts.
- Using a system developed in response to the Implementation of New Format and Content of the Package Inserts of Prescription Drugs, etc., PMDA implemented a test to confirm a series of actions from the notification to publication of package insert information in the XML format (pilot test 2) during the period from June 2018 to November 2018. In addition, based on the notification entitled “Change in Electronic Format of Package Insert Information in Response to Implementation of New Format and Content of Package Inserts of Prescription Drugs, etc.” (PSEHB/SD Notification No. 1122-6 dated November 22, 2018, issued by Director of the Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW), PMDA defined the use of a new electronic format (changed from SGML to XML) in the notification entitled “New Electronic Format (XML) for Package Insert Information in Response to Implementation of New Format and Content of Package Inserts of Prescription Drugs, etc.” (PMDA/OSI Notification No. 1122001 dated November 22, 2018, issued by the Director of Office of Safety I, Pharmaceutical and Medical Devices Agency) and issued it.
- To inform MAHs of procedures in the new system for changing the electronic format of package insert information from SGML to XML in response to the implementation of new format and content of package inserts, PMDA issued an administrative notice and posted it on the exclusive web page for MAHs of prescription drugs.
- Although only submission of instructions for use of Class IV medical devices is required under the PMD Act, notified instructions for the use of Class I, II, and III medical devices have also been made available on the PMDA website.

3.3.(iii).c. Public release of adverse drug reaction reports and device malfunction reports

1) Public release of adverse drug reaction reports
   - The following types of data obtained from adverse drug reaction reports submitted by MAHs in Japan were disclosed within approximately 4 months of receipt: fiscal year and quarter of the year reported, reporting category, type, job category of reporter, investigation status, gender, age group, primary disease, height, body weight, suspected drug name (nonproprietary name and brand name), reason for use, BTC/risk category, route of administration, single-dose, start date of administration, end date of administration, action against suspected drug, adverse drug reactions/adverse events, onset date, recurrence due to re-administration, evaluation, outcome, suspected concomitant drug name (nonproprietary name), and other concomitant drug names (nonproprietary name).
   - Reports received from medical institutions that are investigated by PMDA are also published. At the end of FY 2018, PMDA had posted a total of 561,122 reports submitted by medical institutions and MAHs by November 2018.

- Since April 2012, PMDA has also provided datasets pertaining to adverse drug reaction cases (contained in the Japanese Adverse Drug Event Report database [JADER]) which are released to the public after being exported into CSV format. These datasets become available for public investigation and research purposes approximately four months after their submission.
- The layout of line listing and the structure of JADER table were revised to meet ICH E2B (R3) standard, which was initiated in April 2016. The revised versions have been used and published since August 2016.

2) Public release of information concerning medical device malfunction reports

- The following types of data obtained from medical device malfunction reports submitted by MAHs in Japan have been disclosed within about 4 months from the time of reporting: fiscal year reported, gender, age, outcome, term name, condition of the medical device, and adverse events experienced by patient.

  In total, 166,427 reports (submitted by November 2018) were posted by the end of FY 2018.

3) Public release of information on malfunction reports of regenerative medical products and combination drugs

- PMDA has published (a) reports submitted by MAHs concerning malfunction of regenerative medical products occurring in Japan (since July 2015) and (b) reports on malfunction of the mechanical part of combination drugs submitted by MAHs (since October 2015). In total, 340 reports on regenerative medical products (submitted by November 2018) and 2,909 reports on combination drugs (submitted by November 2018) were published by the end of FY 2018.

3.3.(iii).d. Provision of the Request for Proper Use of Drugs and Medical Devices

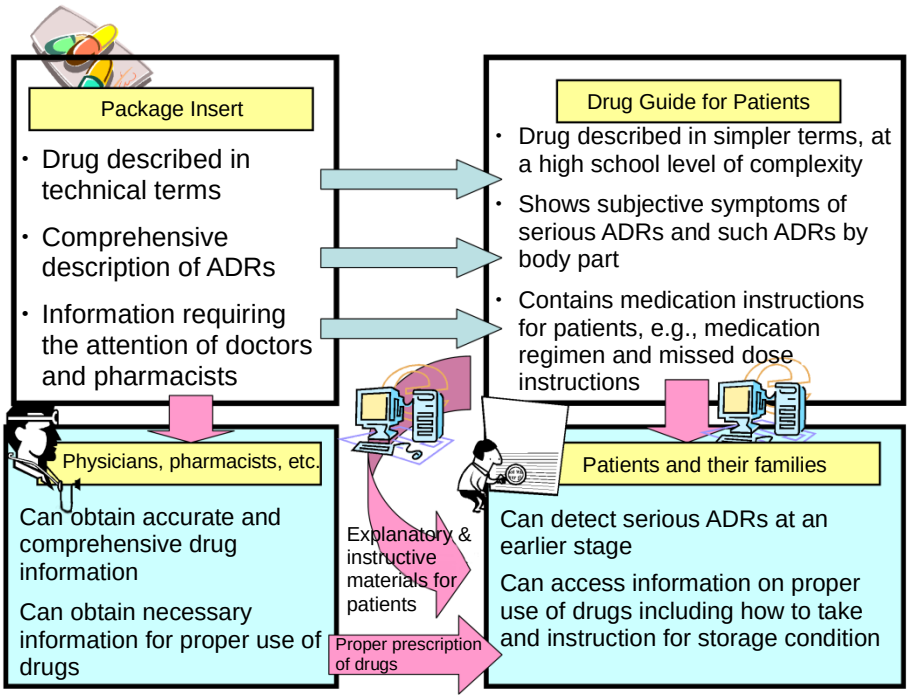
- If specific measures concerning the proper use (including dose and frequency as well as frequency of testing for monitoring adverse reactions) of a drug have already been recommended in its package insert or other materials prepared by the applicable MAH, but it is later determined that improper use persists or testing is being conducted improperly, the corresponding patients' claims for relief benefits for adverse reactions caused by such drugs may be rejected. To avoid such cases and ensure the proper use of drugs that have been associated with adverse drug reactions due to improper use despite repeated precautions having been issued, PMDA prepares "PMDA Request for Proper Use of Drugs" publications to provide the relevant information to healthcare professionals and related academic societies. The notice "PMDA Request for Proper Use of Drugs" has been available on the PMDA website since FY 2010.
- In some cases, the same malfunctions and infections due to medical devices occur repeatedly without reduction in the number of reports, despite the precautionary statements in the labeling of medical devices. To address such cases, PMDA prepares precautionary documents known as "PMDA Request for Proper Use of Medical Devices," to provide easy-to-understand information to healthcare professionals. In FY 2018, PMDA prepared a "PMDA Request for Proper Use of Medical Devices" for transcatheter aortic valve implantation (entitled "Adverse Events associated with the Use of Bioprosthetic for Transcatheter Aortic Valve Implantation") and released it on its website.

3.3.(iii).e. Provision of Safety Information to the Public (Patients)

1) Provision of Drug Guides for Patients

- To promote proper understanding of prescription drugs among patients and to facilitate earlier detection of serious adverse drug reactions, Drug Guides for Patients have been discussed and prepared according to “Guidelines for Developing the Drug Guide for Patients” (PFSB Notification No. 0630001 dated June 30, 2005, issued by the Director General of the Pharmaceutical and Food Safety Bureau, MHLW) and have been available on the PMDA website since January 2006. In FY 2018, 96 Drug Guides for Patients (including 3 for generic drugs) were prepared for products newly marketed or products for which the Precautions had been revised. The number of Drug Guides for Patients available on the PMDA website as of the end of FY 2018 is shown in the table entitled “Number of Information Documents Released on the PMDA’s Website as of the End of FY 2018.”
- PMDA prepared a draft revision of the adverse drug reaction terminology used for preparation and revision of Drug Guides for Patients so that the public can understand them better. The revised terminology document was posted on the PMDA website in September 2018.
- Based on package inserts prepared in accordance with the guidance on “Implementation of New Format and Content of Package Inserts of Prescription Drugs, etc.” (PSEHB Notification No. 0608-1, dated June 8, 2017, by the Director General of the Pharmaceutical Safety and Environmental Health Bureau, MHLW), PMDA prepared a guidance document (supplement) for preparation of Drug Guides for Patients by summarizing the points to consider when preparation of a Drug Guide for Patients is needed, and posted it on the exclusive web pages for MAHs.

Package Inserts for Prescription Drugs and Drug Guide for Patients



2) Provision of Guides for patients receiving vaccinations

- The “Guide for Patients Receiving Vaccinations” has been available on the PMDA website since June 2014, to promote proper understanding of vaccines among persons receiving vaccinations and their families and to enable detection of serious adverse reactions at an earlier stage. This was done after consideration and preparation of several documents, such as

"Guidelines for Developing the Guide for Persons Receiving Vaccinations" (PFSB Notification No. 0331-7 dated March 31, 2014, issued by the Director General of the Pharmaceutical and Food Safety Bureau, MHLW). In FY 2018, 11 Guides for Patients Receiving Vaccinations were prepared (including those not yet published because the relevant vaccines have not yet been marketed). The number of Guides for Patients Receiving Vaccinations available on the PMDA website as of the end of FY 2018 is shown in the table entitled "Number of Information Documents Released on the PMDA's Website as of the End of FY 2018."

3) Provision of manuals for management of individual serious adverse drug reactions

- The manuals for the management of individual serious adverse drug reactions prepared by MHLW in its initiative of comprehensive actions for serious adverse drug reactions have been made available on the PMDA website since November 2006.

  MHLW has been implementing a 5-year plan (since FY 2016) to revise and update these manuals based on the latest knowledge. In FY 2018, MHLW revised 9 manuals including the manual for acute kidney injury (acute tubular necrosis) and newly developed 2 manuals for erythema multiforme and hypokalemia. PMDA published these manuals on its website and notified their publication via PMDA medi-navi to the subscribers.

- The number of manuals available on the PMDA website as of the end of FY 2018 is shown in the table entitled "Number of Information Documents Released on the PMDA's Website as of the End of FY 2018."

4) Provision of other information to the public

- A symposium was planned to increase public knowledge and understanding of drug products, and PMDA organized a symposium program committee consisting of representatives of patient associations, the academic sector, healthcare professionals, and the regulatory sector. Based on the opinions of the committee members, the first interactive symposium for the public was held in October 2018, hosted by the Risk/Benefit Assessment of Drugs-Analysis and Response (RAD-AR) Council (also known as the "Council for Proper Drug Use") and co-hosted by PMDA. The contents of the symposium entitled "Useful Information about Medicines, Quick-working Knowledge Information" included a quiz session for proper use of drugs and presentation of common cases. After the completion of the symposium, the presentation slides and hand-out materials used on-site were posted on the PMDA website to make them available for individuals not participating in the symposium.

3.3.(iii).f. Provision of medical safety information

- PMDA extracts, evaluates, and examines near-incident cases associated with drugs, medical devices, and regenerative medical products from the "Project Report on Collection of Medical Incident Information," "Annual Report of the Project to Collect and Analyze Near-incident Cases from Pharmacies," etc. published by the Japan Council for Quality Health Care. In FY 2018, 2,817 cases associated with drugs and 536 cases associated with medical devices were evaluated and the results were reported to MHLW. These 3,353 cases were posted on the PMDA website as shown in the following table.

Cases	Drugs	Medical Devices
Total applicable cases: 3,353	2,817	536
1) Cases for which safety measures for the use of drugs, medical devices, or regenerative medical products taken by MAHs, etc. were considered necessary or possible.	0	0
2) Cases for which measures have already been taken, or are currently under consideration, by the MAHs, etc.	25	15
3) Cases for which the available information is insufficient for the MAHs to consider safety measures, or cases that were likely to have resulted from human errors or human factors.	2,792	521

- Since November 2007, PMDA has issued PMDA Medical Safety Information publications, which are prepared in reference to input provided by healthcare professionals such as physicians, pharmacists, nurses, and clinical engineers, in addition to non-medical specialists in fields such as ergonomics. These publications provide precautions through not only text, but also easy-to-understand charts to help healthcare professionals use medical products more safely. The information provided addresses events that were reported repeatedly or that led to issuance of revisions to package inserts, among near-incident cases, adverse drug reaction reports, and malfunction reports. In FY 2018, the following 4 issues were posted on the PMDA web page.

PMDA Medical Safety Information

No.	Posted on	Title
No.54	June 2018	Precautions When Using an Indwelling Bladder Catheters
No.55	August 2018	Introduction of Connectors to Prevent Misconnection (Neuraxial Anesthesia)
No.56	February 2019	Precautions When Using Compression Stockings
No.57	February 2019	Precautions When Using Subcutaneous Ports and Catheters

3.3.(iii).g. Release of information on drug risks under evaluation

- To further enhance safety measures for drugs, PMDA releases (1) risk information that PMDA monitors closely because it could lead to revisions to Precautions in package inserts and (2) risk information that has attracted attention from foreign regulatory authorities, academic societies, etc. and is under evaluation by MHLW/PMDA. To provide healthcare professionals with faster access to potentially vital safety information, these types of information have been posted on the PMDA website before the implementation of safety measures as appropriate since July 2011 as “risk information currently under evaluation.”

3.3.(iii).h. Information provision in English

- To disseminate information on safety measures to foreign countries, PMDA translated the following documents into English and published them on the PMDA website:
  Information on drug risks under evaluation for all drugs;
  Information on revision of Precautions of drugs;
  Summaries of investigation results;
  The PMDA Medical Safety Information;
  The PMDA Request for Proper Use of Drugs.

  PMDA also translated the Pharmaceuticals and Medical Devices Safety Information issued by MHLW into English, and posted it on its website.

PMDA also continued providing safety information, including revision of package insert information, to regulatory agencies in Asian countries, in addition to information provision under confidentiality agreements to foreign regulatory agencies. In 2018, India, Papua New Guinea, and Philippines were added to the list of countries participating in this information provision. Thus, the list included a total of 7 countries.

3.3.(iii).i. Responses to consultation requests from MAHs

- To contribute to improvement of post-marketing safety measures by MAHs, PMDA provided various consultations (on post-marketing safety measures for drugs, medical devices, regenerative medical products, and medical safety) requested by MAHs. These medical safety consultations were in particular related to revisions to package inserts, post-marketing risk management plans, consultation on creation of drug guides for patients, naming and labeling of drugs to prevent medical accidents, and improvements in products to prevent medical accidents based on analyses of near-incident cases.
- The number of provided consultations by category for FY 2018 is shown below:

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Drugs Consultations on post-marketing safety measures, etc.	869	991	795	818	629
Consultations on package insert revision in response to Implementation of New Format and Content[*1]	-	-	-	-	863
Medical devices[*2]	325	772	1,597	2,741	503
Medical safety	72	116	78	91	114
Regenerative medical products	0*[3]	4	3	1	11

**1 Consultations on package insert revision in response to the Implementation of New Format and Content of Package Inserts of Prescription Drugs, etc."*

**2 The figures for the period from FY 2014 to FY 2017 include the number of consultations on package insert revision in response to the New Format and Content Requirements.*

**3 Number of cases after enactment of the PMD Act on November 25, 2014*

- Consultations for medical safety conducted in FY 2018 were mainly in respect to names of new drugs, packaging/labeling, and near-incident cases for drugs, medical devices, and regenerative medical products. PMDA provided all consultations in an appropriate and prompt manner.

3.3.(iii).j. Provision of consultations on drugs/medical devices to general consumers and patients

- PMDA offers a telephone consultation service to support safe and secure use of drugs and household medical devices by both patients and general consumers.
- In FY 2018, the number of persons receiving consultations was 14,656 (15,990 calls) for drugs and 390 (420 calls) for medical devices.
- PMDA has identified and compiled a list of consultations related to generic drugs from a larger listing of drug product consultations, and provided this data to the Secretariat of the Generic Drug Quality Information Review Group (a review group consisting of experts established at the National Institute of Health Sciences [NIHS]).

Number of Parties Receiving Consultations on Drugs/Medical Devices

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Persons receiving consultations on drugs [persons/day]	11,556 [47.4]	12,551 [51.7]	13,448 [55.3]	11,327 [46.4]	14,656 [60.1]
(of which consultations on generic drugs)	(543)	(600)	(495)	(346)	(406)
Persons receiving consultations on medical devices [persons/day]	370 [1.5]	406 [1.7]	415 [1.7]	401 [1.6]	390 [1.6]

3.3.(iii).k. Status of accessibility, communication, and use of transmitted safety information within medical institutions

- To promote the proper use of drugs and medical devices, safety information, such as safety measures to be taken, should be appropriately communicated to and used by healthcare professionals in clinical settings. Accordingly, since FY 2010, PMDA has been conducting a survey to ascertain the status of accessibility, communication, and use of safety information in medical institutions and pharmacies, and to discuss measures for promotion of utilization of safety information in clinical settings. The survey results to date are available on the PMDA website.
- PMDA conducted surveys of the status of accessibility, communication, and use of safety information for drugs in 844 hospitals (10% of hospitals nationwide) and 2,934 pharmacies (5% of health insurance pharmacies nationwide) in FY 2017. The survey results were compiled and released on the PMDA website in September 2018. PMDA also provided feedback of the survey results in collaboration with professional organizations such as the Japanese Society of Hospital Pharmacists and the Japan Pharmaceutical Association by giving presentations at academic conferences and various workshops as well as by publishing articles in official journals of these organizations. This contributed to promotion of utilization of safety information in clinical settings.
- In addition, PMDA distributed materials prepared to improve understanding of RMP at academic conferences, etc., and informed healthcare professionals of RMP by posting the materials on the PMDA website and distributing them via the PMDA medi-navi to promote utilization of safety information in clinical settings.

➢ ***Outline of surveys conducted to date***

<table>
<tr><th>FY</th><th>Title</th><th>Target</th><th>Period</th><th>Remarks</th></tr>
<tr><td>2010</td><td>Survey of the status of communication and use of drug safety information</td><td>Hospitals nationwide (8,679 institutions)</td><td>January 13, 2011 to February 10, 2011</td><td>Questionnaire survey (response rate: 41.2%)</td></tr>
<tr><td>2011</td><td>Survey of the status of communication and use of drug safety information</td><td>Hospitals nationwide (8,640 institutions)</td><td>January 20, 2012 to February 10, 2012</td><td>Questionnaire survey (response rate: 25.9%)</td></tr>
<tr><td rowspan="2">2012</td><td rowspan="2">Survey of the status of accessibility, communication, and use of drug safety information</td><td>Hospitals nationwide (8,541 institutions)</td><td>January 7, 2013 to February 28, 2013</td><td>Questionnaire survey (response rate: 53.4%)</td></tr>
<tr><td>Half of all pharmacies nationwide (26,915 institutions)</td><td>January 7, 2013 to February 28, 2013</td><td>Questionnaire survey (response rate: 64.6%)</td></tr>
<tr><td rowspan="2">2013</td><td>Survey of the status of accessibility, communication, and use of good practices on drug safety information</td><td>14 hospitals and clinics/pharmacies near the hospitals in Japan</td><td>October 2013 to February 2014</td><td>Door-to-door survey</td></tr>
<tr><td>Basic survey on the status of accessibility, communication, and use of medical device safety information</td><td>9 hospitals/clinics in Japan</td><td>October 2013 to February 2014</td><td>Door-to-door survey</td></tr>
<tr><td rowspan="4">2014</td><td rowspan="2">Survey of the status of accessibility, communication, and use of drug safety information</td><td>Hospitals nationwide (8,481 institutions)</td><td>December 15, 2014 to March 13, 2015</td><td>Questionnaire survey (response rate: 57.8%)</td></tr>
<tr><td colspan="3">Summary of survey results (excerpt)
1. Obtaining appropriate information based on the characteristics of the information media
2. Use of appropriate information when drugs are selected
3. Secure and effective communication of safety information
4. Promotion of utilization of risk communication tools in clinical settings
5. Promotion of collaboration between hospitals and pharmacies</td></tr>
<tr><td rowspan="2">Survey of the status of accessibility, communication, and use of medical device safety information</td><td>500 general hospitals (sampled randomly)</td><td>February 9, 2015 to March 13, 2015</td><td>Questionnaire survey (response rate: 40.0%)</td></tr>
<tr><td colspan="3">Summary of survey results (excerpt)
1. Improving the information management system and use of information according to the circumstances of institutions
(1) Reliable access to information
(2) Communication of accurate information
(3) Addressing information management at an organizational level
(4) Utilization of electronic information including the PMDA website and the PMDA medi-navi
2. Issues related to information provision by companies and governmental organizations</td></tr>
</table>

<table>
<tr><th>FY</th><th>Title</th><th>Target</th><th>Period</th><th>Remarks</th></tr>
<tr><td rowspan="5">2015</td><td rowspan="5">Survey of the status of accessibility, communication, and use of drug safety information</td><td>10% of general clinics
*limited to institutions providing healthcare services as stipulated by health insurance
(8,737 institutions)</td><td>October 6, 2015 to December 14, 2015</td><td>Questionnaire survey
(response rate: 53.1%)</td></tr>
<tr><td colspan="3">Summary of survey results (excerpt)
1. Use of the PMDA website and the PMDA medi-navi
2. Obtaining important information promptly and comprehensively
3. Obtaining information based on characteristics of the distribution media
4. Sharing patient information between clinics and pharmacies</td></tr>
<tr><td>10% of health insurance pharmacies
(5,664 institutions)</td><td>October 6, 2015 to December 14, 2015</td><td>Questionnaire survey
(response rate: 68.2%)</td></tr>
<tr><td colspan="3">Summary of survey results (excerpt)
1. Utilization of electronic information including the PMDA website and the PMDA medi-navi
2. Obtaining and controlling important information promptly and comprehensively
3. Obtaining appropriate information in a timely fashion based on the characteristics of the information media
4. Sharing patient information between medical institutions and pharmacies</td></tr>
<tr><td rowspan="5">2017</td><td rowspan="5">Survey of the status of accessibility, communication, and use of drug safety information</td><td>10% of hospitals nationwide
(844 hospitals)</td><td>January 9, 2018 to February 16, 2018</td><td>Questionnaire survey
(response rate: 44.2%)</td></tr>
<tr><td colspan="3">Desired future directions (excerpts)
1. Standardization of subjects and tools of communication
2. Proactive utilization of risk communication tools, particularly RMP and materials for additional risk minimization activities
3. Utilization of PMDA medi-navi and its “My Drug List for Safety Updates” function</td></tr>
<tr><td>5% of health insurance pharmacies
(2,934 pharmacies)</td><td>January 9, 2018 to February 16, 2018</td><td>Questionnaire survey
(response rate: 56.3%)</td></tr>
<tr><td colspan="3">Desired future directions (excerpts)
1. Standardization of subjects and tools of communication
2. Understanding of characteristics of the information media, particularly speed
3. Proactive utilization of risk communication tools for drugs, particularly RMP and materials for additional risk minimization activities
4. Utilization of PMDA medi-navi and its “My Drug List for Safety Updates” function</td></tr>
</table>

** See PMDA website for details.*

- PMDA’s activities to communicate how to use safety information effectively in medical institutions, etc., took place mainly at the following academic conferences and workshops:

  Academic conferences and workshops, etc.
  - Kinki Academic meeting of Japanese Society of Hospital Pharmacists
  - Japan Pharmaceutical Association: Workshops

  Publication of articles
  - Journal of Japanese Society of Hospital Pharmacists (February 2019 issue)
  - Journal of the Japan Pharmaceutical Association (March 2019 issue)

3.3.(iii).l. Workshops related to post-marketing safety measures

- PMDA gave presentations on its approaches to improving and strengthening safety measures, revisions to precautions in package inserts, the effective use of the PMDA's web page, and PMDA's consultation services, at various workshops and academic conferences.

3.4. Promotion of Regulatory Science, Internationalization, etc.

3.4.(1) Promotion of regulatory science

3.4.(1).(i) Promotion of the PMDA "Rational Medicine" Initiative

- PMDA continued to promote the concept of its "Rational Medicine" Initiative across the world to promote regulatory science aimed to evaluate drugs, medical devices, and regenerative medical products with the focus on realizing a more rational basis for the provision of medical care with patient's needs and well-being firmly rooted at its core.

3.4.(1).(ii) Establishment of the Regulatory Science Center

- Through its various activities, PMDA has been making efforts to promote regulatory science which contributes to scientific evaluation and decision on the quality, efficacy, and safety of drugs, medical devices, and regenerative medical products. PMDA established the Regulatory Science Center (RSC) on April 1, 2018, so as to manage its regulatory science-related activities in an integrated and systematic manner. PMDA intends to utilize the RSC to ensure the reinforcement and improved efficiency of responses to scientific issues related to operations of PMDA, improved quality of operations for review and safety measures, and active discussion with individual stakeholders by transmission of regulatory science-related information, and thereby to further promote RS.

  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 product review and safety offices, in improving reviews and related services and safety measures.

- On August 1, 2018, PMDA held the PMDA Regulatory Science Center Opening Symposium to introduce the objectives, approaches, and future perspectives of the RSC. In the symposium, several experts delivered speeches, including a keynote speech, on expectations, etc., for the RSC and achievements of the third-term Science Board were presented.

3.4.(1).(iii) Use of the Science Board

- PMDA's Science Board was formed in May 2012 as an independent advisory body to PMDAs tasked with the deliberation of the scientific aspects of drug, medical device, and regenerative medical product reviews to promote appropriate evaluation of products that utilize advanced technologies. The Science Board also works to advance regulatory science and reinforce collaboration and communication with academia and medical professionals to facilitate future innovation in healthcare. Materials relating to individual products may be used for discussion; therefore, meetings are closed to the public. Board members are external experts in such areas as medicine, dentistry, pharmacy, and engineering.

- In the fourth-term Science Board meetings starting in April 2018, issues (themes) to be discussed were determined at the Science Board (parent committee) and then the 2 subcommittees described below were set up for the respective themes. As of March 31, 2019, the parent committee had 5 meetings (including 2 document-based discussions) and individual subcommittees went into more specific discussions:

  (1) Clinical evaluation of antimicrobial agents for treatment of infection with drug-resistant bacteria: Anti-microbial Resistance (AMR) Subcommittee (held twice)

  (2) Points to consider for risk assessment for therapeutic products using genome editing technology: Genome Editing Subcommittee (held 3 times)

- Three reports prepared as the outcome documents of the third-term Science Board meetings (April 2016 to March 2018) were used for not only operations in PMDA but also information provision in and outside Japan. Details are described as follows:

  (1) Subcommittee on Rare Cancers:
  Current state of therapeutic development for rare cancers in Japan, and proposals for improvement

  [1] The English summary of this report, entitled “Current state of therapeutic development for rare cancers in Japan, and proposals for improvement,” was accepted by Cancer Science in FY 2018 (March 2018) and published in this journal in May 2018.

  [2] Considering the status of acceptance/publication of the English summary of this report in Cancer Science, its original Japanese version was posted on the PMDA website (Japanese website) in April 2018.

  (2) Subcommittee on Pharmaceuticals Development:
  Issues in and Proposals for Facilitating Drug Discovery by Collaboration between Academia and Industry 2017 – In the Trend of Rapidly Advancing Science –

  - An English translation of this report, “Issues in and Proposals for Facilitating Drug Discovery by Collaboration between Academia and Industry 2017 – In the Trend of Rapidly Advancing Science –,” was posted on the PMDA website (English website) in July 2018.

  (3) Subcommittee on AI (Artificial Intelligence):
  Regulatory Science on AI-based Medical Devices and Systems

  [1] The English summary of this report, entitled “Regulatory Science on AI-based Medical Devices and Systems” and submitted to Advanced Biomedical Engineering, was accepted in April 2018 and published in this journal in May 2018.

  [2] Considering the status of acceptance/publication of the English summary of this report in Advanced Biomedical Engineering, its original Japanese version was posted on the PMDA website (Japanese website) in May 2018.

  [3] At the RAPS (Regulatory Affairs Professionals Society) Regulatory Convergence held at Vancouver (Canada) in October 2018, PMDA discussed with representatives of industry, government, and academia and provided information on the contents of this report.

- At the PMDA Regulatory Science Center Opening Symposium held on August 1, 2018, PMDA introduced the summary of the third-term Science Board meetings as well as the results of individual subcommittees’ meetings. PMDA also prepared and distributed a booklet entitled “The Third-term Science Board Activity Report” containing 3 reports each summarizing discussion at the three subcommittees to provide information concerning the activities of the Science Board as well as the results of discussion.
- PMDA disclosed materials and minutes of the Science Board meetings and subcommittees meetings (excluding confidential information) on the PMDA website.
- At the International Coalition of Medicines Regulatory Authorities (ICMRA) meeting, PMDA discussed on analytical methods of horizon scanning (an regulatory science-based approach that involves both systematic investigations on what kind of innovative technologies are emerging and assessment of their impacts on regulatory action to help construction of appropriate regulatory framework for such innovative technologies). Furthermore, to investigate the potential of horizon scanning methodologies in the field of pharmaceutical regulatory affairs in Japan, PMDA collected information on horizon scanning methodologies employed by foreign regulatory authorities in the

course of activities for the ICMRA while exploring approaches to horizon scanning in the field other than pharmaceutical regulatory affairs in Japan.

3.4.(1).(iv) Enhancement of regulatory science research

- Concerning analysis of clinical data, etc., across products, technical issues in integration of safety data on multiple products indicated for an identical disease were extracted and investigations of countermeasures were started.
- PMDA compiled measures to promote efficient drug development utilizing real-world data and coordinated opinions with industry to realize product-specific consultations on utilization of registry data. As a result, PMDA set up new consultation categories, one for consultations on appropriateness of registry use and the other for consultations on the integrity of the registry (registries) to be used. Consultations for these categories will be started in FY 2019.
- To ensure the proper execution of product reviews, safety measures, and relief services for adverse health effects, and to enhance the quality of these activities, PMDA is striving to promote regulatory science research on topics including the development of standards, guidelines, and guidance and how to conduct scientific prediction, evaluation, and judgment. Some regulatory science research activities conducted by PMDA are designated as within the scope of PMDA's official operations. This designation is dependent on the research purpose, how the research is related to PMDA's operations, and on comments from the Regulatory Science Research Evaluation Committee. In FY 2018, 6 projects (4 new projects and 2 ongoing projects) were selected as designated research projects, and the results of 8 projects were published in academic journals or conference sessions (2 published in papers, 6 sessions) (reposted).
- For innovative products, see Section 3.2.(2).(i).
- PMDA conducted regulatory science research in collaboration with external organizations such as academic institutions. (33 projects used public research funds, such as AMED and Health and Labour Government-Promoted Research Project Expenditure.) In addition, 1 joint study was conducted in conjunction with the National Institute of Health Sciences.
- In order to conduct the designated research appropriately, PMDA held meetings of the Regulatory Science Research Selection Committee and Regulatory Science Research Evaluation Committee, to select new designated research projects for FY 2019 based on the relevant rules. PMDA also held a meeting where the final report on designated research was presented.
- PMDA conducted expedited review of research projects subject to ethics review (2 projects) based on the Rules for Handling Ethics Reviews at the Pharmaceuticals and Medical Devices Agency.
- In response to the full-scale operation of the MID-NET® system starting in FY 2018, an expert committee consisting of external expert members was established to ensure the appropriate utilization of MID-NET®. This committee held 4 meetings for review of utilization projects.
- PMDA held an exhibition on regulatory science research in FY 2018, as in the previous fiscal years. A total of 42 posters and papers, etc., were exhibited, leading to discussion between the presenter and visitors. Starting in FY 2018, PMDA announced in advance the schedule for the exhibition on the PMDA website. As a result, the exhibition had many visitors from external organizations, etc.
- Concerning medical research in humans implemented by PMDA executives and employees, PMDA executives and employees participating in such research underwent research ethics education.

- PMDA may count engagement in designated research projects (in and after FY 2015) in the personnel evaluation.
- The Pediatric Drugs WG, ICH Q12 WG, Global Clinical Trial WG, and Innovative Manufacturing Technology WG for Projects Across Multi-Offices supported activities of ICH Expert Working groups to develop draft ICH E11A, ICH S11, ICH Q12, ICH E17, and ICH Q13 guidelines, respectively.
- PMDA made presentations at academic conferences regarding discussions held in the Projects Across Multi-Offices and performed PR activities (Companion Diagnostics WG [7 academic conferences/lectures], Omics WG [1 lecture], Pediatric Drugs WG [5 academic conferences/lectures and 3 papers, etc.], Orphan Drugs WG [2 briefing sessions and 1 lecture], ICH Q12 WG [5 academic conferences/lectures], Global Clinical Trial WG [5 academic conferences/lectures], Clinical Innovation Network (CIN) WG [3 academic conferences/lectures], Innovative Manufacturing Technology WG (16 academic conferences/lectures and 1 paper], and Cardiovascular Risk Evaluation WG and Induced Pluripotent Stem Cells (iPSC) WG [2 academic conferences/lectures and 1 paper]).
- Individual WGs for the Projects Across Multi-Offices exchanged opinions about evaluation policy and other issues with foreign regulatory authorities, drug development companies, related industry associations, academic societies, etc. (Pediatric Drugs WG, Orphan Drugs WG, ICH Q12 WG, Nanomedicine Initiative WG, Global Clinical Trial WG, Cardiovascular Risk Evaluation WG, and Innovative Manufacturing Technology WG).
- WGs for the Projects Across Multi-Offices participated in related AMED research projects, thereby contributing to opinion exchange among the industry, academia, and government through cooperation (Pediatric Drugs WG, ICH Q12 WG, Cardiovascular Risk Evaluation WG, CIN WG, Innovative Manufacturing Technology WG, and iPS Cells WG).

3.4.(1).(v) Enhancement of staff training

3.4.(1).(v).a. Lectures and guidance given by experts and on-site training

See Section 2.4.(2) Systematic implementation of staff training.

3.4.(1).(v).b. Overseas dispatch

- PMDA dispatches employees for fixed terms to provide them with opportunities to learn about review and safety-related activities of overseas regulatory authorities (1 employee).
- Based on the National Action Plan on Antimicrobial Resistance (AMR) (April 5, 2016), PMDA cooperated in the MHLW's efforts for the early introduction of AMR therapeutic drugs/diagnostics. Also, in response to the discussion of measures against drug-resistant bacterial infections at the G7 Ise-Shima Summit (May 2016) and other conferences, PMDA made a presentation on efforts of tripartite regulatory collaboration with representatives from the U.S. Food and Drug Administration (US FDA) and the European Medicines Agency (EMA) at the Conference of Drug Development to Meet the Challenge of Antimicrobial Resistance (an academic conference on AMR) in September 2018.

  PMDA held a face-to-face meeting with US FDA and EMA in March 2019. At the meeting, the regulatory agencies shared the latest information regarding application data for product reviews, and agreed to further cooperate with each other to discuss relevant issues.

3.4.(1).(vi) Promotion of interaction with outside researchers and collaboration on investigative research

3.4.(1).(vi).a. Promotion of collaboration and cooperative relationships through comprehensive partnership agreements, etc.

- Since FY 2015, PMDA has reinforced the existing collaborative graduate school program by concluding comprehensive partnership agreement with graduate schools, to reinforce collaboration with academia. PMDA advanced discussions with academia to promote cooperation and collaboration across a broad range of fields with medical and research institutions within a partnership framework, including the National Centers for Advanced and Specialized Medical Care. PMDA concluded comprehensive partnership agreements with the National Cancer Center Japan, Hiroshima University, Keio University, and University of Tsukuba in FY 2015, with the National Center of Neurology and Psychiatry, Tohoku University, and the National Center for Global Health and Medicine in FY 2016, and with the National Cerebral and Cardiovascular Center and the National Center for Child Health and Development in FY 2017. As of the end of March 2019, PMDA has concluded comprehensive partnership agreements with a total of 9 institutions. Under the comprehensive partnership agreements, PMDA conducted human resource exchanges, lectures, study meetings, joint research, etc. as described below, and contributed to human resources development for regulatory science.
- In FY 2018, 9 employees of the National Cancer Center Japan (NCC) worked at PMDA, and 1 PMDA staff member at the NCC as part of personnel exchange program. PMDA officers/employees provided 2 lectures at the NCC. A total of 27 PMDA staff members participated in 5 exclusive training programs (limited to PMDA employees) offered by the NCC (1 study tour program to visit the institutional review board (IRB), 1 study tour program to visit the ethics committee, 2 study tour programs to visit the NEXT Medical Device Innovation Center, and 1 on-site study tour program to visit NCC's pharmacists engaged in outpatient cancer chemotherapy). PMDA invited 3 lecturers from the NCC to speak at the PMDA Asia Training Center (ATC) Multi-Regional Clinical Trial (MRCT) Seminar and a seminar for local regulatory authorities held in Thailand and Myanmar. PMDA also visited the NCC with the Malaysian regulatory agency's officials visiting PMDA. PMDA established a liaison office for the NCC research project, and conducted information sharing and opinion exchanges between staff members from NCC and PMDA. PMDA staff members participated, as research collaborators, in the following NCC-initiated research projects: "Practical Application of Innovative Cancer Medicines: Research on Proper Use of Novel Anticancer Agents based on PK/PD/PGx and Safety Assurance;" "AMED Research on Regulatory Science of Pharmaceuticals and Medical Devices: Investigation on Usefulness of Patient-derived Xenograft Models in Drug Development and Related Issues;" "AMED Research on Regulatory Science of Pharmaceuticals and Medical Devices: Approach towards Standardization of Mass Spectrometric Imaging Technology in Drug Development;" and "AMED Research on Regulatory Science of Pharmaceuticals and Medical Devices: Pharmacodynamics and Exploration of Factors Influencing Efficacy, Estimation of Target Drug Levels, and Exploration of Biomarkers by Pharmacometric Analysis Utilizing Modeling & Simulation Approaches."
- One person from Hiroshima University worked at PMDA as part of personnel exchange program. PMDA staff provided one lecture at the university.
- One person from Keio University worked at PMDA as part of personnel exchange program. PMDA officers/employees provided 7 lectures at the university. A total of 11 PMDA staff members participated in the 5 training programs offered by the university. PMDA invited 2 lecturers from the university to speak at events hosted by PMDA ATC (a pharmacovigilance seminar at PMDA and a visit to PMDA by officials of the Malaysian regulatory agency).

- One person from University of Tsukuba worked at PMDA as part of personnel exchange program. PMDA officers/employees provided 7 lectures at the university.
- Two persons from the National Center of Neurology and Psychiatry (NCNP) worked at PMDA and 1 PMDA staff member at the NCNP, as part of personnel exchange program. Four PMDA staff members participated in 2 exclusive training programs (limited to PMDA employees) offered by the NCNP (a study tour program to visit the IRB and a study tour program to visit the ethics committee). NCNP and PMDA co-sponsored a workshop hosted by the Muscular Dystrophy Clinical Trial Network.
- Three people from Tohoku University worked at PMDA and 1 PMDA staff member at the university, as part of personnel exchange program. A PMDA officer/employee provided 3 lectures at the university.
- Three individuals from the National Center for Global Health and Medicine (NCGM) worked at PMDA as part of personnel exchange program. A PMDA staff member lectured at the NCGM. Ten PMDA staff members participated in 5 exclusive training programs (limited to PMDA employees) offered by NCGM (a study tour program on clinical study management operations, a study tour program to visit the IRB, etc.). A number of programs provided by PMDA-ATC served as part of mutual collaboration in international programs between the two organizations (invitation of lecturers from NCGM to speak at an MRCT seminar, participation of foreign officials, who were participating in an NCGM's project on the promotion of globalization of medical technologies, etc., in a medical device seminar at PMDA, a visit to NCGM by officials from the Malaysian regulatory agency visiting PMDA). PMDA participated in the NCGM International Infectious Diseases Forum as a collaborating organization.
- One person from the National Cerebral and Cardiovascular Center (NCVC) worked at PMDA as part of personnel exchange program. PMDA staff provided 1 lecture at NCVC. Four PMDA staff members participated in an exclusive training program (limited to PMDA employees) offered by NCGM.
- One person from the National Center for Child Health and Development (NCCHD) worked at PMDA as part of personnel exchange program. PMDA staff provided 1 lecture at NCCHD. PMDA invited a lecturer from NCCHD to speak at a PMDA-ATC seminar (co-hosted with US FDA).
- PMDA collaborates with the NCC, NCNP, and NCGM individually, in the AMED research project, through the research group for establishment of disease registration system (patient registry).
- PMDA has the collaborative graduate school partnership agreements with several graduate schools. PMDA staff members (24 delegated PMDA officers/employees) gave 26 lectures at the graduate schools.

3.4.(2) Actions taken for internationalization

- Based on the "PMDA International Strategic Plan 2015" and the "International Pharmaceutical Regulatory Harmonization Strategy" of MHLW (both released in June 2015), PMDA conducted the following activities:

3.4.(2).(i) Strengthening of cooperation with the U.S., EU, Asian countries, and related international organizations

PMDA Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs

- The Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC) was established to provide officers in foreign regulatory agencies with training on a

continuous basis not only in Japan but outside Japan. In FY 2018, PMDA planned and implemented the seminars listed in the table below at PMDA-ATC (a total of 10 seminars with a total of 267 attendees from 31 countries/regions). All the seminars were highly evaluated by participants. Individual seminars were designed specifically (e.g., lectures, case studies, group works, and mock inspections) to achieve their own purposes. PMDA utilized the resources of the ATC Training Institute, established under its Hokuriku Branch Office (located in the Toyama prefectural government's office), to arrange a study tour to visit plants and other activities as part of a seminar featuring review and safety measures for drug products and another seminar featuring quality control of traditional herbal medicines.

Based on the achievements of seminars conducted at the PMDA-ATC, PMDA was certified as an "APEC Life Sciences Innovation Forum (LSIF) Regulatory Harmonization Steering Committee (RHSC) Training Center of Excellence (CoE) for Regulatory Science" in the areas of multi-regional clinical trials/GCP inspections and pharmacovigilance. In FY 2017, PMDA held seminars on multi-regional clinical trials of drugs and pharmacovigilance, as workshops of the APEC LSIF RHSC CoE. The Joint Statement of ASEAN-Japan Health Ministers Meeting announces that the PMDA-ATC would be utilized to improve and harmonize the national regulatory system of pharmaceutical products and medical devices in ASEAN member states. This has been highly appreciated internationally (July 2017).

	Seminar content/area	Date	Venue	No. of participants (No. of countries/ regions)
1	Pediatric Review	June 11-14, 2018	Tokyo (PMDA), Japan	24 (12)
2	Pharmaceuticals Review, Safety Measures, etc.	June 18-22, 2018	Tokyo (PMDA) and Toyama, Japan	30 (16)
3	Good Registration Management (GRM)	September 26-28, 2018	Taipei	29 (11)
4	Pharmaceuticals Review, Safety Measures, etc.	October 15-16, 2018	Naypyidaw (Myanmar)	32 (1)
5	Quality Control (Chinese Medicines)	October 22-24, 2018	Toyama, Japan	15 (14)
6	Medical Devices Review, Safety Measures, etc.	November 12-16, 2018	Tokyo (PMDA), Japan	25 (17)
7	Good Manufacturing Practice (GMP)	November 26-30, 2018	Tochigi, Japan	14 (14)
8	Multi-Regional Clinical Trial (MRCT)*	January 21-24, 2019	Tokyo (PMDA), Japan	21 (13)
9	Pharmaceuticals Review, Safety Measures, etc.	January 28-31, 2019	Jakarta, Indonesia	48 (1)
10	Pharmacovigilance*	February 4-7, 2019	Tokyo (PMDA), Japan	29 (15)

** Workshops of APEC LSIF RHSC Training Centers of Excellence (CoE).*

Information exchanges with regulatory authorities in Europe and the United States, etc.

- PMDA continuously exchanged information regarding consultations held with companies on clinical studies and regarding review and safety measures with the US FDA, EMA, and other organizations, based on the Confidentiality Agreement (CA). PMDA made use of such information to ensure that review and safety measures were correctly implemented based on the latest scientific knowledge available to PMDA.
- PMDA engaged in cluster activities to regularly exchange information with European countries and the US. PMDA was actively involved in cluster activities regarding pediatrics, biosimilars,

regenerative medical products, and pharmacovigilance, and exchanged opinions in a closer manner. In the pediatrics cluster, PMDA hosted, jointly with the US FDA, the PMDA-ATC & U.S. FDA Pediatric Review Seminar 2018 featuring the promotion of development of pediatric drugs (June 2018).

- Based on the Antimicrobial Resistance (AMR) Action Plan (April 5, 2016), PMDA cooperated in the MHLW's efforts for the early introduction of AMR therapeutic drugs/diagnostics. Also, in response to the discussion of measures against drug-resistant bacterial infections at the G7 Ise-Shima Summit (May 2016) and other conferences, PMDA made a presentation on the efforts of tripartite regulatory collaboration with representatives from the US FDA and the EMA at the Conference of Drug Development to Meet the Challenge of Antimicrobial Resistance (an academic conference related to AMR) in September 2018. PMDA proposed and held a face-to-face meeting with the US FDA and the EMA in March 2019. At the meeting, the agencies shared their policies and experiences in product reviews, and agreed to further cooperate with each other to discuss relevant issues. Furthermore, the EMA, FDA, and PMDA jointly hosted a workshop on development of pediatric antimicrobials to share the ideas of the tripartite regulatory authorities with industry and academia (June 2018).

Collaborative relationships with regulatory authorities of the US and European and Asian countries/regions as well as international organizations

- PMDA held meetings with overseas regulatory authorities such as those of the United States (US FDA), the Europe Union (EMA), the United Kingdom (MHRA), Canada (HC), Switzerland (Swissmedic), WHO, India (CDSCO), South Korea (MFDS), China (NMPA/CDE), Brazil (ANVISA), Denmark (DKMA), Saudi Arabia (SFDA), Ireland (HPRA), Taiwan (TFDA), Russia (SID & SP), Malaysia (NPRA), Thailand (Thai FDA), Singapore (HSA), Indonesia (NADFC), Vietnam (DAV), Myanmar (FDA), to further reinforce the collaborative relationships.

  PMDA also concluded a confidentiality agreement (CA) with the regulatory authority of Denmark (Denmark Kingdom Medicines Agency [DKMA]), to further reinforce the collaborative relationships.

- To deepen the collaborative relationship with China, PMDA's Chief Executive and officers of MHLW visited China to hold a meeting with executive officials of the National Medical Products Administration (NMPA) as a public-private mission in December 2018, as in the previous year. As a result, the collaborative relationship between China and Japan has continued and progressed.

Dispatching liaison officers, etc.

- PMDA continued to dispatch liaison officers and PMDA staff members to the agencies in the United States and Europe (PMDA staff were sent to the review and safety divisions in the agencies) to collect information and reinforce collaboration with the agencies.

  Through the liaison officer dispatched to EMA, PMDA obtained information on EMA's scientific committees (e.g., CHMP, PRAC), joined clusters featuring topics such as modeling & simulation and rare disease to exchange information on individual products, and exchanged information and opinions with EMA on risk assessment for products subjected to global recalls and other topics. In addition, the liaison officer stationed at EMA participated in various workshops sponsored by EMA and informed EMA about the trends in Japan.

  Furthermore, PMDA accepted the second EMA staff members under a framework under which PMDA regularly accepts EMA staff members dispatched from EU. This activity was undertaken to deepen the understanding of the Japanese regulatory system among EMA staff, explore the potential of a more collaborative partnership, and to exchange information.

GLP, GCP, GMP, and QMS

- PMDA conducted mutual acceptance of GLP investigation reports based on the OECD's mutual data acceptance system.
- As for information exchange of quality control-related inspection results, PMDA reinforced the collaborative partnership with Taiwan concerning quality management system (QMS) for medical devices. Particularly, in the field of QMS inspections, this partnership contributed to conclusion of a memorandum of cooperation (between the Japan-Taiwan Exchange Association and the Taiwan-Japan Relations Association) on QMS. PMDA exchanged GMP inspection reports with the US FDA, ANVISA (Brazil), Thai FDA, and other agencies to improve inspection efficiency.
- PMDA participated, on a pilot basis, in the EMA-US FDA GCP initiative (from June 2017 to December 2018), which is intended to ensure efficient GLP/GCP/GPSP inspections. As a result, PMDA took part in regular teleconferences and exchanged opinions via e-mail with US FDA and EMA. Mutual attendance at inspections and other achievements, such as the prevention of overlapping inspections and reference to results, were appreciated, and thus, PMDA became an official member of the initiative after the end of the pilot period.

  PMDA conducted the following activities to build a relationship based on trust with foreign regulatory agencies, in order to create an environment that promotes collaboration in GCP activities between PMDA and the agencies:

  (1) Before conducting GCP inspections outside Japan, PMDA contacted the local regulatory agencies in advance, and then conducted the inspections in the presence of representatives of the regulatory agencies, when requested.

  (2) PMDA accompanied, whenever possible, inspections conducted in Japan by overseas regulatory agencies, and shared information with the agencies.

  (3) PMDA dispatched its staff (members of the Office of Non-clinical and Clinical Compliance) to the US FDA and EMA. They participated in training programs, and exchanged opinions on compliance inspection methods with the agencies.
- PMDA supported the negotiations between Japan (MHLW) and the EU to expand the coverage of mutual recognition agreements (MRA) concerning the GMP of drugs (July 2018).

  PMDA has also participated in an international GMP inspection rationalization program for drug substance manufacturers. By exchanging information on GMP inspections, including inspection plans and results etc., with foreign regulatory authorities, PMDA continued international cooperation to ensure more efficient and effective GMP inspections.

Japanese Pharmacopoeia

- PMDA participated in the European Pharmacopoeia (EP) Board meetings as an observer three times a year (June 2018, November 2018, and March 2019), and actively engaged in reinforcement of the collaborative framework and information collection. PMDA also held bilateral meetings by taking this opportunity to promote harmonization activities.
- To promote harmonization activities with U.S. Pharmacopeia (USP), PMDA dispatched an employee as a liaison officer and closely exchanged information by holding teleconferences once a month. PMDA also held dipartite teleconferences, etc., with USP (June and August 2018) to seek public comments on 2 standards for excipients subjected to harmonization activity.
- PMDA jointly hosted the 1st Japan-China Pharmacopeia Forum (June 2018) with the Pharmacopeia of the People's Republic of China based on the MOC (concluded in September

2016). On this occasion, PMDA held a Japan-China bilateral meeting in the area of pharmacopeia, and both parties agreed on further deepening of collaborative relationships in the future.

- PMDA cooperated with MHLW in publication of the English edition of Supplement 1 to the Japanese Pharmacopoeia 17th edition (September 2018).

Major actions taken in APEC-LSIF-RHSC

- The Asia-Pacific Economic Cooperation Life Science Innovation Forum Regulatory Harmonization Steering Committee (APEC-LSIF-RHSC) convened in Australia in August 2018 and Chile in February 2019 (APEC-LSIF-RHSC was established in the APEC Life Science Innovation Forum). PMDA served as a co-chair and led the discussion about the Capacity Building in the APEC region, thereby contributing to reinforcing international collaboration.

  As a result of appreciation of its achievements, the PMDA-ATC was certified as a “Training Center of Excellence (CoE)” that provides training programs in the areas of multi-regional clinical trials/GCP inspections and pharmacovigilance to enhance the capacity of regulators and relevant officials, at the APEC-LSIF-RHSC meeting. Furthermore, the PMDA-ATC was additionally certified as a CoE in the area of medical devices at the APEC-LSIF-RHSC meeting in Chile in February 2019. Among 7 working areas established by APEC-LSIF-RHSC, PMDA held seminars at the PMDA-ATC as a CoE in the areas of multi-regional clinical trials/GCP inspections (January 2019) and pharmacovigilance (February 2019). PMDA reported the achievement of the seminar in the area of multi-regional clinical trials/GCP inspections at the APEC-LSIF-RHSC meeting in Chile (February 2019), which was internationally highly appreciated (the achievement of the seminar in the area of pharmacovigilance will be reported in August 2019).

Regular bilateral meetings and symposiums

- PMDA collaborated with the regulatory authorities of Thailand, South Korea, India, Taiwan, and Brazil to hold the following symposiums and meetings:

  (1) The 5th Thailand-Japan Symposium and the Bilateral Meeting between the regulatory authorities (April 2018)

  (2) The 3rd Japan-South Korea Joint Symposium on Medical Products and the Bilateral Meeting between the regulatory authorities (July 2018)

  (3) The 3rd India-Japan Medical Products Regulation Symposium and the Bilateral Meeting between the regulatory authorities (August 2018)

  (4) The 6th Joint Conference of Taiwan and Japan on Medical Products Regulation and the Bilateral Meeting between the regulatory authorities (October 2018)

  (5) The 4th Brazil-Japan Seminar on Regulation of Pharmaceuticals and Medical Devices and the Bilateral Meeting between the regulatory authorities (December 2018)

  In particular, partnership between Japan and Taiwan was reinforced through conclusion of a memorandum of cooperation on quality management system (QMS) for medical devices and publication of Q&As concerning product registration of medical devices.

3.4.(2).(ii) Strengthening of activities for international harmonization, etc.

Major actions taken at ICMRA Summit

- In accordance with the consensus at the 12th Summit of Heads of Medicines Regulatory Agencies and the meeting of the International Coalition of Medicines Regulation Authorities (ICMRA), PMDA

worked on the establishment of comprehensive frameworks for regulation of regenerative medical products. For example, PMDA contributed to building consensus on two reflection papers: “In vivo Distribution Studies of Gene Therapy Products” and “Basic Principles on Characteristics and Duration of Follow-up of Subjects Receiving Treatment in Clinical Trials of Cell Therapy Products” at the International Pharmaceutical Regulators Programme (IPRP). Furthermore, PMDA supported Japan’s proposal of a new ICH topic based on the IPRP reflection paper “In vivo Distribution Studies of Gene Therapy Products.”

- To proceed with the Innovation Project (early-phase regulatory response to innovative technologies) of the ICMRA, Japan, as the chair of the meeting, led the discussions on the analysis of horizon scanning methodology implemented by individual nations and prepared a report in March 2019. PMDA, as the Japanese regulatory agency, hosted a face-to-face meeting of the Innovation Project in November 2018 and led the proposal of a project concerning informal network as a successor activity of the Innovation Project. Achievements of the Innovation Project were presented at the DIA Japan Annual Meeting (November 2018) and DIA Europe Annual Meeting (February 2019) to externally demonstrate Japan’s contribution.
- PMDA has been playing a central role in the maintenance of the ICMRA official website (developed and made available to the public in FY 2015), contributing to increased awareness of ICMRA activities by posting achievements and meeting results of the ICMRA on this website for public access.

Major actions taken at ICH

- The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) held conferences in Kobe (Japan) in June 2018. PMDA served as the vice chair of the ICH Assembly and the Management Committee and led discussions. The ICH held a conference in Charlotte (US) in November 2018, at which time re-election of the chair and the vice chair of the Management Committee was discussed. As a result, PMDA was successfully re-elected as the chair.

  In addition, a reflection paper on pharmacoepidemiology proposed by Japan was accepted as a topic by the ICH members. Japan will lead the future discussion at the working group for this topic. PMDA actively participated in the discussion on the review of ICH organizational rules and discussion procedures so that discussions at the ICH could be facilitated under the leadership of Japan.

Major actions taken at Asian Network

- PMDA supported the 2nd Asian Network Meeting hosted by MHLW (April 2019) by inviting the leaders of regulatory authorities of Asian countries to participate in the Meeting and arranging bilateral meetings.

Major actions taken concerning medical devices

- PMDA participated in the Management Committee meetings of the International Medical Device Regulators Forum (IMDRF) held in Beijing (China) in September 2018 and in Moscow (Russia) in March 2019. At the meetings, PMDA worked to finalize various IMDRF guidance documents (e.g., IMDRF/PMD WG/N49 FINAL:2018 “Definitions for Personalized Medical Devices,” IMDRF/GRRP WG/N47 FINAL:2018 “Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices,” IMDRF/Standards WG/N51 FINAL:2018 “Optimizing Standards for Regulatory Use”). PMDA also proposed the revision of the adoption process for new work items to ensure more strategic IMDRF activities, led the discussion on it, and finalized the decision. In addition,

PMDA presented an IMDRF guidance document (IMDRF/Standards WG/N51 FINAL:2018 “Optimizing Standards for Regulatory Use”) at the ISO/IEC standards review committee (an international conference) to disseminate it. PMDA actively participated in individual working group meetings (face-to-face meetings and teleconferences) and coordinated opinions to ensure that Japan’s opinions could be adopted.

- PMDA participated in the meetings of the Regulatory Authority Council (RAC) and the Technical Review and Recognition Decision Committee (TRRC) of the Medical Device Single Audit Program (MDSAP), summarized opinions concerning governance and other topics, and led the discussion to ensure smooth management of MDSAP activities. In February 2018, a PMDA staff member took the leadership of the MDSAP quality management system (QMS) activities. This person continued to lead the TRRC and collaborated with representatives of other regulatory agencies participating in MDSAP in the revision of procedures concerning management of the MDSAP. PMDA actively participated in the early-stage discussion on the MDSAP scheme and supported inspections, thereby gaining the trust of other MDSAP members. As a consequence, The PMDA staff member was appointed to serve as the Vice Chair of RAC for 3 years from January 2019.

- PMDA contributed to the Project for Promotion of International Standardization for Innovative Medical Devices, etc., implemented by MHLW. Based on the road map prepared at the time of inception (FY 2014) of this project (the former Project for Promotion of International Standardization Strategy for Medical Devices), PMDA conducted the following activities to ensure that specifications and standards originating in Japan or reflecting the concepts accepted in Japan are adopted globally and then Japan can lead the international standardization: (a) active participation in events such as ISO/IEC international conferences; (b) development of the framework for collaboration with organizations such as national mirror committees, and (c) establishment and reinforcement of a relationship of trust and collaboration with regulatory authorities in Asian, Europe and the US.

  Specifically, PMDA worked on important themes, e.g., medical robots and additive manufacturing systems, for which international standardization should be promoted in a strategic manner. PMDA participated in 116 conferences of the ISO/IEC standards review committee on such themes (23 international conferences, 74 meetings of the Japanese national committee, and 19 teleconferences) to ensure that the committee incorporates opinions from Japan into standards established at these conferences. Also, PMDA promoted the project to support the participation of academia in international conferences. In FY 2018, PMDA dispatched 3 experts in 3 areas to international conferences to participate in standards review and collect information, and held a study meeting that brought together academia experts who had been dispatched to international conferences, to share the outcome of ISO/IEC international conference and the trends of international standards. An academia expert dispatched to international conferences in FY 2016 served as the project leader for the project of 1 standard proposed by Japan, and it was adopted as an international standard in FY 2018.

  Furthermore, PMDA held 2 meetings of the “Standards Review Council Liaison Office,” which were organized by the Japan Federation of Medical Devices Associations (with 17 technical committees [TCs], including ISO/TC276 [Biotechnology], ISO/TC261 [Additive manufacturing], and ISO/TC299 [Robotics]) in FY 2018. PMDA provided necessary information and issues to be solvedfor international standardization of innovative medical devices, etc., and coordinated information sharing among Japanese national mirror committees.

  PMDA aims to promote a collaborative framework for development of international standards in the Asian region. At several conferences such as meetings of the ASEAN Medical Device Committee (AMDC), PMDA implemented activities to disseminate the principles of Japanese schemes such as third-party certification and certification standards which utilize international

standards. These Japanese schemes are globally regarded as the best practice and are one step ahead of other regulators. PMDA strategically conducted educational activities by inviting ASEAN member countries to hold workshops on standards, which actually took place in 2016. In FY 2018, the workshops were held under the leadership of Japan in Philippines (43 participants), Thailand (45 participants plus 2 participants from Brunei), and Myanmar (30 participants) and were highly evaluated by participants in all of these countries. Furthermore, PMDA prepared the English database of Japanese Medical Device Nomenclature (JMDN) which consists of term names and definitions of individual medical devices (covering more than 4,300 devices) serving as the basic concepts of certification standards, etc., and posted it on the PMDA website in December 2018, in response to strong requests from many foreign countries. These activities gained greater understanding and empathy from ASEAN countries and contributed to further enhancement of collaborative framework and a relationship based on trust.

Through participation in meetings of the Standards WG established in IMDRF in FY 2016, PMDA contributed to the development of a guidance document on optimization of standards for regulatory use in FY 2018. PMDA also cooperated in surveys on awareness of international standards and promoted construction of liaison relationships with standards technical committees such as IEC/TC62 (electrical equipment in medical practice) and ISO/TC210 (quality management and corresponding general aspects for medical devices).

- Harmonization by Doing (HBD) Town Hall Meetings were held as part of cardiology-related academic conferences in Japan and the US (held in Kobe in July 2018, San Diego in October 2018, and Washington DC in March 2019). At these meetings, PMDA exchanged opinions with representatives of the US FDA, experts, medical device companies, etc., concerning the utilization of real-world evidence and the use of cardiovascular medical devices in patients at the high risk of hemorrhage. In addition, as a part of the HBD for Children activity concerning the evaluation of pediatric medical devices, PMDA exchanged opinions with counterparts from the US FDA and held HBD Sessions at the meetings of the Japanese Society of Pediatric Cardiology and Cardiac Surgery to support the conduct of multi-regional clinical trials of pediatric medical devices. To widely disseminate outcomes of the HBD activities, PMDA sought to promote provision of information and continuously carry forward the HBD activities by releasing brochures on HBD activities (in both Japanese and English languages) and enriching the contents of the HBD page on the PMDA website.

Major actions taken at PDG

- PMDA participated in the Pharmacopoeial Discussion Group (PDG) meeting (a review committee meeting of Japan-US-Europe Pharmacopoeias) held in Strasburg (France) in October 2018. PMDA also participated in video conferences (April 2018 and March 2019), expert teleconferences (twice in September 2018), and monthly teleconferences. Through these meetings, PMDA had close communication with the EP and USP. This led to agreement on the harmonization of new standards for 1 excipient and the revision of standards for 3 excipients.

  PMDA also sought public comments in Japan on new monographs for 2 excipient and revised monograph 1 testing method and revised monograph for 1 excipient, which are to be harmonized at the PDG meeting.

Major actions taken for international nonproprietary names (INN)

- Two consultations on application for international nonproprietary names (INN) were conducted. PMDA participated in the WHO-hosted INN meetings held in May and October 2018.

Major actions taken at IPRP

- PMDA participated in the meetings of the International Pharmaceutical Regulators Programme (IPRP) held in Kobe (Japan) in June 2018 and Charlotte (US) in November 2018 to exchange information and contributed to building consensus on 2 reflection papers, “In vivo Distribution Studies of Gene Therapy Products” and “Basic Principles on Characteristics and Duration of Follow-up in Subjects Receiving Treatment in Clinical Trials of Cell Therapy Products.” In addition, PMDA actively participated in at the meetings of individual working groups of the IPRP for information exchange. Furthermore, PMDA contributed to the preparation of a paper (on the acceptability of foreign comparator products) at Bioequivalence Working Group for Generics (BEWGG) of the IPRP.

Major actions taken for generic drugs

- PMDA participated in discussion towards consensus on reflection papers concerning generic drugs at the ICH and coordinated opinions for participation in and contribution to the Informal Generic drug Discussion Group (IGDG).

Major actions taken at ICCR

- PMDA participated in the 12th International Corporation on Cosmetics Regulation (ICCR-12) held in Japan in July 2018 and exchanged information with regulatory authorities from the US, the EU, Canada, and Brazil on the regulation of cosmetics and other topics.

Major actions taken at International Meeting of World Pharmacopoeia

- At the 9th International Meeting of World Pharmacopoeia hosted by the WHO and held in Da-nang (Vietnam) in April 2018, PMDA reported the results of a questionnaire survey conducted under the initiative of the Japanese Pharmacopoeia to summarize the current situation of individual pharmacopeias as well as mutual difference in their concepts and perception. This report is planned to serve as basic data for examination of topics to be discussed at future International Meetings of World Pharmacopoeia. PMAD’s activities thus contributed to deepening of discussion at the meeting. At the 10th International Meeting of World Pharmacopoeia held in Geneva (Switzerland) in March 2019, PMDA collaborated with the USP, EP, British Pharmacopoeia (BP), etc., to prepare a draft white paper on the added value of having pharmacopeial standards for public health. Furthermore, on the occasion of these conferences, PMDA hold trilateral meetings with the representatives of USP and EP as well as a bilateral meeting with the representatives of the Pharmacopeia of the People’s Republic of China to address mutual issues to be solved and to establish a cooperative framework.

Major actions taken at OECD

- PMDA participated in the Working Group on GLP of OECD and continued to dispatch an employee to the OECD as the person in charge of GLP, thereby introducing PMDA’s knowledge and expertise into international GLP-related activities.
- PMDA addressed evaluation inspection by OECD under the on-site evaluation system (OSE) for GLP inspections. As a result, PMDA’s GLP inspection system was confirmed to be operated in compliance with the OECD principles as well as with excellent expertise and inspection techniques.

Expansion of the scope of English-language data

- PMDA exchanged opinions with representatives from relevant industries on expanding the scope of English-language data acceptable as the data submitted in support of product applications.

3.4.(2).(iii) Promotion of personnel exchanges

- PMDA dispatched a total of 21 staff members to the FDA of Thailand, NPRA of Malaysia, and NADFC of Indonesia on 6 occasions in June, July, September, October, and December 2018, and January 2019, to share its policy for operations and how actual operations have been implemented by PMDA.
- In addition to training seminars provided by the PMDA-ATC, PMDA accepted trainees as needed from the regulatory authorities of countries/regions including Taiwan, Malaysia, Russia, and Saudi Arabia.
- PMDA held bilateral symposiums and meetings between the regulatory authorities (Thailand in April 2018, South Korea in July 2018, India in August 2018, Taiwan in October 2018, and Brazil in December 2018), and promoted understanding of Japanese pharmaceutical regulations, etc. PMDA also exchanged opinions on human capacity building.

  PMDA also held meetings with regulatory authorities, such as SFDA of Saudi Arabia, NPRA of Malaysia, FDA of Thailand, NADFC of Indonesia, DAV of Vietnam, FDA of Myanmar, to discuss the possibility of information exchanges and collaborative projects and exchange opinions on human capacity building.

3.4.(2).(iv) Development of internationally-oriented human resources with excellent communication skills

Presentations in meetings and other events in English

- PMDA arranged opportunities for its young staff members to give an English presentation on PMDA's latest activities at the Annual Meetings of DIA (Drug Information Association) held in Japan, the US, Europe, and Singapore as well as at the Regulatory Affairs Professionals Society (RAPS).
- PMDA made efforts to cultivate internationally active persons by dispatching several employees to attend an educational program on inspections organized by EMA, and another program regarding drug regulations sponsored by the Maureen and Mike Mansfield Foundation.

Enrichment of English-language training

- PMDA offered an English language training program specifically designed for employees scheduled to be dispatched overseas for a long period to improve their practical English abilities. Employees who give presentations in international conferences received a training program on practical English for international conferences so that they can clearly communicate PMDA's views at academic conferences (one-on-one lessons for all). Employees who use English when conducting their operations, (e.g., attendance at international conferences) received English training programs (one-on-one lessons, group lessons, and correspondence courses) to improve their English skills. PMDA also continued to provide training programs in good practice for learning English and making presentations offered by in-house staff, in order to enhance the motivation of all employees to learn English and raise their awareness of presentation skills, to improve the English ability of all employees.

3.4.(2).(v) Improvement and strengthening of international publicity and provision of information

Translation of review reports into English

- PMDA translated product review reports into English on drugs, medical devices, and regenerative medical products approved in Japan that may have an impact on medical product regulation in foreign countries. The review reports were published on the PMDA website and distributed to approximately 1,000 subscribers including officials of foreign regulatory agencies, to reveal the quality of the regulatory review process in Japan (40 reports published in FY 2018 [37 drugs and 3 medical devices]).

Translation of safety information into English

- To reinforce provision of information in English, major safety information publications were translated into English. The English version was posted on the PMDA website mostly within the same day as the issuance of the Japanese version. Safety information translated into English was provided to regulatory agencies having concluded confidentiality agreements with PMDA (e.g., US FDA, EMA) prior to posting on the PMDA website, while information on package insert revision translated into English was provided to regulatory agencies of 7 countries (Thailand, Indonesia, Myanmar, Azerbaijan, India, Papua New Guinea, and Philippines).

Providing information to foreign countries

- PMDA Updates were distributed monthly to stakeholders to communicate the current status of the efforts being made by PMDA regarding international conferences or bilateral relationships. PMDA Updates were also posted on the PMDA website to widely disseminate information to the general public as well as to the foreign regulatory authorities. In FY 2018, the number of subscribers to PMDA Updates reached approximately 1,000, indicating the contribution of this periodical to improved awareness of PMDA's international activities.

  In FY 2018, PMDA received 485 inquiries (by email) from foreign countries and gave 475 responses. PMDA responded to inquiries from foreign countries by explaining information on the regulation of medical products in Japan appropriately and in a timely fashion.

  PMDA also gained a slot for its session and had booth exhibitions at the DIA Annual Meetings in Europe and the US as well as at the RAPS Annual Meeting, to familiarize attendees with PMDA's policies etc.

- A total of 945 certification standards, the Basic Principles Checklist, etc., were published on the PMDA website by FY 2018. Furthermore, to disseminate information on the basic concepts of the third-party certification for medical devices in Japan as well as certification standards established by utilizing international standards such as those of ISO/IEC, PMDA prepared the English database of Japanese Medical Device Nomenclature (JMDN) which consists of term names and definitions of individual medical devices (covering more than 4,300 devices) and posted it on the PMDA website in FY 2018, in response to strong requests from foreign regulatory authorities (including those of ASEAN and European countries as well as the US) and industry associations in Japan.

  Through its website, PMDA disseminated information in English on the status of activities for the Projects Across Multi-offices for standards development.

3.4.(3) Measures for intractable diseases and orphan diseases, etc.

- In the Orphan Drug Working Group in Projects Across Multi-offices in PMDA, the Agency has been discussing methods for promoting orphan drug development by collaborating with MHLW and by exchanging information with EMA.
- In the CIN WG in Projects Across Multi-Offices, PMDA cooperated with the AMED research group in developing patient registries for muscular dystrophy, amyotrophic lateral sclerosis (ALS), cancer/rare fractions, and brain surgical therapy.
- Companion Diagnostics WG for Projects Across Multi-Offices collaborated with MHLW to develop the following 3 notifications, etc. ("Questions and answers (Q&A) on 'Technical Guidance on Development of In Vitro Companion Diagnostics and Corresponding Therapeutic Products'" [PSEHB/PED/MDED Administrative Notice, dated July 3, 2018, issued jointly by the Pharmaceutical Evaluation Division and the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW], "Questions and answers (Q&A) on Companion Diagnostics and Corresponding Therapeutic Products (Part 2)" [PSEHB/PED/MDED Administrative Notice, dated July 20, 2018, issued jointly by the Pharmaceutical Evaluation Division and the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW], "Questions and answers (Q&A) on 'Legislation Notice to Applicants for Marketing Authorization of DNA Sequencers and Related Products Utilized for Genetic Testing Systems' (Part 2)" [PSEHB/PED/CND Administrative Notice, dated September 12, 2018, issued jointly by the Medical Device Evaluation Division and the Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW]).
- Omics WG for Projects Across Multi-Offices discussed how to establish a system for offering consultations jointly with regulatory authorities in Europe and the US and conducted a consultation on pharmacogenomics/biomarkers.

3.4.(4) Promoting provision of information such as review reports

3.4.(4).a. Improving provision of information

- To encourage the proper use of drugs, medical devices, etc. and to ensure transparency of product reviews, PMDA releases information on reviews of product approval applications (e.g., review reports) on the PMDA website, in collaboration with MHLW and with the cooperation and understanding of relevant companies.

3.4.(4).b. Releasing information related to review reports

- New drugs are classified into 2 categories based on the application data submitted: (1) Drugs to be deliberated on by the Drug Committees of the Pharmaceutical Affairs and Food Sanitation Council (PAFSC) at MHLW (referred to as "deliberation products"); and (2) Drugs to be reported to the Drug Committees of PAFSC (hereinafter referred to as "report products"). For "deliberation products," both "review reports" that describe details and results of reviews and "summaries of product applications" that summarize submitted data are subject to public release. For "report products," "review reports" are subject to public release. These documents are published on the PMDA website after conferring with the relevant companies regarding the content to be released for each product, based on a Notification Issued by the Evaluation and Licensing Division (ELD) of the Pharmaceutical and Food Safety Bureau (PFSB) at MHLW.
- In FY 2018, PMDA released 113 review reports, 81 summaries of product applications, and 92 re-examination reports.

The percentage of review reports released within 1 month after approval was 100% in FY 2018 (100% in FY 2017). The percentage of summaries of product applications released within 3 months after approval was 100% in FY 2018 (100% in FY 2017); the median time from approval to release was 76 days, showing an achievement of 118% compared to the target time of 3 months (90 days).

Note: The median times from approval (for re-examination reports, from notification of results) to data release were 8 days for review reports, 76 days for summary of product applications, and 7 days for re-examination reports.

Review reports on new medical devices

- In FY 2018, PMDA released 15 review reports, 11 summaries of product applications and 11 re-examination reports for new medical devices.

  The percentage of review reports released within 1 month after approval was 100% in FY 2018 (100% in FY 2017). The percentage of summaries of product applications released within 3 months after approval was 100% in FY 2018 (92% in FY 2017); the median time from approval to release was 77 days, showing an achievement of 117% compared to the target time of 3 months (90 days).

  Note: The median times from approval (for re-examination reports, from notification of results) to data release were 14 days for review reports, 77 days for summary of product applications, and 7 days for re-examination reports.

Review reports on new regenerative medical products

- In FY 2018, PMDA released 2 review reports and 2 summaries of product applications for new regenerative medical products.

Review reports on BTC drugs and quasi-drugs

- In FY 2018, PMDA released 1 review report and 1 summary of product applications for BTC drugs, but no review report or summary of product applications for a quasi-drug.

Number of review reports released

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
New drugs	130	118	108	99	113
New medical devices	9	16	9	11	15
New regenerative medical products	-	2	1	-	2
BTC and OTC drugs	3	2	1	3	1
Quasi-drugs	1	3	1	1	0

3.4.(5) Ensuring the impartiality and transparency of judgments by external experts

- It is necessary to take steps to ensure impartiality and transparency in the judgments made by external experts commissioned by PMDA. The Rules for Convening Expert Discussions etc., by the Pharmaceuticals and Medical Devices Agency (December 25, 2008; revised on December 26, 2018) was set forth to ensure transparency of PMDA's services by releasing review reports and information on conflicts of interest among commissioned external experts, thereby allowing outside parties to verify the decision-making process. In accordance with the rules, PMDA discloses all cash contributions and contract payments received by external experts commissioned by PMDA for Expert Discussions on reviews and safety measures. The disclosure is made immediately after confirmation of approval of new product applications, the development

of safety measures, or the development of approval standards or review guidelines for drugs, etc. The information disclosed is reported to the Advisory Council and the Committee on Review and Safety Operations.

3.4.(6) Provision of training in controlled medical device certification standards

- In conjunction with the revision of controlled medical device certification standards (certification standards for mobile ultrasound imaging system, etc.), reviewers working at the registered certification bodies were trained by PMDA to conduct product certification review and compliance assessments based on the standards.

3.4.(7) Improvement of quality of reviews/safety operations through enhancement of information systems

- Since August 25, 2014, PMDA has been operating an application/review computer system that was designed based on the Optimization Plan for Operations and Systems. The system was upgraded in order of priority in order to enable the more effective handling of necessary operations. In August 2016, PMDA began accepting advance notices of new product applications and electronic files using an electronic gateway as part of the operation of the electronic data submission system.
- Final decision documents for regulatory approval of drugs, etc., clinical trial notifications for agents and devices, etc., and minor change notifications for agents and devices, etc. were converted into digital image data to reduce storage space and enable long-term storage. Review process was streamlined and accelerated by using the search function for digital image data.
- In June 2016, at the request of the Osaka prefectural government, Kansai Pharmaceutical Industries Association, the Osaka Chamber of Commerce and Industry, and the Kansai Economic Federation, PMDA launched a video conference consultation system at its Kansai Branch Office in order to improve the convenience of this service for applicants based in the Kansai region. In FY 2018, PMDA conducted 105 video conference consultations, etc. PMDA also conducted 53 RS Strategy Consultations (R&D) (including pre-consultation meetings and pre-consultation meetings for medical devices in special zones) through the web-based conference system.
- PMDA conducted system upgrade for the electronic data submission system. In August 2016, PMDA started to accept electronic files via the gateway, and further modified the system (involving addition of transmission test function and reduction of user workload upon system operation) to increase the usability in response to requests from applicant companies.
- In line with the progress of discussions on the ICH eCTD version 4.0, PMDA procured operations for requirement definition and basic designing (the first-half process) to develop a system to receive and access the eCTD version 4.0 from FY 2017 through FY 2018.

  In FY 2018, PMDA proceeded with preparatory work on the detailed design and development phase (the second-half process) to be procured in FY 2019. PMDA held a briefing session and a Q&A session on details of the first-half process to expand the range of development vendors applying for procurement.

III. SUPPLEMENTARY INFORMATION

Reviews and Safety Measure Services

1. Drug product review services

Number of approved products

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Prescription drugs	3,944	3,664	3,660	3,611	2,843
BTC and OTC drugs	844	752	646	537	452
In vitro diagnostics	109	172	199	187	153
Quasi-drugs	1,779	2,495	1,924	1,891	1,665
Cosmetics	0	0	0	0	0
Total	6,676	7,083	6,429	6,226	5,113

Number of approved new drug applications

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Number of approved new drug applications	118	116	112	104	113
Priority review products among these new drugs	44	37	38	38	47

Reference 1 Approved new drug applications (only those with new active ingredients)

Total review time for new drugs (priority review products)

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Percentile	60th	60th	70th	70th	80th
Total review time (months)	9.1	9.5	9.2	8.9	8.8
Number of approved applications	24	17	19	13	14

Reference

Regulatory review time (months)	3.8	3.8	3.8	4.3	4.4
Applicant's time (months)	5.4	6.0	5.6	5.7	4.7

Note: Figures are calculated based on the products (drugs with new active ingredients) submitted in or after FY 2004.

Total review time for new drugs (standard review products)

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Percentile	60th	70th	70th	80th	80th
Total review time (months)	12.1	11.2	12.0	12.1	12.0
Number of approved applications	28	25	22	25	25

Reference

Regulatory review time (months)	6.5	5.9	7.0	6.3	6.6
Applicant's time (months)	6.5	6.7	7.3	7.6	7.7

Note 1: Figures are calculated based on the products (drugs with new active ingredients) submitted in or after FY 2004.

Note 2: The figures in "regulatory review time" and "applicant's time" represent their respective percentile values. The sum of "regulatory review time" and "applicant's time" may not equal "total review time."

Reference 2 Review time targets of Third Mid-term Plan

Priority review products

Fiscal year	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Total review time (months)	9	9	9	9	9
Percentile	60th	60th	70th	70th	80th

Standard review products

Fiscal year	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Total review time (months)	12	12	12	12	12
Percentile	60th	70th	70th	80th	80th

Application and approval status of BTC and OTC drugs and quasi-drugs by category

BTC and OTC drugs

Application categories	1	2	3-1	3-2	3-3	4	5-1	5-2	5-3	5-4	6	7-1	7-2	8	Pest control agents	Total
Products submitted in FY 2018	1	0	0	0	0	7	0	3	0	4	7	41	6	683	22	774
Products approved in FY 2018	0	0	0	0	1	4	0	1	0	1	1	20	8	394	22	452

Note 1: Application categories for BTC and OTC drugs were revised on January 1, 2009. Application categories in the table are those after the revision.

Note 2: Application categories for BTC and OTC drugs:

Current categories

1: Drugs with new active ingredients (Direct OTC drugs)
2: Drugs with new routes of administration
3-1: Drugs with new indications
3-2: Drugs in new dosage forms
3-3: Drugs with a new dosage
4: BTC (OTC) drugs with new active ingredients (Switch OTC drugs)
5-1: BTC (OTC) drugs with new routes of administration
5-2: BTC (OTC) drugs with new indications
5-3: OTC (BTC) drugs in new dosage forms
5-4: OTC (BTC) drugs with a new dosage
6: New OTC (BTC) combination drugs
7-1: OTC combination drugs with similar prescription
7-2: OTC drugs with similar dosage forms
8: Other drugs (relatively less innovative drugs and drugs that are not innovative)

Note 3: In FY 2018, there were no products approved in the former application categories (i.e., the categories before the revision.)

Former categories

1: Drugs with new active ingredients (Direct OTC drugs)
2: Drugs with new active ingredients for OTC (Switch OTC drugs)
3: Relatively innovative drugs excluding the above "1" and "2"
4-1: Other drugs (Relatively less innovative drugs)
4-2: Other drugs (Drugs that are not innovative)

Note 4: The product category containing pest control agents was revised on November 25, 2014; however, this category is similar to the former category containing insecticides/antimicrobial agents. Accordingly, the above figures cover both product categories.

Quasi-drugs

	Current application categories								
	1	2-1	2-2	2-3	2-4	2-5	3	4	5-1
Products submitted in FY 2018	2	11	0	3	4	0	7	515	1,097
Products approved in FY 2018	0	10	0	2	1	0	9	463	1,028

	Current application categories				Former application categories			Total
	5-2	5-3	Quasi-drugs for pest control	Subtotal	1,3	2	Subtotal	
Products submitted in FY 2018	27	46	67	1,779	-	-	-	1,779
Products approved in FY 2018	26	38	77	1,654	9	2	11	1,665

Note 1: The application categories for quasi-drugs were revised on November 25, 2014. The figures in "Former application categories" represent the number of products approved under the application categories before the revision.

Note 2: Application categories for quasi-drugs:

Former categories
1: Products that contain a new active ingredient
2: Products that are not innovative
3: Innovative products excluding the above "1"

Current categories
1: Quasi-drugs with new active ingredients
2-1: Quasi-drugs with new indications
2-2: Quasi-drugs in new dosage forms
2-3: Quasi-drugs with new strengths
2-4: New combination quasi-drugs
2-5: Quasi-drugs with new routes of administration
3: Quasi-drugs containing new excipients
4: Similar quasi-drugs
5-1: Identical quasi-drugs
5-2: Newly designated quasi-drugs
5-3: Newly categorized quasi-drugs

Note 3: The numbers of "Products submitted in FY 2016" were calculated by category at the time of filing.

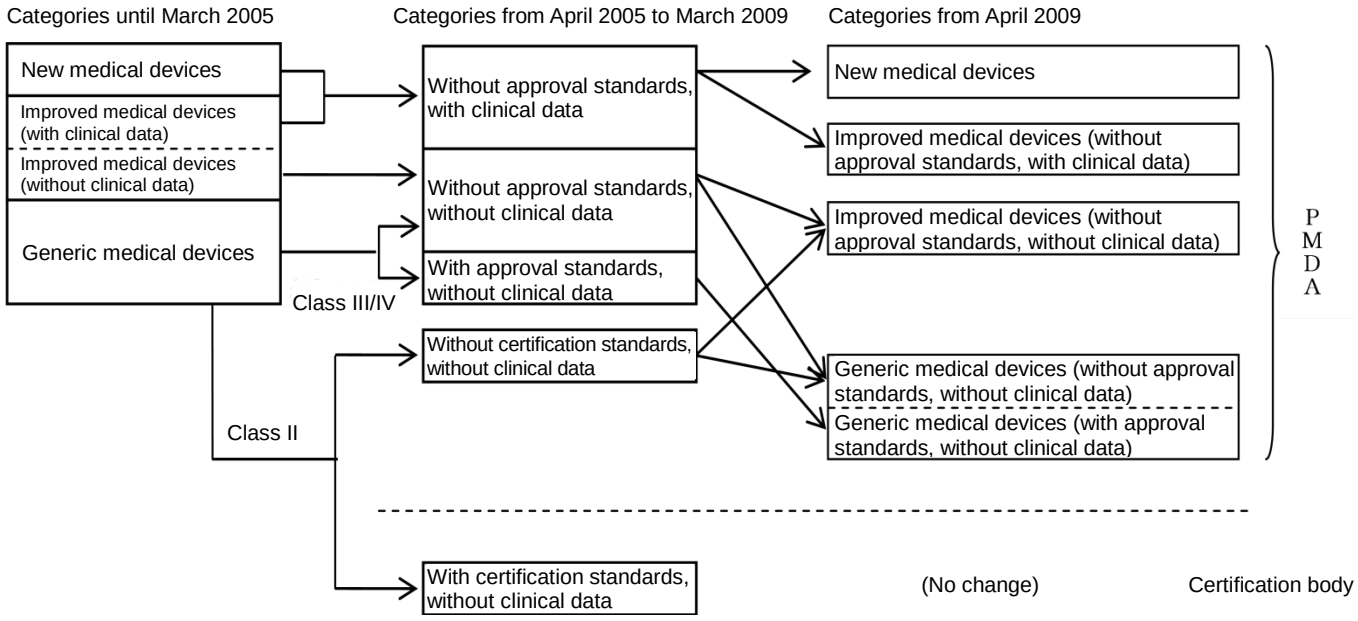
Note 4: The numbers of "Products approved in FY 2016" were calculated by category at the time of approval.

Note 5: The numbers of quasi-drugs in former application categories include pest control agents.

2. Medical device and *in vitro* diagnostic review services

2.(1) Changes in application categories

In accordance with the enactment of the revised Pharmaceutical Affairs Act in April 2005, the former application categories were revised based on the clinical data or approval standards available. With regard to medical devices certified according to the certification standards established by the Minister of Health, Labour and Welfare, the entity that certifies such medical devices was changed from the Minister of Health, Labour and Welfare to third-party certification bodies.



Note: Roman numerals II, III, and IV indicate the classification of medical devices based on risk. If a malfunction occurs, class II medical devices have relatively low risk to the human body; class III medical devices have relatively high risk to the human body; and malfunctions of class IV medical devices may directly lead to life-threatening conditions.

Since the enactment of the revised Pharmaceutical Affairs Act in April 2005, Class II medical devices have been classified as controlled medical devices and class III and IV medical devices as specially controlled medical devices.

Number of approved medical devices

		FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Medical devices		1,235	1,217	1,120	1,153	1,105
Priority review products (included in above figures)		5	8	1*	3	2
Re-listed	New medical devices	67	56	26	27	38
	Improved medical devices (with clinical data) (From FY 2009 onward)	35	53	44	42	52
	Improved medical devices (without clinical data) (From FY 2009 onward)	213	240	225	215	216
	Generic medical devices (From FY 2009 onward)	917	868	825	868	799
	Without approval standards, with clinical data	0	0	0	0	0
	Without approval standards, without clinical data	3	0	0	1	0
	With approval standards, without clinical data	0	0	0	0	0
	Controlled medical devices (without approval and certification standards, without clinical data)	0	0	0	0	0
	Improved medical devices (until FY 2004)	0	0	0	0	0
	Generic medical devices (until FY 2004)	0	0	0	0	0

** One new medical device is included.*

Reference 1 Approval status of and review time for new medical devices

Approval status of and review time for new medical devices (priority review products)

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Percentile	60th	60th	70th	70th	80th
Total review time (months) (Reference, 80th percentile) (months)	8.8 (8.9)	7.9 (8.2)	8.0 (8.0)	8.3 (9.6)	8.3
Number of approved applications	5	8	1	3	2

Note: In FY 2017, a total review time of 10 months was achieved for 2 of 3 products, with an achievement rate of 66.7%; the target for the total review time was achieved from the standpoint of the percentiles of the products but was not achieved from the standpoint of the achievement rate.

Reference

Regulatory review time (months)	4.0	4.2	3.2	5.5	4.2
Applicant's time (months)	3.3	3.8	4.8	3.0	4.8

Note 1: Figures are calculated based on the products submitted in or after April 2004.

Note 2: The FY 2016 and FY 2017 results exclude standalone medical device software newly categorized as "medical devices" from November 25, 2014 according to the PMD Act, if the software was submitted for approval during the transitional period (from November 25, 2014 to February 24, 2015).

Note 3: The figures in "regulatory review time" and "applicant's time" represent their respective percentile values. The sum of "regulatory review time" and "applicant's time" may not equal "total review time."

Reference 2 Review time targets of Third Mid-term Plan

Priority review products

Fiscal year	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Total review time (months)	10	10	10	10	10
Percentile	60th	60th	70th	70th	80th

Standard review products

Fiscal year	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Total review time (months)	14	14	14	14	14
Percentile	60th	60th	70th	70th	80th

Reference 3 Breakdown of approved products for which clinical trial data were submitted

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Number of medical devices with Japanese clinical trial data only	10	23	9	14	14
Number of medical devices with foreign clinical trial data only	24	23	25	26	31
Number of medical devices with multi-regional clinical trial data	0	2	3	2	1
Number of medical devices with clinical evaluation reports	37	23	13	11	19
Others	5	10	4	2	5

Note 1: Others cover products with both foreign and Japanese clinical trial data etc.

2.(2) Review of *in vitro* diagnostic products

2.(2).(i) Approved *in vitro* diagnostic products and their review times

Approximately 83% (127 of 153) of *in vitro* diagnostics applications approved in FY 2018 were processed within the standard administrative processing period (6 months).

Approved in vitro diagnostics applications and their review times

Fiscal Year (FY) of submission	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Number of approved applications	109	172	199	187	153
Median total review time (months)	5.3	7.2	6.4	5.2	5.6
Median regulatory review time (months)	2.6	3.9	3.5	2.9	3.0
Achievement rate	[80%]	[71%]	[76%]	[88%]	[83%]

Note: The percentages in parentheses indicate achievement rates of target regulatory review time (i.e., the percentage of applications for which the review was completed within 6 months.)

2.(2).(ii) Changes in application categories

After the revision of the Pharmaceutical Affairs Act, which came into effect in April 2005, the former application categories were changed to new ones defined according to the level of diagnostic information risk. *In vitro* diagnostics with an extremely low diagnostic information risk were transferred from the Minister's approval system to a self-certification system. Formerly, the Minister of Health, Labour and Welfare approved *in vitro* diagnostics with low diagnostic information risk for which the certification standards have been developed; this approval system was changed to the third-party certification system.

3. Other review-related services

3.(1) Surveys related to clinical trial notifications

PMDA has been conducting surveys of clinical trial notifications for new active ingredients (APIs categorized as new drugs), new medical devices, and new regenerative medical products in order to ensure subject safety. Surveys of clinical trial notifications for new regenerative medical products started in November 2014.

The number of clinical trial notifications for drugs in FY 2018 is shown below. Among them, reviews of 168 notifications were completed, and 2 notifications were withdrawn within FY 2018.

Number of clinical trial notifications for drugs

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Initial clinical trial notification	151 (20)	127 (10)	134 (10)	136 (3)	175 (11)
n-th clinical trial notification	450 (33)	530 (45)	511 (63)	557 (59)	589 (77)
Protocol change notification	4,321	4,566	4,998	5,200	5,485
Trial completion notification	498	507	469	456	477
Trial discontinuation notification	67	70	93	65	98
Development discontinuation notification	117	102	111	100	119
Total	5,604	5,902	6,316	6,514	6,943

Note 1: The figures in parentheses indicate the number of notifications of "investigator-initiated clinical trials."

The number of clinical trial notifications for equipment/devices in FY 2018 is shown below. Among them, reviews of 25 notifications were completed, and 0 notifications were withdrawn within FY 2018.

Number of clinical trial notifications for equipment/devices

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Initial clinical trial notification	31 (7)	31 (8)	34 (8)	25 (9)	24 (6)
n-th clinical trial notification	6 (2)	10 (0)	20 (1)	9 (2)	11 (6)
Protocol change notification	240	283	315	353	294
Trial completion notification	33	22	22	39	31
Trial discontinuation notification	6	5	2	8	13
Development discontinuation notification	2	2	7	6	5
Total	318	353	400	440	378

Note: The figures in parentheses indicate the number of notifications of "investigator-initiated clinical trials."

The number of clinical trial notifications for processed cells, etc. in FY 2018 is shown below. Among them, reviews of 18 notifications were completed, and 1 notification was withdrawn within FY 2018.

Number of clinical trial notifications for processed cells, etc.

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Initial clinical trial notification	3 (1)	10 (2)	16 (7)	13 (8)	18 (8)
n-th clinical trial notification	1 (1)	3 (2)	5 (0)	14 (10)	17 (3)
Protocol change notification	2	19	52	93	151
Trial completion notification	0	0	1	3	7
Trial discontinuation notification	0	0	0	3	1
Development discontinuation notification	0	0	0	1	1
Total	6	32	74	127	195

Note: The figures in parentheses indicate the number of notifications of "investigator-initiated clinical trials."

3.(2) Survey of adverse reaction reports from clinical trials

PMDA examines information regarding reported adverse reactions to drugs, devices, and processed cells, and if necessary, instructs the sponsors (via MHLW) to consider discontinuing clinical trials or taking other actions.

The number of reports on adverse drug reactions etc. from clinical trials in FY 2018 is shown below.

Adverse drug reaction reports from clinical trials

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Number of ADR reports from clinical trials	71,689	86,039	87,876	95,008	96,714
(In Japan)	910	1,339	1,458	1,220	1,370
(Outside Japan)	70,779	84,700	86,418	93,788	95,344

Note 1: The figures represent the numbers of initial reports that were submitted as case reports, research reports, safety measure reports, and other reports.

Note 2: Electronic report submission started on October 27, 2003. Because of the change of the reporting method, the first follow-up reports submitted on or after October 27, 2003 are classified as initial reports even though the actual initial reports had already been filed before the date. On or after the date, one report for co-development product should be submitted by each company.

The number of device malfunction reports from clinical trials in FY 2018 is shown below.

Device malfunction reports from clinical trials

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Number of malfunction reports from clinical trials	2,119	2,966	1,971	2,252	1,320

Note 1: The figures represent the numbers of initial reports that were submitted as case reports, research reports, safety measure reports, and other reports.

Note 2: Electronic report submission has been required since July 1, 2014. Because of the change of the reporting method, the first follow-up reports submitted on or after July 1, 2014 are classified as initial reports even though the actual initial reports had already been filed before the date.

The number of processed cell-related malfunction reports from clinical trials in FY 2018 is shown below.

Number of processed cell-related malfunction reports from clinical trials

	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Number of malfunction reports from clinical trials	0	50	129	196	653

Note:The figures represent the numbers of initial reports that were submitted as case reports, research reports, safety measure reports, and other reports.

3.(3) Registration service for the drug master file

A Drug Master File (DMF) contains information regarding the manufacturing of drug substances submitted for DMF registration by their manufactures (since April 2005).

The number of DMF applications submitted or registered in FY 2018 is shown below.

Number of DMFs submitted and registered

		FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Overall DMF submissions		2,017	2,019	3,163	2,126	1,653
Breakdown	New DMF applications submitted	282	295	259	253	236
	DMF change applications submitted	160	186	190	166	205
	Minor change notifications	1,179	1,189	2,438	1,424	1,068
	Other applications/notifications*	396	349	276	283	144
DMF registered		443	502	449	423	432
Breakdown	New DMFs	282	305	260	258	232
	DMF changes registered	161	197	189	165	200

Note:Including carry-over applications from the previous fiscal year.

**: Other applications/notifications include applications for change, reissuance, and transfer of the registration certificate.*

Table 1. Number of Drugs, etc. Filed and Approved (FY 2014 - FY 2018)

Application Category \ Fiscal Year			Number of products filed					Number of products approved				
			FY 2014	FY 2015	FY 2016	FY 2017	FY 2018	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Drugs, etc.	New drugs	New	115	162	124	143	176	142	109	131	126	126
		Partial change	364	350	349	441	423	362	320	337	389	453
		Total	479	512	473	584	599	504	429	468	515	579
	Generic drugs	New	1,166	905	834	582	838	1,325	635	731	805	620
		Partial change	2,286	2,597	2,329	1,572	1,645	2,122	2,600	2,461	2,291	1,644
		Total	3,452	3,502	3,163	2,154	2,483	3,447	3,235	3,192	3,096	2,264
	BTC/OTC drugs	New	671	523	513	453	577	638	589	450	401	336
		Partial change	211	193	187	171	197	206	163	196	136	116
		Total	882	716	700	624	774	844	752	646	537	452
	In vitro diagnostics	New	89	83	63	73	56	40	80	91	70	60
		Partial change	74	113	86	123	79	69	92	108	117	93
		Total	163	196	149	196	135	109	172	199	187	153
	Quasi-drugs	New	1,666	2,329	1,808	1,585	1,604	1,631	2,322	1,694	1,645	1,491
		Partial change	162	230	254	239	175	148	173	230	246	174
		Total	1,828	2,559	2,062	1,824	1,779	1,779	2,495	1,924	1,891	1,665
	Cosmetics	New	0	0	0	0	0	0	0	0	0	0
		Partial change	0	0	0	0	0	0	0	0	0	0
		Total	0	0	0	0	0	0	0	0	0	0
	Total	New	3,707	4,002	3,342	2,836	3,251	3,776	3,735	3,097	3,047	2,633
		Partial change	3,097	3,483	3,205	2,546	2,519	2,907	3,348	3,332	3,179	2,480
		Total	6,804	7,485	6,547	5,382	5,770	6,683	7,083	6,429	6,226	5,113

Note 1: The number of product applications filed in FY 2018 and their application categories are as of April 2, 2019. The number of product applications and their application categories may be changed if the categories are revised after filing of the application.

Note 2: The number of products filed was calculated based on the date of application.

Note 3: The figures in "New drugs" represent the number of products, including products classified as "administrative review category." The same applies to the other categories.

Table 2. Number of Medical Devices Filed and Approved (FY 2014 - FY 2018)

Application Category \ Fiscal Year		Number of products filed					Number of products approved				
		FY 2014	FY 2015	FY 2016	FY 2017	FY 2018	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
New medical devices	New	37	14	11	20	16	24	22	10	13	18
	Partial change	63	16	18	17	23	43	34	16	14	20
	Total	100	30	29	37	39	67	56	26	27	38
Improved medical devices (with clinical data) (in or after FY 2009)	New	36	23	43	46	24	27	43	38	36	41
	Partial change	9	4	6	14	14	8	10	6	6	11
	Total	45	27	49	60	38	35	53	44	42	52
Improved medical devices (without clinical data) (in or after FY 2009)	New	194	144	155	103	154	156	151	154	153	153
	Partial change	68	74	62	63	51	57	89	71	62	63
	Total	262	218	217	166	205	213	240	225	215	216
Generic medical devices (in or after FY 2009)	New	418	319	355	373	333	396	351	329	344	332
	Partial change	544	469	574	491	477	521	517	496	524	467
	Total	962	788	929	864	810	917	868	825	868	799
Medical devices (with clinical study data) (FY 2005 - FY 2008)	New	-	-	-	-	-	0	0	0	0	0
	Partial change	-	-	-	-	-	0	0	0	0	0
	Total	-	-	-	-	-	0	0	0	0	0
Medical devices (without approval standards, without clinical study data) (FY 2005 - FY 2008)	New	-	-	-	-	-	0	0	0	1	0
	Partial change	-	-	-	-	-	3	3	0	0	0
	Total	-	-	-	-	-	3	3	0	1	0
Medical devices (with approval standards, without clinical study data) (FY 2005 - FY 2008)	New	-	-	-	-	-	0	0	0	0	0
	Partial change	-	-	-	-	-	0	0	0	0	0
	Total	-	-	-	-	-	0	0	0	0	0
Controlled medical devices (without approval standards or certification standards, without clinical study data) (FY 2005 - FY 2008)	New	-	-	-	-	-	0	0	0	0	0
	Partial change	-	-	-	-	-	0	0	0	0	0
	Total	-	-	-	-	-	0	0	0	0	0
Improved medical devices (in or before FY 2004)	New	-	-	-	-	-	0	0	0	0	0
	Partial change	-	-	-	-	-	0	0	0	0	0
	Total	-	-	-	-	-	0	0	0	0	0
Improved medical devices (humans, animals, etc.) (in or before FY 2004)	New	-	-	-	-	-	0	0	0	0	0
	Partial change	-	-	-	-	-	0	0	0	0	0
	Total	-	-	-	-	-	0	0	0	0	0
Generic medical devices (in or before FY 2004)	New	-	-	-	-	-	0	0	0	0	0
	Partial change	-	-	-	-	-	0	0	0	0	0
	Total	-	-	-	-	-	0	0	0	0	0
Total	New	685	500	564	542	527	603	567	531	547	544
	Partial change	684	563	660	585	565	632	653	589	606	561
	Total	1,369	1,063	1,224	1,127	1,092	1,235	1,220	1,120	1,153	1,105

Note 1: The number of product applications filed in FY 2018 and their application categories are as of April 2, 2019. The number of product applications and their application categories may be changed if the categories are revised after filing of the application.

Note 2: The number of products filed was calculated based on the date of application.

Note 3: The number of products approved was calculated according to the categories at the time of approval based on fiscal year of application.

Table 3. Number of Regenerative Medical Products Filed and Approved (FY 2014 - FY2018)

Application Category \ Fiscal Year		Number of products filed					Number of products approved				
		FY 2014	FY 2015	FY 2016	FY 2017	FY 2018	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Regenerative Medical Products	New	2	0	0	1	6	0	2	0	0	3
	Partial change	0	3	2	2	3	0	2	1	3	2
	Total	2	3	2	3	9	0	4	1	3	5

Note 1: The number of products filed was calculated based on the date of application.

Note 2: The figures in the table represent the number of products, including products classified as "administrative review category."

Table 4. New Drugs Approved in FY 2018

Review Category	Approval Date	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Active Ingredient (underlined: new active ingredient)	Notes
1	May 25, 2018	1	Xeljanz Tablets 5 mg (Pfizer Japan Inc.)	Change	Tofacitinib citrate	A drug with a new additional indication and a new dosage for the remission induction and maintenance therapy of moderate to severe ulcerative colitis (for use only in patients who have not sufficiently responded to conventional treatments).
1	Jul. 2, 2018	2	Entyvio for I.V. Infusion 300 mg (Takeda Pharmaceutical Company Limited)	Approval	Vedolizumab (genetical recombination)	A drug with a new active ingredient indicated for the treatment and maintenance therapy of moderate to severe ulcerative colitis (for use only in patients who have not sufficiently responded to conventional treatments).
1	Aug. 21, 2018	3	Linzess Tablets 0.25 mg (Astellas Pharma Inc.)	Change	Linaclotide	A drug with a new additional indication for the treatment of chronic constipation (excluding constipation due to organic diseases).
1	Sep. 21, 2018	4	Movicol Combination Oral Solution (EA Pharma Co., Ltd.)	Approval	Macrogol 4000/Sodium chloride/Sodium bicarbonate/Potassium chloride	A new combination drug indicated for the treatment of chronic constipation (excluding constipation due to organic diseases).
1	Sep. 21, 2018	5	Lagnos NF Jelly for Oral Administration Divided Pack 12 g (Sanwa Kagaku Kenkyusho Co., Ltd.)	Approval	Lactulose crystal	A drug with a new additional indication and a new dosage in an additional dosage form indicated for the treatment of chronic constipation (excluding constipation due to organic diseases).
1	Feb. 21, 2019	6	Imuran Tablets 50 mg (Aspen Japan K.K.) Azanin Tablets 50 mg (Mitsubishi Tanabe Pharma Corporation)	Change Change	Azathioprine	Drugs with a new additional indication for the treatment of autoimmune hepatitis. [Public knowledge-based application after preliminary assessment by the Pharmaceutical Affairs and Food Sanitation Council (PAFSC)]
1	Mar. 26, 2019	7	Ferinject Solution for Injection/Infusion 500 mg (Zeria Pharmaceutical Co., Ltd.)	Approval	Ferric carboxymaltose	A drug with a new active ingredient indicated for the treatment of iron-deficiency anemia.
1	Mar. 26, 2019	8	Aselend Injection 100 μg (Fujimoto Pharmaceutical Corporation)	Approval	Sodium selenite	A drug with a new active ingredient indicated for the treatment of hyposelenemia.
2	Jul. 2, 2018	9	Trerief Tablets 25 mg Trerief OD Tablets 25 mg (Sumitomo Dainippon Pharma Co., Ltd.)	Change Change	Zonisamide	Drugs with a new additional indication and a new dosage for the treatment of parkinsonism in patients with dementia with Lewy bodies (in the cases where parkinsonism persists after using levodopa-containing products).
2	Nov. 21, 2018	10	Praluent 75 mg solution for injection in pre-filled pen Praluent 150 mg solution for injection in pre-filled pen (Sanofi K.K.)	Change Change	Alirocumab (genetical recombination)	Drugs with a new additional indication and a new dosage for the treatment of familial hypercholesterolemia and hypercholesterolemia (for use only in patients who are at higher risk of developing cardiovascular events, and in whom treatment with HMG-CoA reductase inhibitors is not suitable).
2	Jan. 8, 2019	11	Minnebro Tablets 1.25 mg Minnebro Tablets 2.5 mg Minnebro Tablets 5 mg (Daiichi Sankyo Company, Limited)	Approval Approval Approval	Esaxerenone	Drugs with a new active ingredient indicated for the treatment of hypertension.
2	Jan. 8, 2019	12	Demser Capsules 250 mg (Ono Pharmaceutical Co., Ltd.)	Approval	Metirosine	A drug with a new active ingredient indicated for the improvement of the status of excessive catecholamine secretion in patients with pheochromocytoma. [Orphan drug]
2	Jan. 8, 2019	13	(1) Bisono Tape 2 mg (2) Bisono Tape 4 mg (3) Bisono Tape 8 mg (Toa Eiyo Ltd.)	Approval Change Change	Bisoprolol	(1) A drug with a new indication and a new dosage in an additional dosage form indicated for the treatment of tachycardiac atrial fibrillation. (2)(3) Drugs with a new additional indication, a new dosage, and other characteristics indicated for the treatment of tachycardiac atrial fibrillation.
2	Mar. 26, 2019	14	Rosuzet Combination Tablets LD Rosuzet Combination Tablets HD (MSD K.K.)	Approval Approval	Ezetimibe/Rosuvastatin calcium	New combination drugs indicated for the treatment of hypercholesterolemia and familial hypercholesterolemia.

Review Category	Approval Date	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Active Ingredient (underlined: new active ingredient)	Notes
2	Mar. 26, 2019	15	Onoact for Intravenous Infusion 50 mg Onoact for Intravenous Infusion 150 mg (Ono Pharmaceutical Co., Ltd.)	Change Change	Landiolol hydrochloride	Drugs with new additional indications and a new dosage for the following life-threatening cardiac arrhythmia in refractory and urgent cases: ventricular fibrillation and hemodynamically unstable ventricular tachycardia. [Orphan drug]
2	Mar. 26, 2019	16	Vyndaqel Capsules 20 mg (Pfizer Japan Inc.)	Change	Tafamidis meglumine	A drug with a new additional indication and a new dosage for the treatment of transthyretin cardiac amyloidosis (wild-type and hereditary). [SAKIGAKE designation, Orphan drug]
3-1	May 25, 2018	17	Botox for Injection 50 Units Botox for Injection 100 Units (GlaxoSmithKline K.K.)	Change Change	Botulinum toxin type A	Drugs with a new additional indication and a new dosage for the treatment of spasmodic dysphonia.
3-1	Sep. 21, 2018	18	Lora-Pita Intravenous Injection 2 mg (Pfizer Japan Inc.)	Approval	Lorazepam	A drug with a new route of administration indicated for the treatment of status epilepticus.
3-1	Jan. 8, 2019	19	Selincro Tablets 10 mg (Otsuka Pharmaceutical Co., Ltd.)	Approval	Nalmefene hydrochloride hydrate	A drug with a new active ingredient indicated to reduce alcohol consumption in patients with alcohol dependence.
3-1	Jan. 8, 2019	20	(1) Vimpat Dry Syrup 10% (2) Vimpat Tablets 50 mg (3) Vimpat Tablets 100 mg (4) Vimpat for I.V. Infusion 200 mg (UCB Japan Co., Ltd.)	Approval Change Change Approval	Lacosamide	(1)-(3) A drug in an additional dosage form and drugs with a new additional pediatric dosage indicated for the treatment of partial seizures (including secondary generalized seizures) in patients with epilepsy. (4) A drug with a new route of administration indicated for the treatment of partial seizures (including secondary generalized seizures) in patients with epilepsy. It is used as an alternative therapy for lacosamide oral formulation in patients who are temporarily unable to be administered orally.
3-1	Jan. 8, 2019	21	Tarlige Tablets 2.5 mg Tarlige Tablets 5 mg Tarlige Tablets 10 mg Tarlige Tablets 15 mg (Daiichi Sankyo Company, Limited)	Approval Approval Approval Approval	Mirogabalin besilate	Drugs with a new active ingredient indicated for the treatment of peripheral neuropathic pain.
3-1	Feb. 21, 2019	22	Taurine powder 98% "Taisho" (Taisho Pharmaceutical Co., Ltd.)	Change	Taurine	A drug with a new additional indication and a new dosage for the inhibition of stroke-like episodes in patients with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS). [Orphan drug]
3-1	Mar. 26, 2019	23	Vyvanse Capsules 20 mg Vyvanse Capsules 30 mg (Shionogi & Co., Ltd.)	Approval Approval	Lisdexamfetamine mesilate	Drugs with a new active ingredient indicated for the treatment of pediatric attention deficit/hyperactivity disorder (AD/HD).
3-1	Mar. 26, 2019	24	Privigen 10% I.V. Drip Infusion 5 g/50 mL Privigen 10% I.V. Drip Infusion 10 g/100 mL Privigen 10% I.V. Drip Infusion 20 g/200 mL (CSL Behring K.K.)	Approval Approval Approval	pH4-treated acidic normal human immunoglobulin	Drugs with a new active ingredient indicated for the improvement of muscle weakness in chronic inflammatory demyelinating polyneuropathy and for inhibiting progression of motor disability due to chronic inflammatory demyelinating polyneuropathy (in the cases where patients show an improvement in their acute phase treatment).
3-1	Mar. 26, 2019	25	Hizentra 20% S.C. Injection 1 g/5 mL Hizentra 20% S.C. Injection 2 g/10 mL Hizentra 20% S.C. Injection 4 g/20 mL (CSL Behring K.K.)	Change Change Change	pH4-treated acidic normal human immunoglobulin (subcutaneous injection)	Drugs with a new additional indication and a new dosage for inhibiting progression of motor disability due to chronic inflammatory demyelinating polyneuropathy (in the cases where patients show an improvement in their acute phase treatment).
3-2	Jul. 2, 2018	26	Fentos Tape 0.5 mg Fentos Tape 1 mg Fentos Tape 2 mg Fentos Tape 4 mg Fentos Tape 6 mg Fentos Tape 8 mg (Hisamitsu Pharmaceutical Co., Inc.)	Approval Change Change Change Change Change	Fentanyl citrate	Drugs with a new dosage and in additional dosage form indicated for: (1) analgesia in various types of cancer with moderate to severe pain that cannot be managed with non-opioid analgesics or weak opioid analgesics (for use only in patients who switch from other opioid analgesics); or (2) analgesia in moderate to severe chronic pain (for use only in patients who switch from other opioid analgesics).

Review Category	Approval Date	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Active Ingredient (underlined: new active ingredient)	Notes
3-2	Sep. 21, 2018	27	Eybelis Ophthalmic Solution 0.002% (Santen Pharmaceutical Co., Ltd.)	Approval	Omidenepag isopropyl	A drug with a new active ingredient indicated for the treatment of glaucoma and ocular hypertension.
3-2	Nov. 29, 2018	28	Precedex Intravenous Solution 200 μg "Pfizer" Precedex Intravenous Solution 200 μg/50 mL Syringe "Pfizer" (Pfizer Japan Inc.) Precedex Intravenous Solution 200 μg "Maruishi" Precedex Intravenous Solution 200 μg/50 mL Syringe "Maruishi" (Maruishi Pharmaceutical Co., Ltd.)	Change Change Change Change	Dexmedetomidine hydrochloride	Drugs with a new additional pediatric dosage indicated for sedation during artificial respiration and after weaning in patients in intensive care.
3-2	Mar. 26, 2019	29	Lafenta Tape 1.38 mg Lafenta Tape 2.75 mg Lafenta Tape 5.5 mg Lafenta Tape 8.25 mg Lafenta Tape 11 mg (Nippon Zoki Pharmaceutical Co., Ltd.)	Approval Approval Approval Approval Approval	Fentanyl	Drugs in a new dosage form indicated for analgesia in various types of cancer with moderate to severe pain that cannot be managed with non-opioid analgesics or weak opioid analgesics (for use only in patients who switch from other opioid analgesics).
4	Jul. 2, 2018	30	Dafclir Tablets 200 mg (Astellas Pharma Inc.)	Approval	Fidaxomicin	A drug with a new active ingredient indicated for the treatment of infectious enteritis (including pseudomembranous colitis) caused by *C. difficile*.
4	Jul. 2, 2018	31	Spiramycin Tablets 1.5M IU "Sanofi" (Sanofi K.K.)	Approval	Spiramycin	A drug with a new active ingredient indicated for the prophylaxis of congenital toxoplasmosis. [Orphan drug]
4	(1) Aug. 21, 2018 (2) Aug. 22, 2018	32	(1) Valixa Tablets 450 mg (2) Valixa Dry Syrup 5000 mg (Mitsubishi Tanabe Pharma Corporation)	(1) Change (2) Approval	Valganciclovir hydrochloride	Drugs with a new additional pediatric dosage and a drug in an additional dosage form of dry syrup, indicated for the prevention of cytomegalovirus disease in organ transplant patients (excluding hematopoietic stem cell transplantation). [Public knowledge-based application after PAFSC's preliminary assessment]
4	Sep. 21, 2018	33	Oravi Mucoadhesive Tablets 50 mg (Sosei Co., Ltd.)	Approval	Miconazole	A drug in a new dosage form indicated for the treatment of oropharyngeal candidiasis caused by *Candida*.
4	Jan. 8, 2019	34	Zerbaxa Combination for Intravenous Drip Infusion (MSD K.K.)	Approval	Ceftolozane sulfate/Tazobactam sodium	A new combination drug with new active ingredients indicated for the treatment of cystitis, pyelonephritis, peritonitis, intra-abdominal abscess, cholecystitis, and liver abscess caused by Zerbaxa-sensitive *Streptococcus* spp., *Escherichia coli*, *Citrobacter* spp., *Klebsiella* spp., *Enterobacter* spp., *Proteus* spp., or *Pseudomonas aeruginosa*.
4	Jan. 8, 2019	35	Epclusa Combination Tablets (Gilead Sciences K.K.)	Approval	Sofosbuvir/Velpatasvir	A new combination drug with a new active ingredient indicated for: - Improvement of viremia in patients with chronic hepatitis C or compensated cirrhosis type C who have previously been treated. - Improvement of viremia in patients with decompensated cirrhosis type C. [Priority review]
4	Jan. 8, 2019	36	Rebetol Capsules 200 mg (MSD K.K.)	Change	Ribavirin	A drug with a new additional indication and a new dosage, used in combination with sofosbuvir and velpatasvir, for the improvement of viremia in patients with chronic hepatitis C or compensated cirrhosis type C who have previously been treated. [Expedited review]
4	Feb. 21, 2019	37	Famvir Tab. 250 mg (Asahi Kasei Pharma Corporation)	Change	Famciclovir	A drug with a new dosage indicated for the treatment of herpes simplex.
4	Mar. 26, 2019	38	Foscavir Infusion Solution 24 mg/mL (Clinigen K.K.)	Change	Foscarnet sodium hydrate	A drug with a new additional indication and a new dosage indicated for the treatment of human herpesvirus 6 encephalitis after hematopoietic stem cell transplantation. [Public knowledge-based application after PAFSC's preliminary assessment]

Review Category	Approval Date	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Active Ingredient (underlined: new active ingredient)	Notes
5	Jul. 2, 2018	39	Jemina Tablets (Nobelpharma Co., Ltd.)	Approval	Levonorgestrel/Ethinylestradiol	A new combination drug indicated for the treatment of dysmenorrhea.
5	Sep. 21, 2018	40	Beova Tablets 50 mg (Kyorin Pharmaceutical Co., Ltd.)	Approval	Vibegron	A drug with a new active ingredient indicated for the treatment of urinary urgency, urinary frequency, and urge urinary incontinence associated with overactive bladder.
5	Jan. 8, 2019	41	Relumina Tablets 40 mg (Takeda Pharmaceutical Company Limited)	Approval	Relugolix	A drug with a new active ingredient indicated for the alleviation of menorrhagia, lower abdominal pain, backache, and anemia that are associated with uterine fibroids.
5	Feb. 21, 2019	42	Gonalef for Subcutaneous Injection 75 Gonalef for Subcutaneous Injection 150 Gonalef for Subcutaneous Injection Pen 300 Gonalef for Subcutaneous Injection Pen 450 Gonalef for Subcutaneous Injection Pen 900 (Merck Serono Co., Ltd.)	Change Change Change Change Change	Follitropin alfa (genetical recombination)	Drugs with changes in dosage regimen indicated for the induction of spermatogenesis in male hypogonadotropic hypogonadism (MHH) and with a new additional indication and a new dosage for controlled ovarian stimulation in assisted reproductive technology.
5	Mar. 26, 2019	43	Enoras Liquid for Enteral Use (EN Otsuka Pharmaceutical Co., Ltd.)	Approval	N/A for this combination drug	A combination prescription drug with similar formulations indicated for tube feeding, especially for patients with long-term oral feeding difficulties. It also generally can be used for nutrient retention for postoperative patients.
6-1	May 25, 2018	44	Nucala for s.c. Injection 100 mg (GlaxoSmithKline K.K.)	Change	Mepolizumab (genetical recombination)	A drug with a new additional indication and a new dosage for the treatment of eosinophilic granulomatosis with polyangiitis in patients who have not responded sufficiently to conventional treatments. [Orphan drug]
6-1	Jul. 2, 2018	45	Ilaris for S.C. Injection 150 mg Ilaris Solution for S.C. Injection 150 mg (Novartis Pharma K.K.)	Change Change	Canakinumab (genetical recombination)	Drugs with a new additional indication and a new dosage for the treatment of systemic juvenile idiopathic arthritis in patients who have not responded sufficiently to conventional treatments. [Orphan drug]
6-1	Aug. 21, 2018	46	Taltz 80 mg Syringe for SC Injection Taltz 80 mg Auto-Injector for SC Injection (Eli Lilly Japan K.K.)	Change Change	Ixekizumab (genetical recombination)	Drugs with a new dosage indicated for the treatment of plaque psoriasis, psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis in patients who have not responded sufficiently to conventional therapies.
6-1	Sep. 21, 2018	47	Firazyr Subcutaneous Injection 30 mg Syringe (Shire Japan KK)	Approval	Icatibant acetate	A drug with a new active ingredient indicated for the treatment of acute attacks of hereditary angioedema. [Orphan drug]
6-1	Nov. 21, 2018	48	Tremfya Subcutaneous Injection 100 mg Syringe (Janssen Pharmaceutical K.K.)	Change	Guselkumab (genetical recombination)	A drug with a new additional indication for the treatment of palmoplantar pustulosis in patients who have not responded sufficiently to conventional therapies.
6-1	Dec. 21, 2018	49	Cosentyx for S.C. Injection 150 mg Syringe Cosentyx for S.C. Injection 150 mg Pen (Novartis Pharma K.K.)	Change Change	Secukinumab (genetical recombination)	Drugs with a new additional indication and a new dosage for the treatment of ankylosing spondylitis in patients who have not responded sufficiently to conventional treatments.
6-1	Feb. 21, 2019	50	Humira 40 mg for S.C. Injection Syringe 0.4 mL Humira 80 mg for S.C. Injection Syringe 0.8 mL Humira 40 mg for S.C. Injection in pre-filled pen 0.4 mL Humira 80 mg for S.C. Injection in pre-filled pen 0.8 mL (AbbVie GK)	Change Change Change Change	Adalimumab (genetical recombination)	Drugs with a new additional indication and a new dosage for the treatment of hidradenitis suppurativa. [Orphan drug]
6-1	Mar. 26, 2019	51	Skyrizi 75 mg for S.C. Injection Syringe 0.83 mL (AbbVie GK)	Approval	Risankizumab (genetical recombination)	A drug with a new active ingredient indicated for the treatment of plaque psoriasis, psoriatic arthritis, pustular psoriasis and erythrodermic psoriasis in patients who have not responded sufficiently to conventional therapies.

Review Category	Approval Date	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Active Ingredient (underlined: new active ingredient)	Notes
6-1	Mar. 26, 2019	52	Trelegy 100 Ellipta 14 doses Trelegy 100 Ellipta 30 doses (GlaxoSmithKline K.K.)	Approval Approval	Fluticasone furoate/Umeclidinium bromide/Vilanterol trifenatate	New combination drugs indicated for the relief of symptoms in patients with chronic obstructive pulmonary disease (chronic bronchitis, emphysema) (who require a combination therapy with an inhaled corticosteroid, a long-acting inhaled anticholinergic agent and a long-acting beta-2 agonist).
6-1	Mar. 26, 2019	53	Smyraf Tablets 50 mg Smyraf Tablets 100 mg (Astellas Pharma Inc.)	Approval Approval	Peficitinib hydrobromide	Drugs with a new active ingredient indicated for the treatment of rheumatoid arthritis (including prevention of structural joint damage) in patients who have not responded sufficiently to conventional treatments.
6-1	Mar. 26, 2019	54	Dupixent 300 mg Syringe for S.C. Injection (Sanofi K.K.)	Change	Dupilumab (genetical recombination)	A drug with a new additional indication, a new dosage and other characteristics for the treatment of bronchial asthma (for use only in patients with severe or intractable bronchial asthma whose asthmatic responses are uncontrollable with conventional therapies).
6-1	Mar. 26, 2019	55	Actemra 80 mg for Intravenous Infusion Actemra 200 mg for Intravenous Infusion Actemra 400 mg for Intravenous Infusion (Chugai Pharmaceutical Co., Ltd.)	Change Change Change	Tocilizumab (genetical recombination)	Drugs with a new additional indication and a new dosage for the treatment of cytokine release syndrome induced by tumor-specific T-cell infusion therapy. [Expedited review]
6-1	Mar. 26, 2019	56	Rheumatrex Capsules 2 mg (Pfizer Japan Inc.)	Change	Methotrexate	A drug with new additional indications and a new dosage for the treatment of plaque psoriasis in patients who have not responded sufficiently to topical therapy, or psoriatic arthritis, pustular psoriasis and erythrodermic psoriasis . [Public knowledge-based application after PAFSC's preliminary assessment]
6-2	Sep. 21, 2018	57	Tradiance Combination Tablets AP Tradiance Combination Tablets BP (Nippon Boehringer Ingelheim Co., Ltd.)	Approval Approval	Empagliflozin/Linagliptin	New combination drugs indicated for the treatment of type 2 diabetes mellitus (only when a concomitant use of empagliflozin with linagliptin is deemed appropriate).
6-2	Sep. 21, 2018	58	Metoana Combination Tablets LD Metoana Combination Tablets HD (Sanwa Kagaku Kenkyusho Co., Ltd.)	Approval Approval	Anagliptin/Metformin hydrochloride	New combination drugs indicated for the treatment of type 2 diabetes mellitus (only when a concomitant use of anagliptin with metformin hydrochloride is deemed appropriate).
6-2	Dec. 21, 2018	59	Suglat Tablets 25 mg Suglat Tablets 50 mg (Astellas Pharma Inc.)	Change Change	Ipragliflozin L-proline	Drugs with a new additional indication and a new dosage for the treatment of type 1 diabetes mellitus.
6-2	Jan. 8, 2019	60	Evenity Subcutaneous Injection 105 mg Syringe (Amgen Astellas BioPharma K.K.)	Approval	Romosozumab (genetical recombination)	A drug with a new active ingredient indicated for the treatment of osteoporosis with a high risk of fracture.
6-2	Mar. 26, 2019	61	Revcovi 2.4 mg for Intramuscular Injection (Teijin Pharma Limited)	Approval	Elapegademase (genetical recombination)	A drug with a new active ingredient indicated for the treatment of adenosine deaminase deficiency. [Orphan drug]
6-2	Mar. 26, 2019	62	Forxiga 5 mg Tablets Forxiga 10 mg Tablets (AstraZeneca K.K.)	Change Change	Dapagliflozin propylene glycolate hydrate	Drugs with a new additional indication and a new dosage for the treatment of type 1 diabetes mellitus.
In vivo diagnostics	Jul. 2, 2018	63	Diagnogreen for Injection 25 mg (Daiichi Sankyo Company, Limited)	Change	Indocyanine green	A drug with a new additional indication and a new dosage for the evaluation of vascular and tissue blood flow. [Public knowledge-based application after PAFSC's preliminary assessment]
In vivo diagnostics	Sep. 21, 2018	64	Dobutrex Injection 100 mg Dobutrex Kit for Intravenous Infusion 200 mg Dobutrex Kit for Intravenous Infusion 600 mg (Kyowa Pharmaceutical Industry Co., Ltd.) Dobutamine Injection 100 mg [Pfizer] Dobutamine Injection 200 mg Kit [Pfizer] Dobutamine Injection 600 mg Kit [Pfizer] (Mylan Seiyaku Ltd.)	Change Change Change Change Change Change	Dobutamine hydrochloride	Drugs with a new additional indication and a new dosage for stress echocardiography. [Public knowledge-based application after PAFSC's preliminary assessment]

Review Category	Approval Date	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Active Ingredient (underlined: new active ingredient)	Notes
Oncology drugs	May 25, 2018	65	Opdivo Intravenous Infusion 20 mg Opdivo Intravenous Infusion 100 mg (Ono Pharmaceutical Co., Ltd.)	Change Change	Nivolumab (genetical recombination)	Drugs with a new dosage indicated for the treatment of unresectable melanoma. [Orphan drug]
Oncology drugs	May 25, 2018	66	Yervoy Injection 50 mg (Bristol-Myers Squibb K.K.)	Change	Ipilimumab (genetical recombination)	A drug with a new dosage indicated for the treatment of unresectable melanoma. [Orphan drug]
Oncology drugs	Jul. 2, 2018	67	Imfinzi Injection 120 mg Imfinzi Injection 500 mg (AstraZeneca K.K.)	Approval Approval	Durvalumab (genetical recombination)	Drugs with a new active ingredient indicated for the maintenance treatment of locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiation therapy.
Oncology drugs	Jul. 2, 2018	68	Gazyva Intravenous Infusion 1000 mg (Chugai Pharmaceutical Co., Ltd.)	Approval	Obinutuzumab (genetical recombination)	A drug with a new active ingredient indicated for the treatment of CD20-positive follicular lymphoma.
Oncology drugs	Jul. 2, 2018	69	Lynparza Tablets 100 mg Lynparza Tablets 150 mg (AstraZeneca K.K.)	Change Change	Olaparib	Drugs with a new additional indication for the treatment of unresectable or recurrent BRCA mutation-positive and HER2-negative breast cancer in patients who have previously been treated with chemotherapy. [Orphan drug]
Oncology drugs	Jul. 2, 2018	70	Treakisym Injection 25 mg Treakisym Injection 100 mg (SymBio Pharmaceuticals Limited)	Change Change	Bendamustine hydrochloride	Drugs with a new dosage indicated for the treatment of low-grade B-cell non-Hodgkin's lymphoma.
Oncology drugs	Jul. 2, 2018	71	Tafinlar Capsules 50 mg Tafinlar Capsules 75 mg (Novartis Pharma K.K.)	Change Change	Dabrafenib mesilate	Drugs with a new additional indication and a new dosage indicated for the treatment of BRAF mutation-positive melanoma. [Orphan drug]
Oncology drugs	Jul. 2, 2018	72	Mekinist Tablets 0.5 mg Mekinist Tablets 2 mg (Novartis Pharma K.K.)	Change Change	Trametinib dimethyl sulfoxide	Drugs with a new additional indication and a new dosage indicated for the treatment of BRAF mutation-positive melanoma. [Orphan drug]
Oncology drugs	Jul. 2, 2018	73	Imbruvica Capsules 140 mg (Janssen Pharmaceutical K.K.)	Change	Ibrutinib	A drug with a new additional indication for the treatment of chronic lymphocytic leukemia (including small lymphocytic lymphoma). [Orphan drug]
Oncology drugs	Aug. 21, 2018	74	Opdivo Intravenous Infusion 20 mg Opdivo Intravenous Infusion 100 mg (Ono Pharmaceutical Co., Ltd.)	Change Change	Nivolumab (genetical recombination)	(1) Drugs with new indications and a new dosage for the treatment of unresectable or recurrent malignant pleural mesothelioma and melanoma that have progressed after chemotherapy. [Orphan drug] (2) Drugs with a new dosage indicated for the treatment of melanoma, unresectable or recurrent non-small cell lung cancer, unresectable or metastatic renal cell carcinoma, relapsed or refractory classical Hodgkin lymphoma, recurrent or metastatic head and neck cancer, unresectable or recurrent gastric cancer that has progressed after chemotherapy, and (3) unresectable or metastatic renal cell carcinoma. [(3) Priority review]
Oncology drugs	Aug. 21, 2018	75	Yervoy Injection 50 mg (Bristol-Myers Squibb K.K.)	Change	Ipilimumab (genetical recombination)	A drug with a new indication and a new dosage for the treatment of unresectable or metastatic renal cell carcinoma. [Priority review]
Oncology drugs	Aug. 21, 2018	76	Tagrisso Tablets 40 mg Tagrisso Tablets 80 mg (AstraZeneca K.K.)	Change Change	Osimertinib mesilate	Drugs with a new indication for the treatment of inoperable or recurrent epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer. [Priority review]
Oncology drugs	Aug. 21, 2018	77	Poteligeo Injection 20 mg (Kyowa Hakko Kirin Co., Ltd.)	Change	Mogamulizumab (genetical recombination)	A drug with new indications and a new dosage for the treatment of relapsed or refractory cutaneous T-cell lymphoma. [Orphan drug]

Review Category	Approval Date	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Active Ingredient (underlined: new active ingredient)	Notes
Oncology drugs	Sep. 21, 2018	78	Verzenio Tablets 50 mg Verzenio Tablets 100 mg Verzenio Tablets 150 mg (Eli Lilly Japan K.K.)	Approval Approval Approval	Abemaciclib	Drugs with a new active ingredient indicated for the treatment of hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative inoperable or recurrent breast cancer.
Oncology drugs	Sep. 21, 2018	79	Blincyto for Drip Infusion 35 µg (Amgen Astellas BioPharma K.K.)	Approval	Blinatumomab (genetical recombination)	A drug with a new active ingredient indicated for the treatment of relapsed or refractory B-cell acute lymphoblastic leukemia. [Orphan drug]
Oncology drugs	Sep. 21, 2018	80	Lorbrena Tablets 25 mg Lorbrena Tablets 100 mg (Pfizer Japan Inc.)	Approval Approval	Lorlatinib	Drugs with a new active ingredient indicated for the treatment of unresectable or recurrent anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer with resistance or intolerance to ALK tyrosine kinase inhibitors. [Conditional early approval]
Oncology drugs	Sep. 21, 2018	81	Xospata Tablets 40 mg (Astellas Pharma Inc.)	Approval	Gilteritinib fumarate	A drug with a new active ingredient indicated for the treatment of relapsed or refractory FLT3 mutation-positive acute myeloid leukemia. [Orphan drug, SAKIGAKE designation]
Oncology drugs	Sep. 21, 2018	82	Opdivo Intravenous Infusion 240 mg (Ono Pharmaceutical Co., Ltd.)	Approval	Nivolumab (genetical recombination)	(1) A drug with new indications and a new dosage in an additional dosage form for the treatment of unresectable or recurrent malignant pleural mesothelioma and melanoma that have progressed after chemotherapy. [Orphan drug] (2) A drug with a new dosage in an additional dosage form indicated for the treatment of melanoma, unresectable or recurrent non-small cell lung cancer, unresectable or metastatic renal cell carcinoma, relapsed or refractory classical Hodgkin lymphoma, recurrent or metastatic head and neck cancer, unresectable or recurrent gastric cancer that has progressed after chemotherapy, and (3) unresectable or metastatic renal cell carcinoma. [(3) Priority review]
Oncology drugs	Sep. 21, 2018	83	Adcetris for Intravenous Drip Infusion 50 mg (Takeda Pharmaceutical Company Limited)	Change	Brentuximab vedotin (genetical recombination)	A drug with a new indication and a new dosage for the treatment of CD30-positive Hodgkin's lymphoma [Orphan drug]
Oncology drugs	Sep. 21, 2018	84	Elplat I.V. Infusion Solution 50 mg Elplat I.V. Infusion Solution 100 mg Elplat I.V. Infusion Solution 200 mg (Yakult Honsha Co., Ltd.) Oxaliplatin i.v. Infusion 50 mg "Sawai" Oxaliplatin i.v. Infusion 100 mg "Sawai" Oxaliplatin i.v. Infusion 200 mg "Sawai" (Sawai Pharmaceutical Co., Ltd.) Oxaliplatin I.V. Infusion Solution 50 mg "NK" Oxaliplatin I.V. Infusion Solution 100 mg "NK" Oxaliplatin I.V. Infusion Solution 200 mg "NK" (Nippon Kayaku Co., Ltd.) Oxaliplatin I.V. Infusion 50 mg "Nipro" Oxaliplatin I.V. Infusion 100 mg "Nipro" Oxaliplatin I.V. Infusion 200 mg "Nipro" (Nipro Corporation) Oxaliplatin I.V. Drip Infusion 50 mg "DSEP" Oxaliplatin I.V. Drip Infusion 100 mg "DSEP" Oxaliplatin I.V. Drip Infusion 200 mg "DSEP" (Daiichi Sankyo Espha Co., Ltd.)	Change Change Change Change Change Change Change Change Change Change Change Change Change Change Change	Oxaliplatin	Drugs with a new indication and a new dosage for the treatment of small intestine cancer. [Public knowledge-based application after PAFSC's preliminary assessment]

Review Category	Approval Date	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Active Ingredient (underlined: new active ingredient)	Notes
Oncology drugs	Sep. 21, 2018	85	(1) Isovorin Injection 25 mg Isovorin Injection 100 mg (Pfizer Japan Inc.) (2) Levofolinate for I.V. Drip Infusion 25 "Ohara" Levofolinate for I.V. Drip Infusion 100 "Ohara" (Ohara Pharmaceutical Co., Ltd.) (3) Levofolinate for I.V. Infusion 25 mg “Yakult” Levofolinate for I.V. Infusion 100 mg “Yakult” (Yakult Honsha Co., Ltd.) (4) Levofolinate for I.V. Infusion 25 mg "NK" Levofolinate for I.V. Infusion100 mg "NK" (Takata Pharmaceutical Co.,Ltd.) (5) Levofolinate for I.V. Infusion 25 mg "NP" Levofolinate for I.V. Infusion 100 mg "NP" (Nipro Corporation)	Change Change Change Change Change Change Change Change Change Change	Except (2): Levofolinate calcium (2): Calcium levofolinate hydrate	Drugs with a new indication and a new dosage for the treatment of small intestine cancer. [Public knowledge-based application after PAFSC's preliminary assessment]
Oncology drugs	Sep. 21, 2018	86	5-FU Injection 250 mg 5-FU Injection 1000 mg (Kyowa Hakko Kirin Co., Ltd.)	Change Change	Fluorouracil	Drugs with a new indication and a new dosage for the treatment of small intestine cancer. [Public knowledge-based application after PAFSC's preliminary assessment]
Oncology drugs	Sep. 21, 2018	87	Busulfex Injection 60 mg (Otsuka Pharmaceutical Co., Ltd.)	Change	Busulfan	A drug with a new additional once-daily dosage indicated for a conditioning regimen prior to allogeneic hematopoietic stem cell transplantation, and autologous hematopoietic stem cell transplantation for Ewing's sarcoma (ES) family tumors and neuroblastoma. [Public knowledge-based application after PAFSC's preliminary assessment]
Oncology drugs	Oct. 10, 2018	88	Perjeta Intravenous Infusion 420 mg/14 mL (Chugai Pharmaceutical Co., Ltd.)	Change	Pertuzumab (genetical recombination)	A drug with a new indication for the treatment of HER2-positive breast cancer.
Oncology drugs	Dec. 21, 2018	89	Keytruda Injection 100 mg Keytruda Injection 20 mg (MSD K.K.)	Change Change	Pembrolizumab (genetical recombination)	Drugs with new indications and a new dosage for the treatment of: (1) advanced or recurrent microsatellite instability-high (MSI-High) solid tumors that have progressed after cancer chemotherapy (for use only if refractory or intolerant to standard therapies), (2) melanoma, and (3) unresectable advanced or recurrent non-small cell lung cancer. [(1) Conditional early approval, (2) Orphan drug, (3) Priority review]
Oncology drugs	Dec. 21, 2018	90	Tecentriq Intravenous Infusion 1200 mg (Chugai Pharmaceutical Co., Ltd.)	Change	Atezolizumab (genetical recombination)	A drug with a new dosage indicated for the treatment of unresectable advanced or recurrent non-small-cell lung cancer. [Priority review]
Oncology drugs	Jan. 8, 2019	91	Braftovi Capsules 50 mg (Ono Pharmaceutical Co., Ltd.)	Approval	Encorafenib	A drug with a new active ingredient indicated for the treatment of unresectable melanoma with BRAF gene mutation. [Orphan drug]
Oncology drugs	Jan. 8, 2019	92	Mektovi Tablets 15 mg (Ono Pharmaceutical Co., Ltd.)	Approval	Binimetinib	A drug with a new active ingredient indicated for the treatment of unresectable melanoma with BRAF gene mutation. [Orphan drug]
Oncology drugs	Jan. 8, 2019	93	Vizimpro Tablets 15 mg Vizimpro Tablets 45 mg (Pfizer Japan Inc.)	Approval Approval	Dacomitinib hydrate	Drugs with a new active ingredient indicated for the treatment of inoperable or recurrent non-small cell lung cancer with EGFR gene mutation. [Priority review]
Oncology drugs	Jan. 8, 2019	94	Gonax 80 mg for Subcutaneous Injection Gonax 120 mg for Subcutaneous Injection Gonax 240 mg for Subcutaneous Injection (Astellas Pharma Inc.)	Change Change Approval	Degarelix acetate	Drugs with a new dosage and a drug in an additional dosage form indicated for the treatment of prostate cancer.

Review Category	Approval Date	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Active Ingredient (underlined: new active ingredient)	Notes
Oncology drugs	Feb. 21, 2019	95	Zykadia Capsules 150 mg (Novartis Pharma K.K.)	Change	Ceritinib	A drug with a new dosage indicated for the treatment of unresectable advanced/relapsed *ALK* fusion gene-positive non-small-cell lung cancer.
Oncology drugs	Feb. 21, 2019	96	Temodal Capsules 20 mg Temodal Capsules 100 mg Temodal Infusion 100 mg (MSD K.K.) Temozolomide Tab. 20 mg “NK” Temozolomide Tab. 100 mg “NK” (Nippon Kayaku Co., Ltd.)	Change Change Change Change Change	Temozolomide	Drugs with a new additional indication and a new dosage for the treatment of relapsed or refractory Ewing's sarcoma. [Public knowledge-based application after PAFSC's preliminary assessment]
Oncology drugs	Mar. 26, 2019	97	Erleada Tablets 60 mg (Janssen Pharmaceutical K.K.)	Approval	Apalutamide	A drug with a new active ingredient indicated for the treatment of non-metastatic, castration-resistant prostate cancer.
Oncology drugs	Mar. 26, 2019	98	Rethio 100 mg for Intravenous Infusion (Sumitomo Dainippon Pharma Co., Ltd.)	Approval	Thiotepa	A drug with a new active ingredient indicated for the treatment of solid tumors in pediatric patients prior to autologous hematopoietic stem-cell transplantation. [Expedited review]
Oncology drugs	Mar. 26, 2019	99	Rituxan Intravenous Infusion 100 mg Rituxan Intravenous Infusion 500 mg (Zenyaku Kogyo Co., Ltd.)	Change Change	Rituximab (genetical recombination)	Drugs with a new additional indication and a new dosage for the treatment of CD20-positive chronic lymphocytic leukemia. [Orphan drug]
Oncology drugs	Mar. 26, 2019	100	Vepesid Injection 100 mg (Bristol-Myers Squibb K.K.) Lastet Inj. 100 mg/5 mL (Nippon Kayaku Co., Ltd.) Etoposide Intravenous Infusion 100 mg "Sandoz" (Sandoz K.K.) Etoposide Intravenous Infusion 100 mg "Taiyo" (Teva Takeda Pharma Ltd.) Etoposide Intravenous Infusion 100 mg "SN" (Shiono Chemical Co., Ltd.)	Change Change Change Change Change	Etoposide	Drugs with other characteristics indicated for the treatment prior to tumor-specific T-cell infusion therapy. [Expedited review]
Oncology drugs	Mar. 26, 2019	101	Fludara 50 mg for Intravenous Infusion (Sanofi K.K.)	Change	Fludarabine phosphate	A drug with other characteristics indicated for the treatment prior to tumor-specific T-cell infusion therapy. [Expedited review]
Oncology drugs	Mar. 26, 2019	102	Cylocide N Injection 400 mg Cylocide N Injection 1 g (Nippon Shinyaku Co., Ltd.) Cytarabine for I.V. Infusion 400 mg “Teva” Cytarabine for I.V. Infusion 1 g “Teva” (Teva Takeda Pharma Ltd.)	Change Change Change Change	Cytarabine	Drugs with other characteristics indicated for the treatment prior to tumor-specific T-cell infusion therapy. [Expedited review]
Oncology drugs	Mar. 26, 2019	103	Endoxan for Injection 100 mg Endoxan for Injection 500 mg (Shionogi & Co., Ltd.)	Change Change	Cyclophosphamide hydrate	Drugs with other characteristics indicated for the treatment prior to tumor-specific T-cell infusion therapy. [Expedited review]
Oncology drugs	Mar. 26, 2019	104	Treakisym Injection 25 mg Treakisym Injection 100 mg (SymBio Pharmaceuticals Limited)	Change Change	Bendamustine hydrochloride	Drugs with other characteristics indicated for the treatment prior to tumor-specific T-cell infusion therapy. [Expedited review]
AIDS drugs	May 14, 2018	105	Isentress Tablets 600 mg (MSD K.K.)	Approval	Raltegravir potassium	A drug with a new dosage and in an additional dosage form indicated for the treatment of HIV infection. [Orphan drug]
AIDS drugs	Aug. 21, 2018	106	Odefsey Combination Tablets (Janssen Pharmaceutical K.K.)	Approval	Rilpivirine hydrochloride /Emtricitabine/Tenofovir alafenamide fumarate	A new combination drug with a new active ingredient indicated for the treatment of HIV-1 infection. [Orphan drug]
AIDS drugs	Nov. 26, 2018	107	Juluca Combination Tablets (ViiV Healthcare K.K.)	Approval	Dolutegravir sodium/Rilpivirine hydrochloride	A new combination drug with a new active ingredient indicated for the treatment of HIV-1 infection. [Orphan drug]

Review Category	Approval Date	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Active Ingredient (underlined: new active ingredient)	Notes
AIDS drugs	Mar. 26, 2019	108	Biktarvy Combination Tablets (Gilead Sciences K.K.)	Approval	Bictegravir sodium/ Emtricitabine/Tenofovir alafenamide fumarate	A new combination drug with a new active ingredient indicated for the treatment of HIV-1 infection. [Orphan drug]
Vaccines	Mar. 26, 2019	109	Rabipur Intramuscular Injection (GlaxoSmithKline K.K.)	Approval	Freeze-dried inactivated tissue culture rabies vaccine	A drug with a new active ingredient indicated for the pre-exposure and post-exposure prophylaxis against rabies.
Blood products	Jul. 2, 2018	110	Refixia I.V. Injection 500 Refixia I.V. Injection 1000 Refixia I.V. Injection 2000 (Novo Nordisk Pharma Ltd.)	Approval Approval Approval	Nonacog beta pegol (genetical recombination)	Drugs with a new active ingredient indicated for the control of bleeding tendency in patients with coagulation factor IX deficiency.
Blood products	Sep. 21, 2018	111	Jivi for iv injection 250 Jivi for iv injection 500 Jivi for iv injection 1000 Jivi for iv injection 2000 Jivi for iv injection 3000 (Bayer Yakuhin, Ltd.)	Approval Approval Approval Approval Approval	Damoctocog alfa pegol (genetical recombination)	Drugs with a new active ingredient indicated for the control of bleeding tendency in patients with blood coagulation factor VIII deficiency.
Blood products	Dec. 21, 2018	112	Hemlibra s.c. 30 mg Hemlibra s.c. 60 mg Hemlibra s.c. 90 mg Hemlibra s.c. 105 mg Hemlibra s.c. 150 mg (Chugai Pharmaceutical Co., Ltd.)	Change Change Change Change Change	Emicizumab (genetical recombination)	Drugs with a new dosage indicated for the control of bleeding tendency in patients with congenital blood coagulation factor VIII deficiency with blood coagulation factor VIII inhibitors. [Orphan drug]
Blood products	Dec. 21, 2018	113	Hemlibra s.c. 30 mg Hemlibra s.c. 60 mg Hemlibra s.c. 90 mg Hemlibra s.c. 105 mg Hemlibra s.c. 150 mg (Chugai Pharmaceutical Co., Ltd.)	Change Change Change Change Change	Emicizumab (genetical recombination)	Drugs with a new additional indication and a new dosage for the control of bleeding tendency in patients with blood coagulation factor VIII deficiency without blood coagulation factor VIII inhibitors.
Bio-CMC	Jul. 2, 2018	114	Infliximab BS for I.V. Infusion 100 mg [Pfizer] (Pfizer Japan Inc.)	Approval	Infliximab (genetical recombination) [infliximab biosimilar 3]	Follow-on biologics indicated for the treatment of rheumatoid arthritis, psoriasis, Crohn's disease, and ulcerative colitis.
Bio-CMC	Sep. 21, 2018	115	Agalsidase Beta BS I.V. Infusion 5 mg [JCR] Agalsidase Beta BS I.V. Infusion 35 mg [JCR] (JCR Pharmaceuticals Co., Ltd.)	Approval Approval	Agalsidase beta (genetical recombination) [agalsidase beta biosimilar 1]	Follow-on biologics indicated for the treatment of Fabry disease.
Bio-CMC	Sep. 21, 2018	116	Trastuzumab BS for Intravenous Drip Infusions 60 mg "Daiichi Sankyo" Trastuzumab BS for Intravenous Drip Infusions 150 mg "Daiichi Sankyo" (Daiichi Sankyo Company, Limited)	Approval Approval	Trastuzumab (genetical recombination) [trastuzumab biosimilar 2]	Follow-on biologics indicated for the treatment of breast cancer overexpressing HER2 and unresectable advanced or recurrent gastric cancer overexpressing HER2.
Bio-CMC	Sep. 21, 2018	117	Trastuzumab BS for Intravenous Infusion 60 mg [Pfizer] Trastuzumab BS for Intravenous Infusion 150 mg [Pfizer] (Pfizer Japan Inc.)	Approval Approval	Trastuzumab (genetical recombination) [trastuzumab biosimilar 3]	Follow-on biologics indicated for the treatment of breast cancer overexpressing HER2 and unresectable advanced or recurrent gastric cancer overexpressing HER2.
Bio-CMC	Mar. 26, 2019	118	Etanercept BS 10 mg Syringe 1.0 mL for S.C. Inj. "TY" Etanercept BS 25 mg Syringe 0.5 mL for S.C. Inj. "TY" Etanercept BS 50 mg Syringe 1.0 mL for S.C. Inj. "TY" Etanercept BS 50 mg Pen 1.0 mL for S.C. Inj. "TY" (YL Biologics Limited) Etanercept BS 10 mg Syringe 1.0 mL for S.C. Inj. "Nichiiko" Etanercept BS 25 mg Syringe 0.5 mL for S.C. Inj. "Nichiiko" Etanercept BS 50 mg Syringe 1.0 mL for S.C. Inj. "Nichiiko" Etanercept BS 50 mg Pen 1.0 mL for S.C. Inj. "Nichiiko" (Kyowa Pharmaceutical Industry Co., Ltd.)	Approval Approval Approval Approval Approval Approval Approval Approval	Etanercept (genetical recombination) [etanercept biosimilar 2]	Follow-on biologics indicated for the treatment of rheumatoid arthritis (including the prevention of structural joint damage) and polyarticular-course juvenile idiopathic arthritis in patients who have not responded sufficiently to conventional therapies.

Table 5. New Medical Devices Approved in FY 2018

Review Category	Approval Date	Approval Date in US Clinical Study Results: Japanese/Foreign	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Classification Term Name	Notes
Robotic, ICT, and other devices (not classified as other categories)	Apr. 4, 2018 Total review time: 310 days Regulatory review time: 135 days	Jun. 22, 2017 No clinical study results	1	Oncomine Dx Target Test CDx System (Life Technologies Japan Ltd.)	Approval	Instrument & apparatus 17 Analysis system for somatic mutations (to determine the eligibility for antineoplastic agent)	A companion diagnostic system used to determine if dabrafenib mesylate in combination with trametinib dimethyl sulfoxide are indicated based on a V600E mutation in the BRAF gene in patients with non-small cell lung cancer (NSCLC). The system consists of template DNA preparation reagents, a DNA sequencer, and an analysis program. As a study used to evaluate the clinical utility of the product, the result from a foreign study assessing the equivalence between this product and the test method used for the inclusion of subjects in a phase II study of above drugs were submitted.
Robotic, ICT, and other devices (not classified as other categories)	Dec. 11, 2018 Total review time: 355 days Regulatory review time: 231 days	- Japanese clinical study results	2	NESKEEP (Alfresa Pharma Corporation)	Approval	Medical products 4 Absorbable tissue spacer for radiation therapy	A biologically absorbable spacer to provide a space between a malignant tumor and organs at risk in particle radiotherapy. The spacer is an absorbable non-woven fabric made of polyglycolic acid and is placed by laparotomy as a spacer between malignant tumor and organs at risk. A clinical study was conducted in Japan to verify the necessary space was secured and to confirm the safety of the device for patients who have malignant tumors in abdominal cavity or pelvis that require sufficient space between such tumors and organs for particle therapy and have no other effective therapy than particle therapy, and the report was submitted.
Robotic, ICT, and other devices (not classified as other categories)	Dec. 25, 2018 Total review time: 180 days Regulatory review time: 133 days	- No clinical study results	3	OncoGuide NCC OncoPanel System (Sysmex Corporation)	Approval	Instrument & apparatus 17 Analysis set for genetic mutations (to acquire the comprehensive genomic profiling for cancer)	A template DNA preparation reagent and an analysis program to acquire comprehensive genomic profiling pertaining to 114 cancer-related genes obtained from patients with solid tumors which contributes to formulating a therapeutic policy and determining the eligibility of drugs. The study results on analysis performance and clinical performance as a profiling test were submitted.
Robotic, ICT, and other devices (not classified as other categories)	Dec. 27, 2018 Total review time: 286 days Regulatory review time: 186 days	Nov. 30, 2017 No clinical study results	4	FoundationOne CDx Cancer Genomic Profile (Chugai Pharmaceutical Co., Ltd.)	Approval	Program 1 Analysis Program for genetic mutations (to acquire the comprehensive genomic profiling for cancer)	An analysis program to acquire comprehensive genomic profiling pertaining to 324 cancer-related genes obtained from patients with solid tumors which contributes to formulating a therapeutic policy and determining the eligibility of drugs. The study results on analysis performance, clinical performance as a profiling test, and concordance with approved companion diagnostics were submitted. This product also falls under the category of a term name, "Analysis program for somatic gene mutations (to determine the eligibility for an antineoplastic agent)."
Orthopedic and Plastic Surgery	May 2, 2018 Total review time: 356 days Regulatory review time: 137 days	Aug. 23, 2013 Foreign clinical study results	5	Mobi-C Artificial Cervical Disc (Zimmer Biomet G.K.)	Approval	Medical products 4 Total disc replacement prothesis	An artificial cervical disc to restore the functions of one disc or two adjacent discs in the cervical vertebrae (C3 to C7). The product consists of cobalt chromium molybdenum alloy endplates coated with plasma sprayed titanium and hydroxyapatite coating and an ultra-high molecular weight polyethylene mobile bearing insert. The results of foreign clinical studies were submitted to verify the non-inferiority of the treatment using this product to the conventional therapy of anterior cervical discectomy and fusion (ACDF).
Orthopedic and Plastic Surgery	May 2, 2018 Total review time: 187 days Regulatory review time: 152 days	Jul. 7, 2016 Foreign clinical study results	6	PRESTIGE LP Cervical Disc System (Medtronic Sofamor Danek, Co., Ltd.)	Change	Medical products 4 Total disc replacement prothesis	An artificial cervical disc intended to maintain intervertebral mobility by replacing the affected cervical disc with this device after removing factors causing compression, such as herniated nucleus pulposus or osteophytes. The application was submitted to add two-level cervical disc replacement to its intended use and indications. The results of a foreign clinical study were submitted as clinical evaluation data on the product for use in two-level cervical disc replacement.

Review Category	Approval Date	Approval Date in US Clinical Study Results: Japanese/Foreign	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Classification Term Name	Notes
Orthopedic and Plastic Surgery	Jun. 4, 2018	Oct. 25, 2013	7	miraDry System (JMEC Co., Ltd.)	Approval	Instrument & apparatus 29	The device used to ablate and coagulate eccrine glands through microwave heating of the deep dermal layer of skin for the treatment of severe primary axillary hyperhidrosis. The handpiece of the product functions to cool the surface of the skin to prevent damage caused by the heat. The results of foreign clinical studies using the previous-generation products were submitted to evaluate the efficacy in severe primary axillary hyperhidrosis and the acceptability of the anticipated adverse events in comparison with the efficacy.
	Total review time: 363 days Regulatory review time: 209 days	Foreign clinical study results				Microwave scalpel	
Orthopedic and Plastic Surgery	Aug. 20, 2018	Dec. 16, 2005	8	Grafton DBM (Medtronic Sofamor Danek, Co., Ltd.)	Approval	Medical products 4	A resorbable bone reconstruction material using human demineralized bone matrix to fill bony voids and gaps for the purpose of bone tissue reconstruction. The product consists of human demineralized bone matrix and glycerol. A clinical evaluation report primarily consisting of the results of a foreign post-marketing clinical study, a literature review, and an adverse event report was submitted to evaluate the efficacy and safety of the product as a bone reconstruction material.
	Total review time: 356 days Regulatory review time: 217 days	Clinical evaluation report				Resorbable bone reconstruction material using human demineralized bone matrix	
Orthopedic and Plastic Surgery	Nov. 12, 2018	-	9	Mobi-C Artificial Cervical Disc (Zimmer Biomet G. K.)	Change	Medical products 4	An artificial cervical disc to restore the functions of one disc or two adjacent discs in the cervical vertebrae (C3 to C7). The product consists of cobalt chromium molybdenum alloy endplates coated with plasma sprayed titanium and hydroxyapatite coating and an ultra-high molecular weight polyethylene mobile bearing insert. The application was submitted to add a manufacturing site in charge of the primary assembling work. (A "partial change" application submitted during the post-market performance review period)
	Total review time: 52 days Regulatory review time: 17 days	No clinical study results				Total disc replacement prothesis	
Orthopedic and Plastic Surgery	Mar. 27, 2019	-	10	Paxman Scalp Cooling System Orbis (Century Medical, Inc.)	Approval	Instrument & apparatus 12	An electronically controlled cooling device that cools the scalp to prevent hair loss in patients receiving drug therapy for their solid cancer. The product is used in connection with “Paxman Scalp Cooling Cap” (23100BZX00088000). The results of Japanese clinical study for evaluation of the efficacy and safety of this product to prevent chemotherapy induced hair loss in patients with breast cancer were submitted as evaluation data. The results of foreign clinical studies, results of literature search, etc. were also submitted as reference data.
	Total review time: 362 days Regulatory review time: 178 days	Japanese clinical study results				Instrument and device for cooling therapy	
Orthopedic and Plastic Surgery	Mar. 27, 2019	Jun. 7, 2018	11	Paxman Scalp Cooling Cap (Century Medical, Inc.)	Approval	Instrument & apparatus 12	A cooling cap that cools the scalp to prevent hair loss in patients receiving drug therapy for their solid cancer. The product is composed of a silicon cap and a cap cover that protects the cap, and it is used in connection with “Paxman Scalp Cooling System Orbis” (23100BZX00087000). The results of Japanese clinical study for evaluation of the efficacy and safety of this product to prevent chemotherapy induced hair loss in patients with breast cancer were submitted as evaluation data. The results of foreign clinical studies, results of literature search, etc. were also submitted as reference data.
	Total review time: 362 days Regulatory review time: 178 days	Japanese clinical study results				Instrument and device for cooling therapy	
Brain and Circulatory Medicine, Respiratory Medicine, Neurology, and Psychiatry	May 7, 2018	—	12	Gore Viabahn Stent Graft (W. L. Gore & Associates, Co., Ltd.)	Change	Instrument & apparatus 7	A stent graft system consisting of a stent graft with nitinol stent wires wound around the outside of the graft (external stent structure type) and a delivery catheter. The application was submitted to correct discrepancies in descriptions of the raw materials. (A "partial change" application submitted during the post-market performance review period)
	Total review time: 103 days Regulatory review time: 49 days	No clinical study results				Heparin using stent graft in the central circulation	

Review Category	Approval Date	Approval Date in US Clinical Study Results: Japanese/Foreign	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Classification Term Name	Notes
Brain and Circulatory Medicine, Respiratory Medicine, Neurology, and Psychiatry	Jun. 25, 2018 Total review time: 363 days Regulatory review time: 151 days	Apr. 30, 2014 Foreign clinical study results	13	Inspire (Inspire Medical Systems, Inc.)	Approval	Instrument & apparatus 12 Hypoglossal nerve stimulator	An implantable device used to stimulate the hypoglossal nerve in synchronization with breathing to improve airway patency in patients with moderate-to-severe obstructive sleep apnea syndrome who are ineligible for, or intolerant to, continuous positive airway pressure (CPAP) therapy. The product consists of a pulse generator, stimulation lead, sensing lead, programmer for physicians, and programmer for patients. The results of a foreign clinical study that was conducted to confirm the efficacy and safety of the product in patients who are ineligible for, or intolerant to, CPAP were submitted.
Brain and Circulatory Medicine, Respiratory Medicine, Neurology, and Psychiatry	Jun. 29, 2018 Total review time: 102 days Regulatory review time: 24 days	— No clinical study results	14	Revive SE Thrombectomy device (Johnson & Johnson K.K.)	Change	Instrument & apparatus 51 Emboli-removal catheter in the central circulatory system	An emboli-removal catheter in the central circulatory system to restore blood flow by removing clots from blood vessels in the brain in patients with acute-phase cerebral infarction (in principle, within 8 hours of the onset) who are ineligible for intravenous tissue plasminogen activator (t-PA) or who failed to restore blood flow with intravenous t-PA therapy. The application was submitted to change the manufacturing site. (A "partial change" application submitted during the post-market performance review period)
Brain and Circulatory Medicine, Respiratory Medicine, Neurology, and Psychiatry	Aug. 7, 2018 Total review time: 222 days Regulatory review time: 90 days	— No clinical study results	15	Lutonix Drug-Coated Balloon (DCB) Catheter (for femoropopliteal arteries) (Medicon, Inc.)	Change	Instrument & apparatus 51 Balloon-dilating catheter for angioplasty	A balloon-dilating catheter for angioplasty used for purposes including reducing restenosis of target blood vessels in the treatment of de novo or restenotic lesions within the autogenous femoropopliteal artery (excluding those within a stent). The balloon surface of this product is covered with a drug coating primarily consisting of paclitaxel. The application was submitted to add the RX（Rapid exchange)-type catheter form. (A "partial change" application submitted during the post-market performance review period)
Brain and Circulatory Medicine, Respiratory Medicine, Neurology, and Psychiatry	Aug. 30, 2018 Total review time: 37 days Regulatory review time: 16 days	— No clinical study results	16	DC Bead (Eisai Co., Ltd.)	Change	Instrument & apparatus 51 Prosthetic material for embolization in vessels of the central circulation system	Vascular embolization beads used for arterial embolization of “hypervascular tumors” and “arteriovenous malformations.” The application was submitted to remove “uterine fibroids” and “arteriovenous malformations” from the intended use and indications. (A "partial change" application submitted during the post-market performance review period)
Brain and Circulatory Medicine, Respiratory Medicine, Neurology, and Psychiatry	Jan. 8, 2019 Total review time: 95 days Regulatory review time: 84 days	- No clinical study results	17	Pipeline Flex Flow Diverter System (Covidien Japan, Inc.)	Change	Instrument & apparatus 51 Prosthetic material for embolization in vessels of the central circulation system	A flow diverter system used for endovascular therapy for large or giant wide-neck intracranial aneurysms in internal carotid artery from petrous through superior hypophyseal, except for the acute phase of aneurysms that are at risk of rupture. The application was submitted to add a model that supplements MPC polymer to the wire surface of a flow diverter. (A "partial change" application submitted during the post-market performance review period)
Brain and Circulatory Medicine, Respiratory Medicine, Neurology, and Psychiatry	Jan. 21, 2019 Total review time: 364 days Regulatory review time: 197 days	Jan. 1, 2013 Foreign clinical study results	18	Brainsway TMS System (Century Medical, Inc.)	Approval	Instrument & apparatus 12 Repetitive transcranial magnetic stimulator	A repetitive transcranial magnetic stimulator that provides treatment for adult patients with Major Depressive Disorder (MDD) who have not benefitted from conventional antidepressant medication, by stimulating neurons with the electric current induced in the local area of the cerebral cortex using a pulsed magnetic field. The results of foreign clinical studies using the previous-generation products were submitted to evaluate the efficacy and safety of the product in patients with MDD who have not benefitted from conventional antidepressant medication in comparison with the sham treatment group.

Review Category	Approval Date	Approval Date in US Clinical Study Results: Japanese/Foreign	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Classification Term Name	Notes
Brain and Circulatory Medicine, Respiratory Medicine, Neurology, and Psychiatry	Jan. 23, 2019 Total review time: 362 days Regulatory review time: 178 days	Apr. 27, 2004 Foreign clinical study results	19	Excimer Laser Turbo Catheter (Spectranetics Corporation)	Approval	Instrument & apparatus 51 Laser angioplasty catheter	A laser angioplasty catheter used for percutaneous endovascular treatment given to restenotic or reocclusive lesions that occur within a stent placed in the femoropopliteal artery. The product is used with an exclusive laser oscillator, "Excimer Laser Angioplasty Device" (Approval No.21300BZY00528000). The results of foreign clinical studies were submitted to evaluate the efficacy and safety of the product compared to a standard balloon-alone treatment.
Brain and Circulatory Medicine, Respiratory Medicine, Neurology, and Psychiatry	Feb. 21, 2019 Total review time: 329 days Regulatory review time: 146 days	Dec. 11, 2012 Foreign clinical study results	20	Ovation Abdominal Stent Graft System (Endologix, Inc.)	Approval	Instrument & apparatus 7 Aortic stent graft	A stent graft system for the treatment of abdominal aortic aneurysms that obtains adhesion to blood vessels by filling polymer. The product is delivered and placed in a transcatheter manner to abdominal aortic aneurysms and prevents aortic rupture by excluding blood flow into the aortic aneurysms. The result of foreign clinical study was submitted to evaluate the efficacy and safety of the product in patients with abdominal aortic aneurysms.
Brain and Circulatory Medicine, Respiratory Medicine, Neurology, and Psychiatry	Feb. 28, 2019 Total review time: 269 days Regulatory review time: 147 days	Aug. 23, 2011 Clinical evaluation report	21	GORE CTAG Thoracic Endoprosthesis (W. L. Gore & Associates, Co., Ltd.)	Change	Instrument & apparatus 7 Aortic stent graft	An aortic stent graft system used for intravascular treatment of thoracic aortic diseases. The application was submitted to add the indication of the product for chronic complicated Stanford type B aortic dissections. A clinical evaluation report summarizing the contents of Japanese and foreign clinical literatures, etc. was submitted to evaluate the efficacy and safety of the product for this indication. (A "partial change" application submitted during the post-market performance review period)
Brain and Circulatory Medicine, Respiratory Medicine, Neurology, and Psychiatry	Mar. 25, 2019 Total review time: 279 days Regulatory review time: 66 days	- No clinical study results	22	GORE CTAG Thoracic Endoprosthesis (W. L. Gore & Associates, Co., Ltd.)	Change	Instrument & apparatus 7 Aortic stent graft	An aortic stent graft system used for intravascular treatment of thoracic aortic diseases. The application was submitted to mainly add a delivery catheter that expands a stent graft in two deployment steps. (A "partial change" application submitted during the post-market performance review period)
Gastroenterology, Genitourinary, and Reproductive Medicine	Jul. 25, 2018 Total review time: 212 days Regulatory review time: 121 days	— Clinical evaluation report	23	Cool-tip RFA System E Series (Covidien Japan, Inc.)	Change	Instrument & apparatus 29 Radiofrequency ablation system	A radiofrequency ablation system to achieve coagulation and ablation for the purpose of blocking blood flow to part of, or an entire liver tumor, or to an acardiac fetus of acardiac twins. The system primarily consists of an active electrode used to puncture tissues to be coagulated and ablated and a generator unit to supply power to the active electrode. In acardiac twins, the structurally normal fetus may supply blood to the acardiac fetus (a mass of tissue without organ structure that has no chance of growth outside the mother's body) through abnormal vascular connections in the placenta and may eventually develop heart failure due to cardiac overload, which may lead to death. The product has already been approved for the indication of "liver tumor" on August 2, 2011 (Approval No. 22300BZX00335000). The application was submitted for the additional indication of "blood flow blockage to an acardiac fetus of acardiac twins".
Gastroenterology, Genitourinary, and Reproductive Medicine	Jul. 25, 2018 Total review time: 212 days Regulatory review time: 143 days	Apr. 2000 Clinical evaluation report	24	RFA system (Boston Scientific Japan K.K.)	Change	Instrument & apparatus 29 Radiofrequency ablation system	A radiofrequency ablation system for coagulating and ablating malignant hepatic tumor or an acardiac fetus of acardiac twins (only for the purpose of blocking blood flow to the acardiac fetus). The system consists of an electrode used to puncture tissues to be coagulated and ablated and a generator to supply power to the electrode. In acardiac twins, the structurally normal fetus may supply blood to the acardiac fetus (a mass of tissue without organ structure that has no chance of growth outside the mother's body) through abnormal vascular connections in the placenta and may eventually develop heart failure due to cardiac overload, which may lead to death. The product has already been approved for use in "hepatic malignancy" on March 2, 2005 (Approval No. 21700BZY00127000). The application was submitted for the additional indication of "acardiac fetus of acardiac twins (only for the purpose of blocking blood flow to the acardiac fetus)."

Review Category	Approval Date	Approval Date in US Clinical Study Results: Japanese/Foreign	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Classification Term Name	Notes
Gastroenterology, Genitourinary and Reproductive Medicine	Oct. 31, 2018 Total review time: 201 days Regulatory review time: 147 days	Nov. 30, 2017 Foreign clinical study results	25	UroLift System (NeoTract, Inc.)	Approval	Medical products 4 Implantable prostate tissue lifting system	An implantable prostate tissue lifting system indicated for the treatment of dysuria associated with prostatic hyperplasia. The system is composed of an implant to be placed in the prostate and a delivery device which delivers the implant transurethrally to the prostate. By placing the implant in the prostate, the product compresses enlarged prostate tissues and relieves compression on the urethra. The results of foreign clinical studies which were conducted to verify the efficacy and safety of the product in patients with prostatic hyperplasia were submitted.
Ophthalmology and Otorhinolaryngology	Oct. 31, 2018 Total review time: 394 days Regulatory review time: 219 days	- No clinical study results	26	iStent Trabecular Micro-Bypass Stent System (Glaukos Corporation)	Change	Medical products 4 Heparin using intraocular drain	A device consisting of the iStent, a titanium-alloy glaucoma implant designed to maintain a patent outflow of aqueous humor through the trabecular meshwork facilitating its drainage from anterior chamber to the Schlemm's canal and its subsequent natural outflow. This device accompanies its inserter. The application was submitted to add heparin sodium which is a raw material of heparin coating agent for the implant. The humidity test and biological safety test that show the characteristics of heparin coating agent demonstrated its equivalences to these of the approved products, and these test results on the quality of heparin sodium were submitted. (A "partial change" application submitted during the post-market performance review period)
Cardiopulmonary Circulation	Jun. 5, 2018 Total review time: 872 days Regulatory review time: 359 days	Jan. 8, 2016 Foreign clinical study results	27	Perceval Bioprosthetic Valve (Sorin Group Italia S.r.l.)	Approval	Instrument & apparatus 7 Bovine pericardial valve	The device is designed to replace a diseased native aortic valve or a malfunctioning prosthetic aortic valve via open heart surgery. The device primarily consists of a bioprosthetic valve composed of bovine pericardium and a self-expandable metallic stent made of nickel-titanium alloy, a holder handle to position and deploy the bioprosthetic valve at the aortic valve position, and a dilating balloon to expand the bioprosthetic valve after implantation. Unlike conventional bioprosthetic valves for aortic valve replacement (AVR), this device does not require suturing of the bioprosthetic valve with suturing threads because all sutures are eventually removed. The stent's radial force allows stable anchoring of the bioprosthetic valve as the stent of the valve fits in the aortic root (the sinus of Valsalva). The results of a clinical study conducted in Europe were submitted to evaluate the efficacy and safety of the product in patients with aortic valve stenosis or aortic valve stenosis and regurgitation requiring AVR.
Cardiopulmonary Circulation	Jun. 7, 2018 Total review time: 359 days Regulatory review time: 147 days	Oct. 27, 2016 Foreign clinical study results	28	CorPath GRX System (Corindus, Inc.)	Approval	Instrument & apparatus 51 Catheter manipulation equipment for use in the cardiac and central circulatory system	Remote catheter manipulation equipment to be installed in a cardiac catheterization room to manipulate and hold guiding catheters, guidewires, rapid exchange balloon dilatation catheters for coronary angioplasty, and rapid exchange coronary stent catheters that are used for percutaneous coronary intervention (PCI). The product consists of a remote work space, a bed-side unit, and single-use articles. The results of a foreign clinical study using the previous generation model of the product were submitted to evaluate the efficacy and safety of the product in patients who undergo PCI.
Cardiopulmonary Circulation	Jun. 29, 2018 Total review time: 301 days Regulatory review time: 225 days	Mar. 20, 2017 Foreign clinical study results	29	CoreValve Evolut PRO (Medtronic Japan Co., Ltd.)	Approval	Instrument & apparatus 7 Transcatheter porcine pericardial valve	A prosthetic cardiac valve system used for transcatheter valve implantation in the native aortic valve for patients with severe symptomatic native aortic stenosis caused by the calcification of native aortic valve leaflets, and who are unable to undergo surgery. The product consists of a porcine pericardial-derived bioprosthetic valve and a delivery set composed of a delivery catheter system and a loading system. An outer skirt is attached to the inflow part of the bioprosthetic valve of the approved product, "CoreValve Evolut R" (Approval No. 22800BZX00414000) to reduce paravalvular regurgitation. The results of a clinical study conducted in the US to examine the efficacy and safety of the product were submitted.

Review Category	Approval Date	Approval Date in US Clinical Study Results: Japanese/Foreign	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Classification Term Name	Notes
Cardiopulmonary Circulation	Jul. 11, 2018	Apr. 1, 2016	30	HeartLight Endoscopic Ablation System (Japan Lifeline Co., Ltd.)	Change	Instrument & apparatus 51	A balloon-type laser ablation catheter with an endoscope to treat drug-resistant recurrent symptomatic paroxysmal atrial fibrillation. The application was submitted to add a method to sterilize balloon fill media, a manufacturing site in charge of sterilization, and a method to re-sterilize the endoscope fiber. (A "partial change" application submitted during the post-market performance review period)
	Total review time: 107 days Regulatory review time: 61 days	No clinical study results				Cardiovascular ablation catheter	
Cardiopulmonary Circulation	Sep. 27, 2018	—	31	EDWARDS INTUITY Elite Valve System (Edwards Lifesciences Limited)	Change	Instrument & apparatus 7	A bioprosthetic valve with a bovine pericardial-derived valve intended as a substitute for the function of a malfunctioning cardiac valve. The application was submitted primarily to add bovine pericardium produced in Australia as a raw material for valve leaflets and to add raw materials for band-covering and wire-shaped fabrics. (A "partial change" application submitted during the post-market performance review period)
	Total review time: 34 days Regulatory review time: 29 days	No clinical study results				Bovine pericardial valve	
Cardiopulmonary Circulation	Oct. 9, 2018	-	32	Jarvik 2000 Implantable Ventricular Assist Device (Century Medical, Inc.)	Change	Instrument & apparatus 7	The device is an implantable ventricular assist device system used to improve the blood circulation until heart transplant. The device is used for severe cardiac failure patients who are qualified to receive heart transplant, shown continuous decompensation in spite of drug therapy or circulation assist techniques, such as an external ventricular assist system and considered difficult to survive without heart transplant. The application was submitted to add a PA model which has the same blood pump portion as that of the existing abdominal model but is fixed with an intracorporeal cable in the postauricular region, and a kink preventing cover, etc. (A "partial change" application submitted during the reexamination period)
	Total review time: 285 days Regulatory review time: 217 days	Clinical evaluation report				Implantable ventricular assist device	
Cardiopulmonary Circulation	Dec. 5, 2018	-	33	SATAKE HotBalloon Catheter (Toray Industries, Inc.)	Change	Instrument & apparatus 51	A balloon ablation catheter utilizing a high-frequency current to treat drug-resistant recurrent symptomatic paroxysmal atrial fibrillation. The application was submitted to add a highly rigid model, a dilution rate of an applicable contrast media, an esophagus cooling tube as a component, and to change the maximum guide wire diameter for use in combination, and also to make other adjustments to the descriptions. (A "partial change" application submitted during the post-market performance review period)
	Total review time: 103 days Regulatory review time: 88 days	No clinical study results				Cardiovascular ablation catheter	
Cardiopulmonary Circulation	Jan. 24, 2019	Mar. 1, 2018	34	CorPath GRX System (Corindus, Inc.)	Change	Instrument & apparatus 51	Catheter manipulation equipment for use in the cardiac and central circulatory system that remotely performs the delivery and manipulation of guidewires, rapid exchange balloon catheter, stent catheter, and guiding catheter during percutaneous coronary intervention (PCI). The application was submitted to add a function that allows a guidewire to automatically rotate when the guidewire is pulled back and also a change of the guidewire's rotation angle on a touch panel. (A "partial change" application submitted during the post-market performance review period)
	Total review time: 139 days Regulatory review time: 101 days	No clinical study results				Catheter manipulation equipment for use in the cardiac and central circulatory system	
Cardiopulmonary Circulation	Feb. 21, 2019	Mar. 13, 2015	35	WATCHMAN Left Atrial Appendage Closure Device (Boston Scientific Japan K. K.)	Approval	Instrument & apparatus 51	This device was developed to reduce the risk of ischemic stroke and systemic embolism from the left atrial appendage in patients with non-valvular atrial fibrillation who are at increased risk for thromboembolism. The device consists of a delivery system loaded with a closure device, a sheath for delivering the delivery system to the left atrial appendage, and a dilator. By closing the left atrial appendage with a percutaneously delivered closure device, it is intended to reduce the risk of ischemic stroke and systemic embolism caused by left atrial appendage thrombus. The results of foreign and Japanese clinical studies using the product were submitted to evaluate the efficacy and safety of the product.
	Total review time: 267 days Regulatory review time: 99 days	Foreign and Japanese clinical study results				Endocardial prosthetic material	

Review Category	Approval Date	Approval Date in US Clinical Study Results: Japanese/Foreign	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Classification Term Name	Notes
Cardiopulmonary Circulation	Feb. 22, 2019	-	36	EDWARDS INTUITY Elite Valve System (Edwards Lifesciences Limited)	Change	Instrument & apparatus 7	A bovine pericardial valve intended as a substitute for the function of a malfunctioning aortic valve. The application was submitted to add a manufacturing site in charge of the primary assembling work and to adjust the descriptions in the manufacturing method column. (A "partial change" application submitted during the post-market performance review period)
	Total review time: 113 days Regulatory review time: 19 days	No clinical study results				Bovine pericardial valve	
Cardiopulmonary Circulation	Mar. 25, 2019	Jul. 8, 2010	37	Impella Controller (Abiomed, Inc.)	Change	Instrument & apparatus 7	An external controller for exclusive catheter-based blood pump (hereinafter referred to the catheter pump) that controls the performance and monitors the catheter position of the catheter pump, and controls the flow rate of the purge cassette. The application was submitted in connection with the addition of a new type of pump catheter for the concomitant device, "Impella Circulatory Assist Pump Catheter" (Approval No. 22800BZI00032000). (A "partial change" application submitted during the post-market performance review period)
	Total review time: 179 days Regulatory review time: 143 days	No clinical study results				Controller of implantable pump catheter for ventricular support	
Cardiopulmonary Circulation	Mar. 25, 2019	May 30, 2008	38	Impella Circulatory Assist Pump Catheter (Abiomed, Inc.)	Change	Instrument & apparatus 51	The catheter-based blood pump that assists systemic circulation in patients with drug resistant acute heart failure, such as cardiogenic shock, can be inserted through femoral artery and placed in the left ventricle. This device pulls blood directly from the left ventricle and expels the blood from the catheter into the ascending aorta. The application was submitted to add Impella CP as a new type of pump catheter. (A "partial change" application submitted during the post-market performance review period)
	Total review time: 179 days Regulatory review time: 84 days	No clinical study results				Implantable pump catheter for ventricular support	

Table 6. Improved Medical Devices (with Clinical Data) Approved in FY 2018

Approval Date	Approval Date in US Clinical Study Results: Japanese/Foreign	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Classification Term Name	Notes
May 25, 2018	Oct. 5, 2012	1	Dexcom G4 PLATINUM System (Dexcom, Inc.)	Approval	Instrument & apparatus 20	The device is a continuous glucose monitoring system indicated for detecting trends and tracking patterns by measuring interstitial fluid glucose concentration in persons with diabetes. The device continuously records interstitial fluid glucose concentration obtained by a sensor that is inserted subcutaneously and displays the collected information on a monitor. Patterns and trends of interstitial fluid glucose concentration obtained by the device can be used to optimize the management of diabetes. It is used to complement self-blood glucose monitoring. The results of foreign clinical studies were submitted to evaluate the efficacy and safety of this product.
Total review time: 428 days Regulatory review time: 96 days	Foreign clinical study results				Glucose monitoring system	
Apr. 10, 2018	-	2	PELNAC G plus (GUNZE Limited)	Approval	Medical products 4	PELNAC G plus is a bilayer collagen-based artificial dermis made of a gelatin-containing collagen sponge and a silicone film. This product is based on the company's approved product, "PELNAC" and its improvements are the inclusion of gelatin in the raw material as well as the introduction of a single-layer fenestrated type. The results of a single-arm clinical study on patients with refractory skin ulcers in Japan were submitted to evaluate the efficacy and safety of this product.
Total review time: 256 days Regulatory review time: 183 days	Japanese clinical study results				Collagen-based artificial skin	
Apr. 26, 2018	-	3	Comprehensive Shoulder Nanostem (Zimmer Biomet G.K.)	Approval	Medical products 4	A humeral stem component system used proximally in the humerus to substitute for shoulder joint functions during total shoulder arthroplasty or shoulder humeral head replacement. The improved point is the adoption of a humeral stem that is shorter than the conventional one to reduce the invasiveness to the bone marrow cavity, thereby allowing bone preservation. A clinical evaluation report summarizing the contents of foreign clinical literatures, post-marketing surveillance, and malfunction reports was submitted to evaluate the risks of looseness, dislocation, etc. caused by this improved point.
Total review time: 121 days Regulatory review time: 65 days	Clinical evaluation report				Humeral component for shoulder prosthesis	
May 7, 2018	Dec. 26, 2013	4	Long-Pulsed Laser GentleMax Pro (Syneron Candela K.K.)	Approval	Instrument & apparatus 31	The device intended to achieve stable long-term hair reduction by selective photothermolysis. The device is a combination device with which 755 nm Alexandrite laser or 1064 nm Nd:YAG laser can be selected. The functions of the Alexandrite laser are the same as those of the company's previous model, "Long-Pulsed Alexandrite Laser GentleLase Pro" (Approval No. 22800BZX00446000). A clinical evaluation report summarizing clinical literatures on the previous generation product was submitted to evaluate the long-term hair reduction effect and the absence of permanent adverse events.
Total review time: 138 days Regulatory review time: 89 days	Clinical evaluation report				Neodymium:YAG laser	
May 18, 2018	Mar. 10, 2015	5	Mediostar Next Pro (Medical U&A, Inc.)	Approval	Instrument & apparatus 31	The device is intended to achieve stable long-term hair reduction by selective photothermolysis. Diode lasers at wavelengths of 808 nm and 940 nm are delivered simultaneously. A clinical evaluation report summarizing clinical literatures on the previous generation product was submitted to evaluate the long-term hair reduction effect and the absence of permanent adverse events.
Total review time: 259 days Regulatory review time: 94 days	Clinical evaluation report				Diode laser	
Jun. 1, 2018	Mar. 17, 2017	6	Juvederm Vista Volift XC (Allergan Japan K.K.)	Approval	Medical products 4	An injectable material to a soft tissue using hyaluronic acid to be injected into the middle and deep dermis to correct moderate to severe wrinkles and folds in the facial skin. The improved point is that a lower concentration of the hyaluronic acid gel of the company's approved product 1, "Juvederm Vista Voluma XC" (22800BZX00338000) used for correcting volume deficit, is used for optimal correction of wrinkles and folds. The results of a foreign clinical study were submitted to evaluate the efficacy and safety of the impact of the improved point on the correction of wrinkles and folds.
Total review time: 430 days Regulatory review time: 137 days	Foreign clinical study results				Injectable material to a soft tissue using hyaluronic acid	

Approval Date	Approval Date in US Clinical Study Results: Japanese/Foreign	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Classification Term Name	Notes
Oct. 26, 2018	May 31, 2016	7	Juvederm Vista Volbella XC (Allergan Japan K. K.)	Approval	Medical products 4	An Injectable material to a soft tissue using hyaluronic acid used to correct facial wrinkles by injecting it intradermally (from the middle to deep dermis), to correct facial hollows by injecting it subcutaneously or into the deep part on the periosteum, and to augment the lip by injecting it subcutaneously into the lip mucosa. The improvement was made for the product to optimize the injection into the lip or more shallow part of the facial skin by decreasing the concentration of hyaluronic acid gel of the company's approved product, "Juvederm Vista Voluma XC" (22800BZX00338000). The results of foreign clinical studies were submitted to evaluate the efficacy and safety of the product by this improvement.
Total review time: 648 days Regulatory review time: 423 days	Foreign clinical study results				Injectable material to a soft tissue using hyaluronic acid	
Dec. 11, 2018	Mar. 5, 2008	8	XTRAC (JMEC Co., Ltd.)	Approval	Instrument & apparatus 31	An excimer laser that treats skin diseases subject to medium-wave UV therapy by irradiating laser light with wavelength 308 nm in the UV region which is generated by gas mixture containing xenon and chloride to the affected site through a handpiece. While the existing certified UV treatment device used for the equivalent purpose uses excimer lamp as a light source, but this product uses excimer laser as a light source. This point is the difference between this product and the existing certified products. The clinical evaluation report prepared based on overseas literatures, including the clinical results of this device and the previous generation device in other countries, was submitted to evaluate the efficacy and safety of the product equivalent to those of the existing UV treatment devices.
Total review time: 257 days Regulatory review time: 132 days	Clinical evaluation report				Excimer laser	
Apr. 23, 2018	May 22, 2015	9	Misago 2 (Terumo Corporation)	Approval	Instrument & apparatus 7	A nickel-titanium alloy vascular stent used for vascular expansion and maintenance of a lumen in symptomatic artery disease of the iliac arteries and the superficial femoral artery region, and for the treatment of acute or impending occlusion associated with unsuccessful intervention treatment of the superficial femoral artery region. Sharing the basic design with the approved product, "Misago" (Approval No. 22400BZX00463000), a stent for use in superficial femoral arteries, Misago 2 has an additional sized model with a wider diameter for iliac artery. The results of a clinical study of the product for use in the iliac arteries and the superficial femoral artery region were submitted to evaluate the efficacy and safety of the product.
Total review time: 257 days Regulatory review time: 96 days	Foreign and Japanese clinical study results				Stent for iliac artery	
Apr. 25, 2018	-	10	ONYX Liquid Embolic System LD (Covidien Japan, Inc.)	Change	Instrument & apparatus 51	A liquid embolic agent comprised of ethylene vinyl alcohol copolymer dissolved in dimethyl sulfoxide, and that is used for the embolization of cerebral vascular malformations. The application was submitted for the additional indication of dural arteriovenous fistula for which it is difficult to achieve satisfactory treatment goals with intravenous embolization. The results of a Japanese clinical study that evaluated the efficacy and safety of the product in patients with dural arteriovenous fistula were submitted.
Total review time: 264 days Regulatory review time: 116 days	Japanese clinical study results				Prosthetic material for embolization in vessels of the central circulation system	
Oct. 18, 2018	Mar. 30, 2015	11	Adherus Dural Sealant (Medical U&A, Inc.)	Approval	Medical products 4	A synthetic absorbent material used as an absorbable prosthetic material to close a gap between the dura maters, the sutured site of the dura mater, or a gap between the duraplasty material and the dura mater. The results of a foreign clinical study conducted to verify the non-inferiority of this product to approved products for cerebrospinal fluid (CSF) leaks after surgery, etc. were submitted.
Total review time: 927 days Regulatory review time: 338 days	Foreign clinical study results				Absorbable tissue reinforcement material	

Approval Date	Approval Date in US Clinical Study Results: Japanese/Foreign	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Classification Term Name	Notes
Dec. 5, 2018	Jun. 11, 2018	12	Cerebral Thrombus Aspiration Catheter (Terumo Corporation)	Approval	Instrument & apparatus 51	An emboli-removal catheter in the central circulatory system used for revascularization of patients with acute ischemic stroke (in principle, within 8 hours of symptom onset) who are ineligible for intravenous tissue plasminogen activator (t-PA) or who failed in revascularization with intravenous t-PA therapy. The product is different from the approved product, "Penumbra System" (Approval No. 22300BZX00269000) in that it aspirates and retrieves thrombus only with a catheter without using a separator (A Direct Aspiration first Pass Technique, hereinafter referred to as "ADAPT"), and also it aspirates thrombus manually with a syringe. A clinical evaluation report summarizing the contents of Japanese and foreign clinical literatures, etc. was submitted to evaluate the efficacy and safety of ADAPT.
Total review time: 252 days Regulatory review time: 158 days	Clinical evaluation report				Emboli-removal catheter in the central circulatory system	
Dec. 5, 2018	Mar. 28, 2014	13	Supera Stent (Century Medical, Inc.)	Approval	Instrument & apparatus 7	A self-expanding vascular stent used for the treatment of symptomatic vascular disease with a lesion length up to 140 mm in the native superficial femoral artery and proximal popliteal artery with reference vessel diameter of 4.0-6.5mm, and for the treatment of acute or impending occlusion in the aforementioned sites following the failure of interventional treatment. The results of foreign clinical studies conducted to evaluate the performance of the product were submitted.
Total review time: 250 days Regulatory review time: 201 days	Foreign clinical study results				Stent for blood vessel	
Dec. 6, 2018	Sep. 18, 2018	14	Eluvia Drug-Eluting Vascular Stent System (Boston Scientific Japan K. K.)	Approval	Instrument & apparatus 7	A drug-eluting stent used for the treatment of symptomatic vascular disease with a lesion length up to 190 mm in the native femoropopliteal artery with reference vessel diameter of 4 -6 mm for each limb, and for the treatment of acute or impending occlusion in the aforementioned sites following the failure of interventional treatment. The product is a combination of the company's approved stent system and drug coating. The results of the randomized controlled global clinical study conducted to evaluate the performance of the product with a lesion length up to 140 mm using other company's approved product, "Zilver PTX Drug-Eluting Peripheral Stent" (Approval No. 22400BZX00013000) as a control and the results of the single-arm global clinical study conducted to evaluate the performance of the product with a lesion length up to 190 mm were submitted.
Total review time: 190 days Regulatory review time: 150 days	Global clinical trial				Drug-eluting femoral artery stent	
Dec. 11, 2018	-	15	Tron FX Thrombectomy Device (JIMRO Co., Ltd.)	Approval	Instrument & apparatus 51	A Central circulatory system embolectomy catheter that is intended for use in removing intracerebral clots to restore blood flow in patients with acute ischemic stroke (generally within 8 hours of symptom onset) in whom IV t-PA therapy is not indicated or fails to achieve reperfusion. The results of Japanese clinical studies that evaluated the efficacy and safety of the product for acute ischemic stroke were submitted.
Total review time: 256 days Regulatory review time: 160 days	Japanese clinical study results				Emboli-removal catheter in the central circulatory system	
Mar. 7, 2019	Jul. 1999	16	DuraGen Artificial Dura Mater (EPJ Medical Service Co., Ltd.)	Approval	Medical products 4	A collagen-using absorbent artificial dura mater used for prosthesis for deficiency part of dura mater. The product is different from the existing artificial dura maters in that the spinal dura mater is included as the indicated site and suture is not necessary for prosthesis. A clinical evaluation report summarizing the contents of foreign clinical studies, literatures, etc. was submitted to evaluate the efficacy and safety of the product.
Total review time: 629 days Regulatory review time: 206 days	Clinical evaluation report				Collagen-using absorbent artificial dura mater	
Mar. 20, 2019	Feb. 15, 2018	17	Trevo Pro Clot Retriever (Stryker Japan K. K.)	Change	Instrument & apparatus 51	An emboli-removal catheter in the central circulatory system intended to restore blood flow by removing thrombus for patients with acute-phase cerebral infarction who are ineligible for intravenous tissue plasminogen activator (t-PA) or who failed to restore blood flow with intravenous t-PA therapy. The application was submitted to add the indication of the product for patients with occlusion in the proximal part of the anterior major artery whose outcome is expected to improve with endovascular thrombectomy and who are within 24 hours from when s/he was confirmed to be healthy last time. The results of foreign clinical study conducted for this indication were submitted.
Total review time: 229 days Regulatory review time: 200 days	Foreign clinical study results				Emboli-removal catheter in the central circulatory system	

Approval Date	Approval Date in US Clinical Study Results: Japanese/Foreign	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Classification Term Name	Notes
Mar.26, 2019	-	18	COOK Zenith Dissection Endovascular System (Cook Japan Inc.)	Change	Instrument & apparatus 7	A stent graft system used for the treatment of complicated Stanford type B aortic dissection. The application was submitted to add chronic complicated Stanford type B aortic dissection to the indication of the product. A clinical evaluation report compiling the data from a foreign clinical study and Japanese and foreign literature reports was submitted to evaluate the efficacy and safety of the product for this indication.
Total review time: 236 days Regulatory review time: 48 days	Foreign clinical study results Clinical evaluation report				Aortic stent graft	
Apr. 17, 2018	-	19	EBL Device (Akita Sumitomo Bakelite Co., Ltd.)	Approval	Instrument & apparatus 30	A medical device to be mounted on the end of an endoscope, and that is intended to be used to ligate internal hemorrhoids or colonic diverticular bleeding points with an O ring by drawing them into the device. Ligation of tissues with an O ring stops bleeding and causes tissue necrosis to block the diverticula. The device was developed by improving the company's approved product, "Pneumatic EVL Device (with cuff)" (Approval No. 22100BZX01110000), an endoscopic esophageal varix ligation set, and is designed for use in the large intestine. Three different sizes are available depending on the size of the endoscope.
Total review time: 183 days Regulatory review time: 131 days	Clinical evaluation report				Device for endoscopic loop ligation	
Apr. 24, 2018	-	20	Hemodiafilter FX HDF (Fresenius Medical Care Japan K.K.)	Approval	Instrument & apparatus 7	A hemodiafilter used to remove fluid and uremic substances stored in the body due to uremia. This device is indicated for patients with extremely impaired renal function caused by chronic or acute kidney failure. The improved point is that the product uses a semi-permeable membrane that is identical to the one used in the company's approved product, a hollow fiber dialyzer "Fresenius Dialyzer FX Series (Approval No. 22000BZX00037000)", as a hemodiafilter to meet market needs.
Total review time: 109 days Regulatory review time: 59 days	Japanese clinical study results				Hemodiafilter	
Sep. 10, 2018	-	21	UT Filter A (Nipro Corporation)	Approval	Instrument & apparatus 7	The device is used for slow continuous hemofiltration in patients with acute renal failure or those with chronic renal failure with unstable hemodynamics. The device slowly removes and adjusts unwanted metabolites, water, and electrolytes in the blood. The device was developed as a slow continuous hemofilter by changing the size variation of the approved hemodiafilter product (Brand name: Fineflux, Approval No. 22600BZX00004000).
Total review time: 167 days Regulatory review time: 129 days	Japanese clinical study results				Slow continuous hemofilter	
Oct. 26, 2018	Feb. 2003	22	ABTHERA Dressing Kit (KCI K.K.)	Approval	Medical products 4	A dressing kit for open abdominal wounds intended to facilitate early closure of the peritoneum. The product provides the protection of abdominal contents from external environment, efficient drainage, suppression of inflammation, and alleviation of edema by covering the organs inside the abdomen and applying controlled negative pressure in the case where open abdominal wounds are accompanied by exposure of abdominal organs and also abdominal closure by primary suture is difficult. The product is composed of the tubing set, drape, blue foam, and protective layer. An optional item of the product, ABTHERA Negative Pressure Maintenance Controller, is used to transmit negative pressure. Also, this device may be used in combination with the negative pressure maintenance controller of the approved product, "InfoV.A.C. Therapy System" or "V.A.C.Ulta Therapy System."
Total review time: 182 days Regulatory review time: 113 days	Clinical evaluation report				Dressing kit for open abdominal wounds	
Nov. 21, 2018	-	23	Liftal K (Kaigen Pharma Co., Ltd.)	Approval	Medical products 4	A vial product filled with 20 mL of 0.6% sodium alginate solution. The product largely dissociates a gap between the mucosal layer and the muscle layer by staying the submucosa using its viscoelasticity which is the feature of sodium alginate solution. As a result, it allows to form and maintain the bulge of lesions site (mucosal layer) when resecting or dissecting the mucosal layer. Thus, the product is a submucosal filling material for endoscopy intended to improve the operability of resection or dissection of lesion sites during Endoscopic Submucosal Dissection (EDS) and Endoscopic Mucosal Resection (EMR). The results of Japanese clinical studies conducted to verify the efficacy and safety of the product were submitted.
Total review time: 265 days Regulatory review time: 156 days	Japanese clinical study results				Submucosal filling material for endoscope	

Approval Date	Approval Date in US Clinical Study Results: Japanese/Foreign	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Classification Term Name	Notes
Dec. 20, 2018	-	24	Okamoto Condoms VG (Okamoto Industries, Inc.)	Approval	Hygiene products 2	A contraceptive condom for males intended to help contraception and prevention of sexually transmitted diseases. The product is composed of a condom itself and dressing agent (anti-adhesion agent, lubricant). The lubricant contains 0.5% of SPL7013. Regarding the safety evaluation for SPL7013, a clinical evaluation report that mainly includes the overseas clinical study data of SPL7013 gel for bacterial vaginosis, which has not been approved in Japan, was submitted.
Total review time: 266 days Regulatory review time: 130 days	Clinical evaluation report				Contraceptive condom for males	
Feb. 7, 2019	Mar. 18, 2016	25	FibroScan 530 Compact (Echosens)	Change	Instrument & apparatus 12	A Versatile ultrasound diagnostic imaging device that provides qualitative information by measuring liver stiffness non-invasively. The application was submitted to add a measuring function of controlled attenuation parameter (CAP) level that quantitatively measures the liver fat volume. A clinical evaluation report on the evaluation of fatty liver grade using the CAP level in liver biopsy was submitted.
Total review time: 195 days Regulatory review time: 145 days	Clinical evaluation report				Versatile ultrasound diagnostic imaging device	
Jul. 10, 2018	-	26	Neo Sight One Day Aero (Aire Inc.)	Approval	Instrument & apparatus 72	Daily wear, single-use, colored contact lenses for correction of visual acuity. The lens is composed of silicone hydrogel with a moisture content of 45% and an oxygen permeability (Dk) of 58.5. Due to the novelty of the raw material, a Japanese clinical study was conducted to confirm the efficacy and safety of the product as a contact lens for visual correction.
Total review time: 270 days Regulatory review time: 132 days	Japanese clinical study results				Single-use colored contact lenses for correcting visual acuity	
Aug. 17, 2018	-	27	Lentis Comfort (Santen Pharmaceutical Co., Ltd.)	Approval	Instrument & apparatus 72	A multifocal posterior chamber lens to be inserted as a substitute for a crystalline lens to correct far and intermediate vision of an aphakic eye. The improved points are that the product has a refractive multifocal mechanism with two regions with different curvature radius of the optic zone, a pair of plate supports, and that it uses new raw materials. A Japanese clinical study was conducted to confirm the clinical efficacy and safety of the product including visual function as a multifocal posterior chamber lens.
Total review time: 268 days Regulatory review time: 224 days	Japanese clinical study results				Multifocal posterior chamber lens	
Aug. 21, 2018	Dec. 16, 2009	28	da Vinci Surgical System (Intuitive Surgical G.K.)	Change	Instrument & apparatus 12	A device to assist surgeons' manipulation of endoscopic surgical instruments during endoscopic surgery in the areas of general digestive surgery, thoracic surgery, cardiac surgery (limited to intracardiac surgical operations under cardiac arrest), urology, and gynecology, to hold tissues or foreign matters, perform incisions, blunt/sharp dissection, proximal ligation, incision/coagulation using high-frequency current, suturing and operation, and insertion/delivery of surgical accessories. The application was submitted for the additional indication of head and neck surgery (limited to transoral surgery). A clinical evaluation report, which summarized a Japanese clinical study and a US clinical study in patients with oropharyngeal cancer, hypopharyngeal cancer, laryngeal cancer, etc., and foreign literatures, was submitted to evaluate the efficacy and safety of the product in transoral head and neck surgery.
Total review time: 266 days Regulatory review time: 212 days	Clinical evaluation report				Surgical robot, operation unit	
Aug. 21, 2018	Dec. 16, 2009	29	da Vinci Si Surgical System (Intuitive Surgical G.K.)	Change	Instrument & apparatus 12	A device to assist surgeons' manipulation of endoscopic surgical instruments during endoscopic surgery in the areas of general digestive surgery, thoracic surgery, cardiac surgery (limited to intracardiac surgical operations under cardiac arrest), urology, and gynecology, to hold tissues or foreign matters, perform incisions, blunt/sharp dissection, proximal ligation, incision/coagulation using high-frequency current, suturing and operation, and insertion/delivery of surgical accessories. The application was submitted for the additional indication of head and neck surgery (limited to transoral surgery). A clinical evaluation report, which summarized a Japanese clinical study and a US clinical study in patients with oropharyngeal cancer, hypopharyngeal cancer, laryngeal cancer, etc., and foreign literatures, was submitted to evaluate the efficacy and safety of the product in transoral head and neck surgery.
Total review time: 266 days Regulatory review time: 212 days	Clinical evaluation report				Surgical robot, operation unit	

Approval Date	Approval Date in US Clinical Study Results: Japanese/Foreign	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Classification Term Name	Notes
Aug. 21, 2018	-	30	da Vinci Xi Surgical System (Intuitive Surgical G.K.)	Change	Instrument & apparatus 12	A device to assist surgeons' manipulation of endoscopic surgical instruments during endoscopic surgery in the areas of general digestive surgery, thoracic surgery, cardiac surgery (limited to intracardiac surgical operations under cardiac arrest), urology, and gynecology, to hold tissues or foreign matters, perform incisions, blunt/sharp dissection, proximal ligation, incision/coagulation using high-frequency current, suturing and operation, and insertion/delivery of surgical accessories. The application was submitted for the additional indication of head and neck surgery (limited to transoral surgery). A clinical evaluation report, which summarized a Japanese clinical study and a US clinical study in patients with oropharyngeal cancer, hypopharyngeal cancer, laryngeal cancer, etc., and foreign literatures, was submitted to evaluate the efficacy and safety of the product in transoral head and neck surgery.
Total review time: 266 days Regulatory review time: 212 days	Clinical evaluation report				Surgical robot, operation unit	
Aug. 24, 2018	May 26, 2016	31	Ultimate 1 Day SH (Sincere Co., Ltd.)	Approval	Instrument & apparatus 72	Daily wear, single-use, colored contact lenses for correction of visual acuity. The lens is composed of silicone hydrogel (Olifilcon B) with a moisture content of 47% and an oxygen permeability (Dk) of 120.0. Due to the novelty of the raw material, a foreign clinical study was conducted to confirm the efficacy and safety of the product as a contact lens for visual correction.
Total review time: 269 days Regulatory review time: 90 days	Foreign clinical study results				Single-use colored contact lenses for correcting visual acuity	
Sep. 14, 2018	Apr. 3, 2016	32	Triggerfish Sensor (SEED Co., Ltd.)	Approval	Instrument & apparatus 72	A contact lens-type pressure sensor that is mounted on the front part of the eye to monitor changes in the corneal curvature induced by changes in the intraocular pressures and to detect peak patterns of variation in intraocular pressure. The device is used in combination with Triggerfish (Approval No. 23000BZX00273000). The results of a foreign clinical study in patients with primary open-angle glaucoma and healthy adults were submitted to confirm the capability to detect changes in corneal curvature, etc.
Total review time: 266 days Regulatory review time: 211 days	Foreign clinical study results				Measuring device for corneal curvature variation	
Sep. 14, 2018	Apr. 3, 2016	33	Triggerfish (SEED Co., Ltd.)	Approval	Instrument & apparatus 21	A device to monitor changes in the corneal curvature induced by changes in the intraocular pressure, to detect peak patterns of variation in intraocular pressure, and to receive and record data measured by Triggerfish Sensor (Approval No. 23000BZX00272000), etc. The results of a foreign clinical study in patients with primary open-angle glaucoma and healthy adults were submitted to confirm the capability to detect changes in corneal curvature, etc.
Total review time: 266 days Regulatory review time: 209 days	Foreign clinical study results				Telemetry measuring device for biological signals	
Oct. 23, 2018	Jul. 13, 2016	34	Avaira v (CooperVision Japan Inc.)	Approval	Instrument & apparatus 72	Reusable colored contact lenses for daily wear intended for the correction of visual acuity. The lens is made of fanfilcon A, a silicone hydrogel. A novel material was developed to improve oxygen permeability and UV absorption, and the results of foreign clinical studies, etc. conducted to evaluate the efficacy and safety were submitted.
Total review time: 208 days Regulatory review time: 170 days	Foreign clinical study results				Reusable colored contact lenses for correcting visual acuity	
Oct. 23, 2018	-	35	Rohto 2 Week Clear View (CooperVision Japan Inc.)	Approval	Instrument & apparatus 72	A product with multiple brand name of "Avaira v."
Total review time: 208 days Regulatory review time: 170 days	No clinical study results				Reusable colored contact lenses for correcting visual acuity	
Oct. 23, 2018	-	36	Rohto 2 Week Fresh View (CooperVision Japan Inc.)	Approval	Instrument & apparatus 72	A product with multiple brand name of "Avaira v."
Total review time: 208 days Regulatory review time: 170 days	No clinical study results				Reusable colored contact lenses for correcting visual acuity	

Approval Date	Approval Date in US Clinical Study Results: Japanese/Foreign	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Classification Term Name	Notes
Nov. 7, 2018	Jul. 31, 2015	37	Tecnis Toric 1-Piece (AMO Japan K.K.)	Change	Instrument & apparatus 72	A one-piece monofocal posterior chamber lens to be inserted into an aphakic eye after cataract surgery accompanied with corneal astigmatism. The application was submitted to mainly add a high cylindrical power model. The results of foreign clinical studies, etc. to evaluate the efficacy and safety of the product in patients with aphakic eyes with severe corneal astigmatism were submitted.
Total review time: 257 days Regulatory review time: 223 days	Foreign clinical study results				Posterior chamber lens	
Dec. 26, 2018	Apr. 5, 2017	38	XprESS ENT Dilation System (Entellus Medical, Inc.)	Approval	Instrument & apparatus 51	XprESS is a balloon catheter used for dilation of the cartilaginous portion to the isthmus of the Eustachian tube for treating persistent Eustachian tube stenosis through transnasal approach. The product has a new intended use and indication. The improved feature of the product is that it is used for a different treatment site from that of the existing “endoscopic dilatation catheter” in Japan. The results of foreign clinical studies were submitted to evaluate the clinical efficacy and safety of the product for Eustachian tube dysfunction.
Total review time: 383 days Regulatory review time: 276 days	Foreign clinical study results				Endoscopic dilatation catheter	
Dec. 26, 2018	-	39	HOYA Vivinex Toric (HOYA Corporation)	Approval	Instrument & apparatus 72	The product is a one-piece monofocal posterior chamber lens to be inserted into an aphakic eye after cataract surgery accompanied with corneal astigmatism. The improvement was made to the product in that correction function of corneal astigmatism was added to the rear face of the monofocal posterior chamber lens of the company’s approved product, “HOYA Vivinex iSert” (Approval No. 22400BZX00498000). The results of Japanese clinical studies were submitted to evaluate the clinical efficacy and safety of the product including astigmatic correction function.
Total review time: 147 days Regulatory review time: 104 days	Japanese clinical study results				Posterior chamber lenses with an injector	
Feb. 20, 2019	-	40	Alcon AcrySof IQ PanOptix Single-Piece (Alcon Japan Ltd.)	Approval	Instrument & apparatus 72	The product is a single-piece multifocal posterior chamber lens to be inserted into an aphakic eye after cataract surgery. The improvement was made to the product in that it has a trifocal diffractive structure, while the company’s approved product, “Alcon AcrySof IQ ReSTOR Single-Piece” (Approval No. 22000BZX00970000) has a bifocal diffractive structure. The results of Japanese clinical studies were submitted to evaluate the clinical efficacy and safety of the product including its multifocal mechanism, in addition to the performance evaluation of its multifocal mechanism.
Total review time: 216 days Regulatory review time: 156 days	Japanese clinical study results				Multifocal posterior chamber lens	
Feb. 20, 2019	-	41	Alcon AcrySof IQ PanOptix Toric Single-Piece (Alcon Japan Ltd.)	Approval	Instrument & apparatus 72	The product is a single-piece multifocal posterior chamber lens to be inserted into an aphakic eye after cataract surgery accompanied with corneal astigmatism. The improvement was made to the product in that it has a trifocal diffractive structure the same as that of “Alcon AcrySof IQ PanOptix Single Piece” (Approval No. 23100BZX00042000), while the company’s approved products, “Alcon AcrySof IQ ReSTOR +2.5D Toric Single Piece” (Approval No. 22700BZX00006000) and “Alcon AcrySof IQ ReSTOR Toric Single Piece” (Approval No. 22600BZX00007000) each have a bifocal diffractive structure. Since the evaluation of aberrations of cylindrical axis for the company’s approved products showed that trifocusing on the front of the optical part does not affect the rotation, the efficacy and safety of the product were evaluated based on the results of a Japanese clinical study of “Alcon AcrySof IQ PanOptix Single Piece.”
Total review time: 211 days Regulatory review time: 152 days	Japanese clinical study results				Multifocal posterior chamber lens	
Apr. 4, 2018	-	42	XIENCE Xpedition Drug Eluting Stent (Abbott Vascular Japan Co., Ltd.)	Change	Instrument & apparatus 7	A stent system consisting of an everolimus-eluting stent used for the treatment of patients with symptomatic ischemic heart disease who have a de novo coronary lesion (a lesion length of 42 mm or less) with a reference vessel diameter of 2.25-3.75 mm and a delivery catheter used to implant the stent to the site of stenosis. The application was submitted to add a 48 mm long stent to allow further variation in size. Data related to the results of a foreign clinical study on the additional model were submitted.
Total review time: 243 days Regulatory review time: 178 days	Foreign clinical study results				Coronary stent	

Approval Date	Approval Date in US Clinical Study Results: Japanese/Foreign	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Classification Term Name	Notes
Apr. 4, 2018	May 22, 2018	43	XIENCE Sierra Drug Eluting Stent (Abbott Vascular Japan Co., Ltd.)	Approval	Instrument & apparatus 7	A stent system consisting of a drug-eluting stent used for the treatment of patients with symptomatic ischemic heart disease who have a de novo coronary lesion (a lesion length of 32 mm or less) with a reference vessel diameter of 2.25-4.25 mm and a delivery catheter used to implant the stent to the site of stenosis. The product was developed by slightly changing the design of the stent and changing the design of the delivery system to improve deliverability from those of the company's approved product, "XIENCE Alpine Drug Eluting Stent" (Approval No. 22600BZX00529000). The results of Japanese and foreign clinical studies were attached to evaluate the efficacy and safety of the product.
Total review time: 182 days Regulatory review time: 115 days	Foreign and Japanese clinical study results				Coronary stent	
May 24, 2018	Dec. 2, 2016	44	Edwards Sapien 3 (Edwards Lifesciences Limited)	Change	Instrument & apparatus 7	A prosthetic cardiac valve system used for transcatheter valve implantation for patients with severe symptomatic aortic valve stenosis and for whom surgical aortic valve replacement cannot be performed. The application was submitted to add transapical/transaortic delivery systems to achieve transapical/transaortic approaches in transcatheter aortic valve replacement. The results of a foreign clinical study were submitted to evaluate the efficacy and safety of implantation of the product by transapical/transaortic approaches.
Total review time: 206 days Regulatory review time: 116 days	Foreign clinical study results				Transcatheter bovine pericardial valve	
May 24, 2018	-	45	PLATINIUM SonR CRT-D (Sorin CRM SAS)	Approval	Instrument & apparatus 7	An implantable biventricular pacing pulse generator with defibrillation function to supply an appropriate defibrillation pulse to the myocardium to reduce the heart rate to the normal range as necessary when tachycardia is detected, and to supply a pacing pulse to increase the heart rate to the normal range when bradycardia is detected. This device was developed based on the approved product, "PLATINIUM CRT-D" (Approval No. 22800BZI00022000). A major improved point is the addition of a CRT optimization function to automatically regulate AV and VV delays according to the endocardial acceleration signals from the acceleration sensor equipped in "SonRtip lead" (Approval No. 23000BZI00013000), which is used in combination with the device. The results of a foreign clinical study were submitted to evaluate the efficacy and safety of the CRT optimization function.
Total review time: 265 days Regulatory review time: 113 days	Foreign clinical study results				Implantable biventricular pacing pulse generator with defibrillator function	
May 24, 2018	-	46	SonRtip lead (Sorin CRM SAS)	Approval	Instrument & apparatus 7	A pacemaker lead with an acceleration sensor to convert endocardial acceleration into electrical signals equipped in the tip, which is used as an atrial pacing lead for "PLATINIUM SonR CRT-D" (Approval No. 23000BZI00012000) with CRT optimization function. The results of a foreign clinical study were submitted to evaluate the efficacy and safety of the CRT optimization function.
Total review time: 265 days Regulatory review time: 113 days	Foreign clinical study results				Implantable defibrillator/ pacemaker lead	
Jun. 20, 2018	Feb. 22, 2019	47	Orsiro Sirolimus Eluting Coronary Stent System (Biotronik Japan, Inc.)	Change	Instrument & apparatus 7	A stent system consisting of a sirolimus-eluting stent used for the treatment of patients with symptomatic ischemic heart disease who have a de novo coronary lesion (a lesion length of 36 mm or less) with a reference vessel diameter of 2.25-4.0 mm and a delivery catheter used to implant a stent to the site of stenosis. The application was submitted for additional stent size variations of 35 mm and 40 mm. Data related to the results of a foreign clinical study on the additional stent size models were submitted.
Total review time: 145 days Regulatory review time: 121 days	Foreign clinical study results				Coronary stent	
Aug. 2, 2018	May 6, 2017	48	Percepta MRI CRT-P Series (Medtronic Japan Co., Ltd.)	Approval	Instrument & apparatus 7	The device is an implantable biventricular pacing pulse generator without a defibrillator function. Patients implanted with the device can conditionally undergo an MRI scan only when the patient's condition is suitable for the requirements for imaging. The device was developed based on the approved product, "Medtronic Viva CRT-P" (Approval No. 22600BZX00304000). Major improved points are conditionally allowed MRI scans and an additional feature to assess the efficacy of CRT pacing during atrial fibrillation (AF) and to regulate the pacing rates according to the assessment (EffectivCRT during AF feature). The results of a foreign clinical study were submitted to evaluate the efficacy and safety of the EffectivCRT during AF feature.
Total review time: 464 days Regulatory review time: 93 days	Foreign clinical study results				Implantable biventricular pacing pulse generator without defibrillator function	

Approval Date	Approval Date in US Clinical Study Results: Japanese/Foreign	No.	Brand Name (Applicant Company)	New Approval/ Partial Change	Classification Term Name	Notes
Aug. 21, 2018	Apr. 11, 2016	49	BioMonitor 2 (Biotronik Japan, Inc.)	Approval	Instrument & apparatus 21	An implantable data recorder for electrocardiogram, subcutaneously implanted to diagnose arrhythmia in patients who presented with symptoms such as syncope and in whom the cause of the symptom could not be identified despite a careful examination, and to detect atrial fibrillation in patients with cryptogenic cerebral infarction. The results of a foreign clinical study were submitted to evaluate the arrhythmia detection function and safety.
Total review time: 174 days Regulatory review time: 92 days	Foreign clinical study results				Implantable data recorder for electrocardiogram	
Sep. 21, 2018	Feb. 5, 2016	50	Bridge Occlusion Balloon Catheter (Spectranetics Corporation)	Approval	Instrument & apparatus 51	A balloon catheter for temporary use in the superior vena cava for the purpose of emergency hemostasis during lead extraction. Since the existing occlusion balloon catheter has a shorter balloon length that is not long enough to achieve emergency hemostasis during lead extraction, this product was developed as a balloon catheter that can cover the entire superior vena cava. A clinical evaluation report summarizing the foreign literatures on the use of this product or similar products was submitted to evaluate the efficacy and safety of the product.
Total review time: 267 days Regulatory review time: 109 days	Clinical evaluation report				Intravascular catheter for embolization of the central circulation system	
Nov. 20, 2018	Aug. 18, 2013	51	PDA Closure Set II (Abbott Medical Japan Co., Ltd.)	Approval	Instrument & apparatus 51	A self-expanding duct occluder and delivery system intended to be used for percutaneous closure of an opening of the arterial duct in patients with patent ductus arteriosus (PDA). The product was developed to improve the placement of the product into smaller arterial ducts and the compatibility with different forms of arterial ducts based on the approved product, “PDA Closure Set” (Approval No. 22000BZX01768000). The results of foreign clinical studies were submitted to verify the clinical efficacy and safety of the product.
Total review time: 270 days Regulatory review time: 108 days	Foreign clinical study results				Prosthetic material for embolization in vessels of the central circulation system	
Dec. 6, 2018	Nov. 20, 2012	52	Implantable Ventricular Assist Device System HVAD (Medtronic Japan Co., Ltd.)	Approval	Instrument & apparatus 7	The device is an implantable ventricular assist device system used to improve the blood circulation until heart transplant. The device is used for patients who are qualified to receive heart transplant, shown continuous decompensation in spite of drug therapy or circulation assist techniques, such as an external ventricular assist system and considered difficult to survive without heart transplant. A blood pump of the product is a small-sized centrifugal pump compared to that of similar approved products. An impeller inside the pump rotates by the magnetic levitation mechanism and dynamic pressure mechanism. As clinical evaluation data, the results of foreign and Japanese clinical studies were submitted.
Total review time: 462 days Regulatory review time: 122 days	Foreign and Japanese clinical study results				Implantable ventricular assist device	

Table 7. New Regenerative Medical Products Approved in FY 2018

Review Category	Approval Date	Brand Name (Applicant Company)	New Approval/ Partial Change	Classification	Non-proprietary Name	Notes
Regenerative Medical Products	Dec. 28, 2018	JACE (Japan Tissue Engineering Co., Ltd.)	Change	Human somatic cell-processed product	Human (autologous) epidermis-derived cell sheet	A product consisting of a human (autologous) epidermis-derived cell sheet (main component), which is produced using Green's technique, and a container (filled with tissue transport fluid) for transporting the patient's skin tissue to the manufacturing site (sub-component). To prepare the cell sheet, epidermal cells derived from a postage-stamp-sized piece of skin taken from the patient's own skin tissue are co-cultured with mouse embryo-derived 3T3-J2 feeder cells and formed into a sheet. The product has already been approved for the indications for cases of serious and extensive burns, and giant congenital melanocytic nevus. The application was submitted for the additional indications for the treatment of "dystrophic epidermolysis bullosa" and "junctional epidermolysis bullosa." (A "partial change" application) [Orphan regenerative medical products]
Regenerative Medical Products	Dec. 28, 2018	STEMIRAC Inj. (Nipro Corporation)	Conditional/ Time-limited Approval	Human somatic stem cell-processed products	Human (autologous) bone marrow-derived mesenchymal stem cell	A product consisting of human (autologous) bone marrow-derived mesenchymal stem cells (main component), and blood collection and bone marrow harvesting kits (sub-components). To prepare the main component, mesenchymal stem cells in bone marrow fluid taken from the patient are cultured and proliferated in vitro, and then cryopreserved. The sub-components are used for collecting the patient's peripheral blood and bone marrow fluid at medical institutions and for transporting these to the manufacturing site. The cultured bone marrow-derived mesenchymal stem cells are administered via intravenous infusion and used for treatment to improve neurological symptoms and functional disorders associated with spinal cord injury (only for use in patients with traumatic spinal cord injury and ASIA Impairment Scale A, B, or C). [SAKIGAKE designation, Regenerative medical products]
Regenerative Medical Products	Mar. 26, 2019	Kymriah Suspension for Intravenous Infusion (Novartis Pharma K.K.)	Approval	Human somatic cell-processed products	Tisagenlecleucel	The product is a human somatic cell-processed product composed of genetically modified autologous T cells which are cultured and proliferated after introducing chimeric antigen receptor (CAR) which specifically recognizes CD19 antigen using a lentiviral vector into the T cells derived from the patient's peripheral blood. It is given as a single infusion (drip) into a vein and used for the treatment of CD19-positive relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) and CD19-positive relapsed or refractory diffuse large B-cell lymphoma (DLBCL). [Orphan regenerative medical products]
Gene Therapy Products	Mar. 26, 2019	Collategene Intramuscular Injection 4 mg (AnGes, Inc.)	Approval	Plasmid vector products	Beperminogene perplasmid	The product is an injection of plasmid vector composed of 5,181 base pair including cDNA which encodes human hepatocyte growth factor. It is administered intramuscularly to an ischemic site of the lower limb and used for the treatment of ulcers in patients with chronic arterial occlusion (arteriosclerosis obliterans and Burger's disease) who have not responded sufficiently to the standard drug therapy and are unable to undergo revascularization.

Table 8. Changes in the Number of Reports of Adverse Reactions/Malfunctions

(1) Drugs

Fiscal year	Reports from MAHs (Japan)*	Reports from MAHs (outside Japan)*	Reports from healthcare professionals*			Total	Research reports
			Safety information reporting system	Vaccines	Disease reports		
FY 2014	49,276	300,216	4,782	1,398	-	355,672	1,099
FY 2015	51,103	345,253	4,891	1,238	-	402,485	1,219
FY 2016	56,478	394,951	4,960	1,091	-	457,480	1,117
FY 2017	62,092	428,248	6,618	1,018	-	497,976	1,206
FY 2018	63,763	493,243	9,084	863	3	566,956	1,078

** The reports in FY 2015 include case reports of suspected malfunction of device parts in combination products.*

(2) Medical Devices

Fiscal year	Reports from MAHs (Japan)	Reports from MAHs (outside Japan)	Reports from healthcare professionals		Total	Research reports
			Safety information reporting system	Disease reports		
FY 2014	13,994	16,624	420	-	31,038	20
FY 2015	17,603	26,395	406	-	44,404	598
FY 2016	16,283	32,280	548	-	49,111	1,289
FY 2017	16,719	34,168	441	-	51,328	2,701
FY 2018	17,210	35,334	487	0	53,031	2,314

(3) Regenerative Medical Products

Fiscal year	Reports from MAHs (Japan)	Reports from MAHs (outside Japan)	Reports from healthcare professionals	Total	Research reports
FY 2014*	12	0	0	12	0
FY 2015	35	0	0	35	0
FY 2016	88	0	0	88	0
FY 2017	110	0	0	110	0
FY 2018	163	0	0	163	0

** The number of reports submitted after the enactment of the PMD Act on November 25, 2014.*

Table 9. Revisions of PRECAUTIONS for Drugs, etc. and Other Information as Directed by MHLW during FY 2018

○ Revisions of PRECAUTIONS for drugs, etc. and other information implemented by MHLW based on PMDA reports in FY 2018

	Drugs	Medical devices
Directions concerning revisions to PRECAUTIONS in product package insert	94	1
Information published as Pharmaceuticals and Medical Devices Safety Information	23	0

○ Revisions of PRECAUTIONS for Drugs, as Directed by MHLW during FY 2018

Date	Drug name
Apr. 19, 2018	01. Omarigliptin Saxagliptin hydrate Trelagliptin succinate 02. Cladribine 03. Pembrolizumab (genetical recombination) 04. Tosufloxacin tosilate hydrate (oral)
Jun. 5, 2018	01. Amiodarone hydrochloride 02. Filgrastim (genetical recombination) Filgrastim (genetical recombination, follow-on biologic 1) Filgrastim (genetical recombination, follow-on biologic 2) Filgrastim (genetical recombination, follow-on biologic 3) Pegfilgrastim (genetical recombination) Lenograstim (genetical recombination) 03. Everolimus (tablets 2.5mg/5mg, dispersible tablets 2mg/3mg) 04. Eftrenonacog alfa (genetical recombination) 05. Metronidazole (oral, injection) Vonoprazan fumarate/Amoxicillin hydrate/Metronidazole Rabeprazole sodium/Amoxicillin hydrate/Metronidazole Lansoprazole/Amoxicillin hydrate/Metronidazole
Jul. 10, 2018	01. Tacrolimus hydrate (ophthalmic solution) 02. Tacrolimus hydrate (ointment) 03. Azathioprine 04. Ciclosporin (oral, injection) 05. Tacrolimus hydrate (oral, injection)
Aug. 2, 2018	01. Apremilast 02. Ceftriaxone sodium hydrate
Sep. 18, 2018	01. Radium (223Ra) chloride 02. Sunitinib malate 03. Ampicillin hydrate Bacampicillin hydrochloride Ampicillin sodium/Cloxacillin sodium hydrate 04. Ampicillin sodium 05. Sultamicillin tosilate hydrate 06. Ampicillin hydrate/Cloxacillin sodium hydrate 07. Dolutegravir sodium 08. Dolutegravir sodium/Abacavir sulfate/Lamivudine
Oct. 16, 2018	01. Atorvastatin calcium hydrate Ezetimibe/Atorvastatin calcium hydrate Pravastatin sodium Amlodipine basilate/Atorvastatin calcium hydrate

Date	Drug name
	02. Clinofibrate 03. Clofibrate 04. Simvastatin 05. Pitavastatin calcium hydrate 06. Fenofibrate Bezafibrate 07. Fluvastatin sodium 08. Pemafibrate 09. Rosuvastatin calcium
Oct. 23, 2018	01. Lamotrigine 02. Secukinumab (genetical recombination) 03. Lenvatinib mesilate
Nov. 27, 2018	01. Aluminum potassium sulfate hydrate/Tannic acid (with saline) 02. Aluminum potassium sulfate hydrate/Tannic acid (with analgesic agents) 03. Calcitriol (injection) 04. Freeze-dried live attenuated varicella vaccine
Jan. 10, 2019	01. Nusinersen sodium 02. Axitinib 03. Lenalidomide hydrate 04. Ofloxacin (oral) Garenoxacin mesilate hydrate Ciprofloxacin Tosufloxacin tosilate hydrate (oral; with dosage and administration for pediatric use) Pazufloxacin mesilate Moxifloxacin hydrochloride (oral) Levofloxacin hydrate (oral, injection) Lomefloxacin hydrochloride 05. Sitafloxacin hydrate Ciprofloxacin hydrochloride hydrate Tosufloxacin tosilate hydrate (oral; without dosage and administration for pediatric use) Norfloxacin (oral) Prulifloxacin 06. Asunaprevir Daclatasvir hydrochloride Daclatasvir hydrochloride/Asunaprevir/Beclabuvir hydrochloride
Feb. 12, 2019	01. Eliglustat tartrate 02. Trastuzumab (genetical recombination) Trastuzumab (genetical recombination) follow-on biologic 1 Trastuzumab (genetical recombination) follow-on biologic 2 Trastuzumab (genetical recombination) follow-on biologic 3 03. Nivolumab (genetical recombination) 04. Palbociclib 05. Pembrolizumab (genetical recombination) 06. Glecaprevir hydrate/Pibrentasvir
Mar. 1, 2019	01. Oseltamivir phosphate 02. Baloxavir marboxil
Mar. 19, 2019	01. Quetiapine fumarate 02. Clozapine 03. Vonoprazan fumarate 04. Denosumab (genetical recombination) (120 mg product)

Date	Drug name
	05. Vonoprazan fumarate/Amoxicillin hydrate/Clarithromycin Vonoprazan fumarate/Amoxicillin hydrate/Metronidazole 06. Intravenous injection containing sorbitol as excipient 07. Intravenous injection containing fructose as excipient

**Note: More detailed information is available on the PMDA website.*

Table 10. Revisions of PRECAUTIONS for Medical Devices and Other Information, as Directed by MHLW Based on Reports from PMDA during FY 2018

Date	Title
August 8, 2018	Revision of Precautions in the Package Inserts of Ultrasonic Surgical Aspirator Devices

**Note: More detailed information is available on the PMDA website.*

Table 11. FY 2018 Pharmaceuticals and Medical Devices Safety Information (No. 352-361)

Date	No.	Table of Contents
April 17, 2018	352	1. Introduction of the International Standards (ISO [IEC] 80369 series) Related to Connectors for Prevention of Interconnection - Switching of small-bore connectors for neuraxial anesthesia - 2. Important Safety Information (1) Tolvaptan (2) Anagliptin, linagliptin, teneligliptin hydrobromide hydrate, teneligliptin hydrobromide hydrate/canagliflozin hydrate (3) Anagliptin (4) Sterile talc 3. Revision of Precautions (No. 293) Tolvaptan (and 5 others) 4. List of Products Subject to Early Post-marketing Phase Vigilance
May 22, 2018	353	1. Initiative for the Compilation of Database-stored Data and Provision of Information concerning Pediatric Drugs 2. Important Safety Information (1) Pembrolizumab (genetical recombination) 3. Revision of Precautions (No. 294) (1) Omarigliptin (2) Saxagliptin hydrate (3) Trelagliptin succinate (and 3 others) 4. List of Products Subject to Early Post-marketing Phase Vigilance
July 3, 2018	354	1. Guidance of Appropriate Medication for Elderly Patients (general) 2. Important Safety Information (1) Pegfilgrastim (genetical recombination) (2) Filgrastim (genetical recombination, follow on biologics) (3) Lenograstim (genetical recombination) 3. Revision of Precautions (No. 295) Amiodarone hydrochloride (and 4 others) 4. List of Products Subject to Early Post-marketing Phase Vigilance
August 7, 2018	355	1. Review of Contraindications for Immunosuppressants in Pregnant Women, etc. 2. List of Products Subject to Early Post-marketing Phase Vigilance (Reference) Revision of the Ministerial Ordinance on Good Post-marketing Study Practice (GPSP Ordinance)
September 4, 2018	356	1. Guidance on Safe and Secure Radio Wave Utilization in Medical Institutions 2. Important Safety Information (1) Ceftriaxone sodium hydrate 3. Revision of Precautions (No. 296) Apremilast (and 1 other) 4. List of Products Subject to Early Post-marketing Phase Vigilance
October 16, 2018	357	1. Initiative of Revision of the Manuals for Management of Various Serious Adverse Drug Reactions (Part 2) 2. Summary of the Relief System for Adverse Drug Reaction and Request for Cooperation with the System 3. Revision of Precautions (No. 297) Amantadine hydrochloride (and 13 others) 4. List of Products Subject to Early Post-marketing Phase Vigilance

Date	No.	Table of Contents
November 20, 2018	358	1. Safety Measures for Influenza Antiviral Drugs 2. Results of a Survey Investigating Access, Communication, and Utilization of Drug Safety Information at Hospitals and Pharmacies and Desirable Directions 3. Important Safety Information (1) Secukinumab (genetical recombination) (2) Lamotrigine (3) Lenvatinib mesilate 4. Revision of Precautions (No. 298) (1) Atorvastatin calcium hydrate (2) Ezetimibe/atorvastatin calcium hydrate (3) Pravastatin sodium (4) Amlodipine basilate/atorvastatin calcium hydrate (and 11 others) 5. List of Products Subject to Early Post-marketing Phase Vigilance
December 25, 2018	359	1. Safety of Influenza Antiviral Drugs 2. Suspected Adverse Reactions to Influenza Vaccines in the 2017 Season 3. Important Safety Information (1) [1] Aluminum potassium sulfate hydrate/tannic acid (with saline) [2] Aluminum potassium sulfate hydrate/tannic acid (with analgesic agents) (2) Calcitriol (injectable dosage form) (3) Freeze-dried live attenuated varicella vaccine 4. Revision of Precautions (No. 299) Aluminum potassium sulfate hydrate/tannic acid (with saline) (and 3 others) 5. List of Products Subject to Early Post-marketing Phase Vigilance
February 5, 2019	360	1. Package Inserts of Prescription Drugs under the Revised Instructions 2. Important Safety Information (1) Nusinersen sodium (2) Axitinib 3. Revision of Precautions (No. 300) Nusinersen sodium (and 5 others) 4. List of Products Subject to Early Post-marketing Phase Vigilance
March 12, 2019	361	1. Genome Research relating to Drug-induced Muscle Disorders 2. Important Safety Information (1) Trastuzumab (genetical recombination) and other follow-on biologics (2) Nivolumab (genetical recombination) (3) Palbociclib (4) Pembrolizumab (genetical recombination) 3. Revision of Precautions (No. 301) Eliglustat tartrate (and 5 others) 4. List of Products Subject to Early Post-marketing Phase Vigilance

**Note: More detailed information is available on the PMDA website.*

Table 12. FY 2018 PMDA Medical Safety Information

No.	Month and year published	Title
54	June 2018	Precautions When Using an Indwelling Bladder Catheter
55	August 2018	Introduction of Connectors to Prevent Misconnection (Neuraxial Anesthesia)
56	February 2019	Precautions When Using Compression Stockings
57	February 2019	Precautions When Using Subcutaneous Ports and Catheters

**Note: More detailed information is available on the PMDA website.*

Table 13. List of User Fees for Drugs

List of user fees for reviews etc. of pharmaceuticals, quasi-drugs, and cosmetics based on the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Act No. 145 of 1960)

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.

(Yen)

Classification			User fees		
			Review	Inspection	Total
Assessment for manufacturing license of drugs					
	New license	On-site		159,900	159,900
				Article 31, Paragraph 1, Item 1 (a)	
		Document		120,400	120,400
				Article 31, Paragraph 1, Item 1 (b)	
	Renewal of existing license	On-site		105,200	105,200
				Article 31, Paragraph 1, Item 2 (a)	
		Document		59,700	59,700
				Article 31, Paragraph 1, Item 2 (b)	
	Change/addition of classification	On-site		105,200	105,200
				Article 31, Paragraph 1, Item 3 (a)	
		Document		59,700	59,700
				Article 31, Paragraph 1, Item 3 (b)	
Assessment for foreign manufacturers' accreditation of drugs					
	New accreditation	On-site		143,900 + overseas travel expenses	143,900 + overseas travel expenses
				Article 31, Paragraph 2, Item 1 (a)	
		Document		62,600	62,600
				Article 31, Paragraph 2, Item 1 (b)	
	Renewal of existing license	On-site		69,700 + overseas travel expenses	69,700 + overseas travel expenses
				Article 31, Paragraph 2, Item 2 (a)	
		Document		42,900	42,900
				Article 31, Paragraph 2, Item 2 (b)	
	Change/addition of classification	On-site		69,700 + overseas travel expenses	69,700 + overseas travel expenses
				Article 31, Paragraph 2, Item 3 (a)	
		Document		42,900	42,900
				Article 31, Paragraph 2, Item 3 (b)	

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.

(Yen)

Classification				User fees		
				Review	Inspection	Total
Review for approval of drugs (new approval)						
New drugs (No. 1) (non-orphan drugs)		First application products		28,545,700	8,096,400 (+ overseas travel expenses *1)	36,642,100 (+ overseas travel expenses *1)
				Article 32, Paragraph 1, Item 1 (a)-(1)	Article 32, Paragraph 2, Item 1 (a)	
		Line extension products		2,956,800	2,023,900 (+ overseas travel expenses *1)	4,980,700 (+ overseas travel expenses *1)
				Article 32, Paragraph 1, Item 1 (a)-(3)	Article 32, Paragraph 2, Item 1 (c)	
New drugs (No. 1) (orphan drugs)		First application products		23,921,000	4,056,000 (+ overseas travel expenses *1)	27,977,000 (+ overseas travel expenses *1)
				Article 32, Paragraph 1, Item 1 (a)-(2)	Article 32, Paragraph 2, Item 1 (b)	
		Line extension products		2,473,800	1,009,800 (+ overseas travel expenses *1)	3,483,600 (+ overseas travel expenses *1)
				Article 32, Paragraph 1, Item 1 (a)-(4)	Article 32, Paragraph 2, Item 1 (d)	
New drugs (No. 2) (non-orphan drugs)		First application products		13,623,700	3,040,300 (+ overseas travel expenses *1)	16,664,000 (+ overseas travel expenses *1)
				Article 32, Paragraph 1, Item 1 (a)-(5)	Article 32, Paragraph 2, Item 1 (e)	
		Line extension products		1,409,100	760,300 (+ overseas travel expenses *1)	2,169,400 (+ overseas travel expenses *1)
				Article 32, Paragraph 1, Item 1 (a)-(7)	Article 32, Paragraph 2, Item 1 (g)	
New drugs (No. 2) (orphan drugs)		First application products		11,214,800	1,521,200 (+ overseas travel expenses *1)	12,736,000 (+ overseas travel expenses *1)
				Article 32, Paragraph 1, Item 1 (a)-(6)	Article 32, Paragraph 2, Item 1 (f)	
		Line extension products		1,204,900	382,800 (+ overseas travel expenses *1)	1,587,700 (+ overseas travel expenses *1)
				Article 32, Paragraph 1, Item 1 (a)-(8)	Article 32, Paragraph 2, Item 1 (h)	
Generic drugs		with inspections		649,100	346,700 (+ overseas travel expenses *1)	995,800 (+ overseas travel expenses *1)
				Article 32, Paragraph 1, Item 1 (a)-(9)	Article 32, Paragraph 2, Item 1 (i)	
		without inspection		649,100		649,100
				Article 32, Paragraph 1, Item 1 (a)-(9)		
BTC/OTC drugs	Switch to OTC status, etc.	First application products	with inspections	1,356,100	346,700 (+ overseas travel expenses *1)	1,702,800 (+ overseas travel expenses *1)
				Article 32, Paragraph 1, Item 1 (a)-(10)	Article 32, Paragraph 2, Item 1 (i)	
			without inspection	1,356,100		1,356,100
				Article 32, Paragraph 1, Item 1 (a)-(10)		
		Line extension products	with inspections	1,356,100	346,700 (+ overseas travel expenses *1)	1,702,800 (+ overseas travel expenses *1)
				Article 32, Paragraph 1, Item 1 (a)-(10)	Article 32, Paragraph 2, Item 1 (i)	
			without inspection	1,356,100		1,356,100
				Article 32, Paragraph 1, Item 1 (a)-(10)		
	Others		with inspections	115,800	346,700 (+ overseas travel expenses *1)	462,500 (+ overseas travel expenses *1)
				Article 32, Paragraph 1, Item 1 (a)-(11)	Article 32, Paragraph 2, Item 1 (i)	
			without inspection	115,800		115,800
				Article 32, Paragraph 1, Item 1 (a)-(11)		
Quasi-drugs		New active ingredients		3,130,100		3,130,100
				Article 32, Paragraph 1, Item 1 (b)-(1)		
		New dosage, etc.		258,900		258,900
				Article 32, Paragraph 1, Item 1 (b)-(2)		
		Others		66,600		66,600
				Article 32, Paragraph 1, Item 1 (b)-(6)		

(*1) Overseas travel expenses (Article 32, Paragraph 3) are added to the user fees if an inspection is conducted overseas.

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.

(Yen)

Classification			User fees		
			Review	Inspection	Total
Review for approval of drugs (new approval)					
Pest control agents	New active ingredients		5,237,200 Article 32, Paragraph 1, Item 1 (a)-(12) and (b)-(3)		5,237,200
	New dosage, etc.		411,800 Article 32, Paragraph 1, Item 1 (a)-(13) and (b)-(4)		411,800
	Others		100,200 Article 32, Paragraph 1, Item 1 (a)-(14) and (b)-(5)		100,200
Cosmetics			66,600 Article 32, Paragraph 1, Item 1 (c)		66,600
New application for change or replacement of brand name			37,300 Article 32, Paragraph 1, Item 1 (d)		37,300
Review for approval of drugs (approval for partial changes to approved matters)					
New drugs (No. 1) (non-orphan drugs)	Changes in indications, etc.	First application products	12,228,600 Article 32, Paragraph 1, Item 2 (a)-(1)	3,040,300 (+ overseas travel expenses *1) Article 32, Paragraph 2, Item 2 (a)	15,268,900 (+ overseas travel expenses *1)
		Line extension products	1,268,800 Article 32, Paragraph 1, Item 2 (a)-(2)	760,300 (+ overseas travel expenses *1) Article 32, Paragraph 2, Item 2 (b)	2,029,100 (+ overseas travel expenses *1)
	Others		246,100 Article 32, Paragraph 1, Item 2 (a)-(3)	149,000 (+ overseas travel expenses *1) Article 32, Paragraph 2, Item 2 (c)	395,100 (+ overseas travel expenses *1)
New drugs (No. 1) (orphan drugs)	Changes in indications, etc.	First application products	10,121,100 Article 32, Paragraph 1, Item 2 (a)-(4)	1,521,200 (+ overseas travel expenses *1) Article 32, Paragraph 2, Item 2 (d)	11,642,300 (+ overseas travel expenses *1)
		Line extension products	1,050,700 Article 32, Paragraph 1, Item 2 (a)-(5)	382,800 (+ overseas travel expenses *1) Article 32, Paragraph 2, Item 2 (e)	1,433,500 (+ overseas travel expenses *1)
	Others		159,200 Article 32, Paragraph 1, Item 2 (a)-(6)	135,400 (+ overseas travel expenses *1) Article 32, Paragraph 2, Item 2 (f)	294,600 (+ overseas travel expenses *1)
New drugs (No. 2) (non-orphan drugs)	Changes in indications, etc.	First application products	12,228,600 Article 32, Paragraph 1, Item 2 (a)-(1)	3,040,300 (+ overseas travel expenses *1) Article 32, Paragraph 2, Item 2 (a)	15,268,900 (+ overseas travel expenses *1)
		Line extension products	1,268,800 Article 32, Paragraph 1, Item 2 (a)-(2)	760,300 (+ overseas travel expenses *1) Article 32, Paragraph 2, Item 2 (b)	2,029,100 (+ overseas travel expenses *1)
	Others		246,100 Article 32, Paragraph 1, Item 2 (a)-(3)	149,000 (+ overseas travel expenses *1) Article 32, Paragraph 2, Item 2 (c)	395,100 (+ overseas travel expenses *1)
New drugs (No. 2) (orphan drugs)	Changes in indications, etc.	First application products	10,121,100 Article 32, Paragraph 1, Item 2 (a)-(4)	1,521,200 (+ overseas travel expenses *1) Article 32, Paragraph 2, Item 2 (d)	11,642,300 (+ overseas travel expenses *1)
		Line extension products	1,050,700 Article 32, Paragraph 1, Item 2 (a)-(5)	382,800 (+ overseas travel expenses *1) Article 32, Paragraph 2, Item 2 (e)	1,433,500 (+ overseas travel expenses *1)
	Others		159,200 Article 32, Paragraph 1, Item 2 (a)-(6)	135,400 (+ overseas travel expenses *1) Article 32, Paragraph 2, Item 2 (f)	294,600 (+ overseas travel expenses *1)

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.

(Yen)

Classification						User fees		
						Review	Inspection	Total
	Generic drugs	Changes in indications, etc.	First application products			10,700,000	2,660,200 (+ overseas travel expenses *1)	13,360,200 (+ overseas travel expenses *1)
						Article 32, Paragraph 1, Item 2 (a)-(7)	Article 32, Paragraph 2, Item 2 (g)	
			Line extension products			1,110,200	665,200 (+ overseas travel expenses *1)	1,775,400 (+ overseas travel expenses *1)
						Article 32, Paragraph 1, Item 2 (a)-(8)	Article 32, Paragraph 2, Item 2 (h)	
		Changes based on guidelines, etc.				56,000		56,000
						Article 32, Paragraph 1, Item 2 (a)-(9)		
		Others				323,000	195,500 (+ overseas travel expenses *1)	518,500 (+ overseas travel expenses *1)
						Article 32, Paragraph 1, Item 2 (a)-(10)	Article 32, Paragraph 2, Item 2 (i)	
	BTC/OTC drugs	Switch to OTC status, etc.	Changes in indications, etc.	First application products	with inspections	10,700,000	195,500 (+ overseas travel expenses *1)	10,895,500 (+ overseas travel expenses *1)
						Article 32, Paragraph 1, Item 2 (a)-(7)	Article 32, Paragraph 2, Item 2 (i)	
					without inspection	10,700,000		10,700,000
						Article 32, Paragraph 1, Item 2 (a)-(7)		
				Line extension products	with inspections	1,110,200	195,500 (+ overseas travel expenses *1)	1,305,700 (+ overseas travel expenses *1)
						Article 32, Paragraph 1, Item 2 (a)-(8)	Article 32, Paragraph 2, Item 2 (i)	
					without inspection	1,110,200		1,110,200
						Article 32, Paragraph 1, Item 2 (a)-(8)		
			Others		with inspections	59,200	195,500 (+ overseas travel expenses *1)	254,700 (+ overseas travel expenses *1)
						Article 32, Paragraph 1, Item 2 (a)-(11)	Article 32, Paragraph 2, Item 2 (i)	
					without inspection	59,200		59,200
						Article 32, Paragraph 1, Item 2 (a)-(11)		
		Changes based on guidelines, etc.			with inspections	37,300	195,500 (+ overseas travel expenses *1)	232,800 (+ overseas travel expenses *1)
						Article 32, Paragraph 1, Item 2 (a)-(12)	Article 32, Paragraph 2, Item 2 (i)	
					without inspection	37,300		37,300
						Article 32, Paragraph 1, Item 2 (a)-(12)		
		Others			with inspections	59,200	195,500 (+ overseas travel expenses *1)	254,700 (+ overseas travel expenses *1)
						Article 32, Paragraph 1, Item 2 (a)-(11)	Article 32, Paragraph 2, Item 2 (i)	
					without inspection	59,200		59,200
						Article 32, Paragraph 1, Item 2 (a)-(11)		
	Quasi-drugs					37,300		37,300
						Article 32, Paragraph 1, Item 2 (b)-(1)		
	Cosmetics					37,300		37,300
						Article 32, Paragraph 1, Item 2 (c)		
	Pest control agents					50,800		50,800
						Article 32, Paragraph 1, Item 2 (a)-(13) and (b)-(2)		

(*1) Overseas travel expenses (Article 32, Paragraph 3) are added to the user fees if an inspection is conducted overseas.

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.

(Yen)

Classification				User fees		
				Review	Inspection	Total
GMP inspection of drugs						
	Approval, partial change and manufacture for export	New drugs	In Japan		875,000	875,000
					Article 32, Paragraph 5, Item 1 (b)-(1)	
			Overseas		1,104,200 (+ overseas travel expenses *2)	1,104,200 (+ overseas travel expenses *2)
					Article 32, Paragraph 5, Item 1 (b)-(2)	
		Biological drugs/Radiopharmaceuticals, etc.	In Japan		787,800	787,800
					Article 32, Paragraph 5, Item 1 (a)-(1)	
			Overseas		998,800 (+ overseas travel expenses *2)	998,800 (+ overseas travel expenses *2)
					Article 32, Paragraph 5, Item 1 (a)-(2)	
		Sterile drugs/Sterile quasi-drugs	In Japan		548,700	548,700
					Article 32, Paragraph 5, Item 1 (c)-(1)	
			Overseas		691,200 (+ overseas travel expenses *2)	691,200 (+ overseas travel expenses *2)
					Article 32, Paragraph 5, Item 1 (c)-(2)	
		Other Drugs/Quasi-drugs	In Japan		398,400	398,400
					Article 32, Paragraph 5, Item 1 (d)-(1)	
			Overseas		501,900 (+ overseas travel expenses *2)	501,900 (+ overseas travel expenses *2)
					Article 32, Paragraph 5, Item 1 (d)-(2)	
		Packaging, labeling, storage, external testing, etc.	In Japan		75,400	75,400
					Article 32, Paragraph 5, Item 2 (a) and Paragraph 6, Item 1 (a)	
			Overseas		100,200 (+ overseas travel expenses *2)	100,200 (+ overseas travel expenses *2)
					Article 32, Paragraph 5, Item 2 (b) and Paragraph 6, Item 1 (b)	

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.

(Yen)

Classification					User fees		
					Review	Inspection	Total
	Renewal of approval/Renewal of manufacture for export	Biological drugs/Radiopharmaceuticals, etc.	Basic	In Japan		787,800 Article 32, Paragraph 5, Item 3 (a)-(1)	787,800
				Overseas		998,800 (+ overseas travel expenses *2) Article 32, Paragraph 5, Item 3 (a)-(2)	998,800 (+ overseas travel expenses *2)
			Addition of products	In Japan		36,100 Article 32, Paragraph 5, Item 3 (a)-(1)	36,100
				Overseas		36,100 Article 32, Paragraph 5, Item 3 (a)-(2)	36,100
		Sterile drugs/Sterile quasi-drugs	Basic	In Japan		548,500 Article 32, Paragraph 5, Item 3 (b)-(1)	548,500
				Overseas		691,200 (+ overseas travel expenses *2) Article 32, Paragraph 5, Item 3 (b)-(2)	691,200 (+ overseas travel expenses *2)
			Addition of products	In Japan		14,700 Article 32, Paragraph 5, Item 3 (b)-(1)	14,700
				Overseas		14,700 Article 32, Paragraph 5, Item 3 (b)-(2)	14,700
		Other Drugs/Quasi-drugs	Basic	In Japan		398,400 Article 32, Paragraph 5, Item 3 (c)-(1)	398,400
				Overseas		501,900 (+ overseas travel expenses *2) Article 32, Paragraph 5, Item 3 (c)-(2)	501,900 (+ overseas travel expenses *2)
			Addition of products	In Japan		11,300 Article 32, Paragraph 5, Item 3 (c)-(1)	11,300
				Overseas		11,300 Article 32, Paragraph 5, Item 3 (c)-(2)	11,300
		Packaging, labeling, storage, external testing, etc.	Basic	In Japan		305,700 Article 32, Paragraph 5, Item 3 (d)-(1) and Paragraph 6, Item 2 (a)	305,700
				Overseas		399,900 (+ overseas travel expenses *2) Article 32, Paragraph 5, Item 3 (d)-(2) and Paragraph 6, Item 2 (b)	399,900 (+ overseas travel expenses *2)
			Addition of products	In Japan		8,000 Article 32, Paragraph 5, Item 3 (d)-(1) and Paragraph 6, Item 2 (a)	8,000
				Overseas		8,000 Article 32, Paragraph 5, Item 3 (d)-(2) and Paragraph 6, Item 2 (b)	8,000

(*2) Overseas travel expenses (Article 32, Paragraph 7) are added to the user fees if an inspection is conducted overseas.

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.

(Yen)

Classification					User fees		
					Review	Inspection	Total
GLP inspection of drugs							
	GLP	In Japan				2,545,600 Article 32, Paragraph 4, Item 1 (a)	2,545,600
		Overseas				2,817,400 + overseas travel expenses Article 32, Paragraph 4, Item 1 (b)	2,817,400 + overseas travel expenses
GCP inspection of drugs							
	New GCP	First application products	In Japan	New		3,361,200 Article 32, Paragraph 4, Item 2 (a)-(1)	3,361,200
				Partial change		3,361,200 Article 32, Paragraph 4, Item 2 (b)-(1)	3,361,200
			Overseas	New		3,717,600 + overseas travel expenses Article 32, Paragraph 4, Item 2 (a)-(2)	3,717,600 + overseas travel expenses
				Partial change		3,717,600 + overseas travel expenses Article 32, Paragraph 4, Item 2 (b)-(2)	3,717,600 + overseas travel expenses
		Line extension products	In Japan	New		889,600 Article 32, Paragraph 4, Item 2 (a)-(3)	889,600
				Partial change		889,600 Article 32, Paragraph 4, Item 2 (b)-(3)	889,600
			Overseas	New		927,900 + overseas travel expenses Article 32, Paragraph 4, Item 2 (a)-(4)	927,900 + overseas travel expenses
				Partial change		927,900 + overseas travel expenses Article 32, Paragraph 4, Item 2 (b)-(4)	927,900 + overseas travel expenses
	GCP inspection of generic drugs		In Japan	New		696,700 Article 32, Paragraph 4, Item 2 (a)-(5)	696,700
				Partial change		696,700 Article 32, Paragraph 4, Item 2 (b)-(5)	696,700
			Overseas	New		1,026,200 + overseas travel expenses Article 32, Paragraph 4, Item 2 (a)-(6)	1,026,200
				Partial change		1,026,200 + overseas travel expenses Article 32, Paragraph 4, Item 2 (b)-(6)	1,026,200
	GCP inspection of BTC /OTC drugs		In Japan	New		696,700 Article 32, Paragraph 4, Item 2 (a)-(5)	696,700
				Partial change		696,700 Article 32, Paragraph 4, Item 2 (b)-(5)	696,700
			Overseas	New		1,026,200 + overseas travel expenses Article 32, Paragraph 4, Item 2 (a)-(6)	1,026,200
				Partial change		1,026,200 + overseas travel expenses Article 32, Paragraph 4, Item 2 (b)-(6)	1,026,200

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.

(Yen)

Classification				User fees		
				Review	Inspection	Total
Re-examination of drugs						
	Re-examination	First application products		967,800	3,300,100 (+ overseas travel expenses *3)	4,267,900 (+ overseas travel expenses *3)
				Article 32, Paragraph 9, Item 1	Article 32, Paragraph 10, Item 1 (a)	
		Line extension products		325,800	1,101,100 (+ overseas travel expenses *3)	1,426,900 (+ overseas travel expenses *3)
				Article 32, Paragraph 9, Item 2	Article 32, Paragraph 10, Item 1 (b)	
	GLP for re-examination	In Japan			2,545,600	2,545,600
					Article 32, Paragraph 10, Item 2 (a)-(1)	
		Overseas			2,817,400 (+ overseas travel expenses *3)	2,817,400 (+ overseas travel expenses *3)
					Article 32, Paragraph 10, Item 2 (a)-(2)	
	GPSP	First application products	In Japan		2,707,200	2,707,200
					Article 32, Paragraph 10, Item 2 (b)-(1)	
			Overseas		2,974,200 (+ overseas travel expenses *3)	2,974,200 (+ overseas travel expenses *3)
					Article 32, Paragraph 10, Item 2 (b)-(2)	
		Line extension products	In Japan		928,900	928,900
					Article 32, Paragraph 10, Item 2 (b)-(3)	
			Overseas		953,200 (+ overseas travel expenses *3)	953,200 (+ overseas travel expenses *3)
					Article 32, Paragraph 10, Item 2 (b)-(4)	

(*3) Overseas travel expenses (Article 32, Paragraph 11) are added to the user fees if an inspection is conducted overseas.

Revised on April 1, 2018

Table 14-1. List of User Fees for Medical Devices and In Vitro Diagnostics

List of user fees for reviews etc. of medical devices and in vitro diagnostics under the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Act No. 145 of 1960)

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. (Yen)

Classification				User fees		
				Review	Inspection	Total
Review for approval of medical devices and *in vitro* diagnostics (new approval)						
New medical devices (Class IV)				14,581,400 Article 33, Paragraph 1, Item 1 (a)-(1)	1,144,700 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 1 (a)	15,726,100 (+ overseas travel expenses *1)
New medical devices (Class II/III)				10,406,700 Article 33, Paragraph 1, Item 1 (a)-(3)	1,144,700 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 1 (a)	11,551,400 (+ overseas travel expenses *1)
Improved medical devices with clinical data (Class IV)				8,325,300 Article 33, Paragraph 1, Item 1 (a)-(2)	915,800 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 1 (b)	9,241,100 (+ overseas travel expenses *1)
Improved medical devices with clinical data (Class II/III)				4,986,300 Article 33, Paragraph 1, Item 1 (a)-(4)	915,800 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 1 (b)	5,902,100 (+ overseas travel expenses *1)
Improved medical devices without clinical data, without approval standards (Class IV)				2,779,300 Article 33, Paragraph 1, Item 1 (a)-(7)	83,100 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 1 (c)	2,862,400 (+ overseas travel expenses *1)
Generic medical devices without clinical data, without approval standards (Class IV)				2,085,800 Article 33, Paragraph 1, Item 1 (a)-(8)	83,100 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 1 (c)	2,168,900 (+ overseas travel expenses *1)
Improved/generic medical devices without clinical data, without approval standards (Class II/III)				1,663,600 Article 33, Paragraph 1, Item 1 (a)-(9)	83,100 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 1 (c)	1,746,700 (+ overseas travel expenses *1)
Generic medical devices with approval standards (Class IV)				506,400 Article 33, Paragraph 1, Item 1 (a)-(5)	83,100 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 1 (c)	589,500 (+ overseas travel expenses *1)
Generic medical devices with approval standards (Class II/III)				406,000 Article 33, Paragraph 1, Item 1 (a)-(6)	83,100 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 1 (c)	489,100 (+ overseas travel expenses *1)
Re-processed single-use medical devices		(Class IV)		8,325,300 Article 33, Paragraph 1, Item 1 (a)-(2)	915,800 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 1 (b)	9,241,100 (+ overseas travel expenses *1)
		(Class II/III)		4,986,300 Article 33, Paragraph 1, Item 1 (a)-(4)	915,800 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 1 (b)	5,902,100 (+ overseas travel expenses *1)
In vitro diagnostics	New products	Excluding companion diagnostics		2,534,000 Article 33, Paragraph 1, Item 1 (b)-(2)		2,534,000
		Companion diagnostics		4,295,000 Article 33, Paragraph 1, Item 1 (b)-(3)		4,295,000
	Out of scope of approval standards	With clinical data	Excluding companion diagnostics	2,534,000 Article 33, Paragraph 1, Item 1 (b)-(2)		2,534,000
			Companion diagnostics	4,295,000 Article 33, Paragraph 1, Item 1 (b)-(3)		4,295,000
		Without clinical data		2,362,200 Article 33, Paragraph 1, Item 1 (b)-(4)		2,362,200
	Nonconformity with approval standards	With clinical data	Excluding companion diagnostics	2,534,000 Article 33, Paragraph 1, Item 1 (b)-(2)		2,534,000
			Companion diagnostics	4,295,000 Article 33, Paragraph 1, Item 1 (b)-(3)		4,295,000
		Without clinical data		1,096,500 Article 33, Paragraph 1, Item 1 (b)-(6)		1,096,500
	Conformity with approval standards	Without clinical data		380,100 Article 33, Paragraph 1, Item 1 (b)-(5)		380,100
	Addition of series			63,300 Article 33, Paragraph 1, Item 1 (b)-(1)		63,300
Change of brand name				37,300 Article 33, Paragraph 1, Item 1 (c)		37,300

(*1) Overseas travel expenses (Article 33, Paragraph 3) are added to the user fees if an inspection is conducted overseas.

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.

(Yen)

Classification				User fees		
				Review	Inspection	Total
Review for approval of medical devices and *in vitro* diagnostics (approval for partial changes to approved matters)						
New medical devices (Class IV)				7,298,400 Article 33, Paragraph 1, Item 2 (a)-(1)	1,144,700 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (a)	8,443,100 (+ overseas travel expenses *1)
New medical devices (Class II/III)				5,208,900 Article 33, Paragraph 1, Item 2 (a)-(3)	1,144,700 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (a)	6,353,600 (+ overseas travel expenses *1)
Improved medical devices with clinical data (Class IV)				4,167,100 Article 33, Paragraph 1, Item 2 (a)-(2)	915,800 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (b)	5,082,900 (+ overseas travel expenses *1)
Improved medical devices with clinical data (Class II/III)				2,509,000 Article 33, Paragraph 1, Item 2 (a)-(4)	915,800 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (b)	3,424,800 (+ overseas travel expenses *1)
Improved medical devices without clinical data, without approval standards (Class IV)				1,393,800 Article 33, Paragraph 1, Item 2 (a)-(7)	45,000 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (c)	1,438,800 (+ overseas travel expenses *1)
Generic medical devices without clinical data, without approval standards (Class IV)				1,043,300 Article 33, Paragraph 1, Item 2 (a)-(8)	45,000 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (c)	1,088,300 (+ overseas travel expenses *1)
Improved/generic medical devices without clinical data, without approval standards (Class II/III)				837,200 Article 33, Paragraph 1, Item 2 (a)-(9)	45,000 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (c)	882,200 (+ overseas travel expenses *1)
Generic medical devices with approval standards (Class IV)				256,700 Article 33, Paragraph 1, Item 2 (a)-(5)	45,000 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (c)	301,700 (+ overseas travel expenses *1)
Generic medical devices with approval standards (Class II/III)				204,800 Article 33, Paragraph 1, Item 2 (a)-(6)	45,000 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (c)	249,800 (+ overseas travel expenses *1)
Others (medical devices)				169,300 Article 33, Paragraph 1, Item 2 (a)-(10)	45,000 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (c)	214,300 (+ overseas travel expenses *1)
Reprocessed single-use medical devices		With design/ manufacturing data for reprocessing	(Class IV)	4,167,100 Article 33, Paragraph 1, Item 2 (a)-(2)	915,800 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (b)	5,082,900 (+ overseas travel expenses *1)
			(Class II/III)	2,509,000 Article 33, Paragraph 1, Item 2 (a)-(4)	915,800 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (b)	3,424,800 (+ overseas travel expenses *1)
		Without design/ manufacturing data for reprocessing	(Class IV)	1,043,300 Article 33, Paragraph 1, Item 2 (a)-(8)	45,000 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (c)	1,088,300 (+ overseas travel expenses *1)
			(Class II/III)	837,200 Article 33, Paragraph 1, Item 2 (a)-(9)	45,000 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (c)	882,200 (+ overseas travel expenses *1)
		Others		169,300 Article 33, Paragraph 1, Item 2 (a)-(10)	45,000 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (c)	214,300 (+ overseas travel expenses *1)
In vitro diagnostics	Out of scope of approval standards	With clinical data	Excluding companion diagnostics	1,048,200 Article 33, Paragraph 1, Item 2 (b)-(2)		1,048,200
			Companion diagnostics	1,996,600 Article 33, Paragraph 1, Item 2 (b)-(3)		1,996,600
		Without clinical data	Excluding companion diagnostics	528,700 Article 33, Paragraph 1, Item 2 (b)-(4)		528,700
			Companion diagnostics	1,007,200 Article 33, Paragraph 1, Item 2 (b)-(5)		1,007,200
	Nonconformity with approval standards	With clinical data	Excluding companion diagnostics	1,048,200 Article 33, Paragraph 1, Item 2 (b)-(2)		1,048,200
			Companion diagnostics	1,996,600 Article 33, Paragraph 1, Item 2 (b)-(3)		1,996,600
		Without clinical data	Excluding companion diagnostics	528,700 Article 33, Paragraph 1, Item 2 (b)-(4)		528,700
			Companion diagnostics	1,007,200 Article 33, Paragraph 1, Item 2 (b)-(5)		1,007,200
	Conformity with approval standards	Without clinical data		216,500 Article 33, Paragraph 1, Item 2 (b)-(6)		216,500
	Addition of series			33,400 Article 33, Paragraph 1, Item 2 (b)-(1)		33,400
Others (*in vitro* diagnostics)				150,600 Article 33, Paragraph 1, Item 2 (b)-(7)		150,600

(*1) Overseas travel expenses (Article 33, Paragraph 3) are added to the user fees if an inspection is conducted overseas.

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.

(Yen)

Classification					User fees		
					Review	Inspection	Total
QMS inspection of medical devices and *in vitro* diagnostics							
	Issuance fee for certification of conformity with approval standards					50,400 Article 33, Paragraph 5, Item 1 (a), Item 2 (a), and Item 3 (a); and Paragraph 6, Item 1 (a), Item 2 (a), and Item 3 (a)	50,400
	Fee paid by MAH	New	New medical devices			386,600 Article 33, Paragraph 5, Item 1 (a)-(2)	386,600
				MAHs of class II medical devices		386,600 Article 33, Paragraph 6, Item 1 (a)-(2)	386,600
			Class IV			374,500 Article 33, Paragraph 5, Item 1 (a)-(3)	374,500
			Biological products			398,500 Article 33, Paragraph 5, Item 1 (a)-(1)	398,500
				MAHs of class II medical devices		398,500 Article 33, Paragraph 6, Item 1 (a)-(1)	398,500
			Other medical devices			374,500 Article 33, Paragraph 5, Item 1 (a)-(4)	374,500
				MAHs of class II medical devices		262,100 Article 33, Paragraph 6, Item 1 (a)-(3)	262,100
			In vitro diagnostics			272,900 Article 33, Paragraph 5, Item 1 (a)-(5)	272,900
		Partial change	Class IV			134,000 Article 33, Paragraph 5, Item 2 (a)-(2)	134,000
			Biological products			145,600 Article 33, Paragraph 5, Item 2 (a)-(1)	145,600
				MAHs of class II medical devices		145,600 Article 33, Paragraph 6, Item 2 (a)-(1)	145,600
			Other medical devices			127,800 Article 33, Paragraph 5, Item 2 (a)-(3)	127,800
				MAHs of class II medical devices		89,400 Article 33, Paragraph 6, Item 2 (a)-(2)	89,400
			In vitro diagnostics			93,200 Article 33, Paragraph 5, Item 2 (a)-(4)	93,200
		Renewal	Class IV			167,600 Article 33, Paragraph 5, Item 3 (a)-(2)	167,600
			Biological products			176,900 Article 33, Paragraph 5, Item 3 (a)-(1)	176,900
				MAHs of class II medical devices		176,900 Article 33, Paragraph 6, Item 3 (a)-(1)	176,900
			Other medical devices			149,200 Article 33, Paragraph 5, Item 3 (a)-(3)	149,200
				MAHs of class II medical devices		104,400 Article 33, Paragraph 6, Item 3 (a)-(2)	104,400
			In vitro diagnostics			129,700 Article 33, Paragraph 5, Item 3 (a)-(4)	129,700

Note: The lower rows in the “User fees” column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.

(Yen)

Classification				User fees		
				Review	Inspection	Total
	New	Design			86,100	86,100
					Article 33, Paragraph 5, Item 1 (b)-(1) and Paragraph 11, Item 1 (a)	
			MAHs of class II medical devices		60,200	60,200
					Article 33, Paragraph 6, Item 1 (b)-(1)	
		Sterilization			91,200	91,200
					Article 33, Paragraph 5, Item 1 (b)-(3) and Paragraph 11, Item 1 (c)	
			MAHs of class II medical devices		63,800	63,800
					Article 33, Paragraph 6, Item 1 (b)-(3)	
		Assembly/Cleaning			104,100	104,100
					Article 33, Paragraph 5, Item 1 (b)-(2) and Paragraph 11, Item 1 (b)	
			MAHs of class II medical devices		72,800	72,800
					Article 33, Paragraph 6, Item 1 (b)-(2)	
		Others			90,500	90,500
					Article 33, Paragraph 5, Item 1 (b)-(4) and Paragraph 11, Item 1 (d)	
			MAHs of class II medical devices		63,200	63,200
					Article 33, Paragraph 6, Item 1 (b)-(4)	
		Unregistered			87,500	87,500
					Article 33, Paragraph 5, Item 1 (b)-(5) and Paragraph 11, Item 1 (e) and Paragraph 12, Item 1	
			MAHs of class II medical devices		61,200	61,200
					Article 33, Paragraph 6, Item 1 (b)-(5)	

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.

(Yen)

Classification			User fees		
			Review	Inspection	Total
QMS inspection of medical devices and *in vitro* diagnostics					
Partial change	Design			64,400	64,400
				Article 33, Paragraph 5, Item 2 (b)-(1)	
		MAHs of class II medical devices		45,000	45,000
				Article 33, Paragraph 6, Item 2 (b)-(1)	
	Sterilization			75,900	75,900
				Article 33, Paragraph 5, Item 2 (b)-(3)	
		MAHs of class II medical devices		53,100	53,100
				Article 33, Paragraph 6, Item 2 (b)-(3)	
	Assembly/Cleaning			87,700	87,700
				Article 33, Paragraph 5, Item 2 (b)-(2)	
		MAHs of class II medical devices		61,300	61,300
				Article 33, Paragraph 6, Item 2 (b)-(2)	
	Others			75,800	75,800
				Article 33, Paragraph 5, Item 2 (b)-(4)	
		MAHs of class II medical devices		53,000	53,000
				Article 33, Paragraph 6, Item 2 (b)-(4)	
	Unregistered			75,900	75,900
				Article 33, Paragraph 5, Item 2 (b)-(3)	
		MAHs of class II medical devices		53,100	53,100
				Article 33, Paragraph 6, Item 2 (b)-(3)	
Renewal	Design			68,800	68,800
				Article 33, Paragraph 5, Item 3 (b)-(1) and Paragraph 11, Item 2 (a)	
		MAHs of class II medical devices		48,100	48,100
				Article 33, Paragraph 6, Item 3 (b)-(1)	
	Sterilization			80,100	80,100
				Article 33, Paragraph 5, Item 3 (b)-(3) and Paragraph 11, Item 2 (c)	
		MAHs of class II medical devices		56,000	56,000
				Article 33, Paragraph 6, Item 3 (b)-(3)	
	Assembly/Cleaning			97,400	97,400
				Article 33, Paragraph 5, Item 3 (b)-(2) and Paragraph 11, Item 2 (b)	
		MAHs of class II medical devices		68,100	68,100
				Article 33, Paragraph 6, Item 3 (b)-(2)	
	Others			79,600	79,600
				Article 33, Paragraph 5, Item 3 (b)-(4) and Paragraph 11, Item 2 (d)	
		MAHs of class II medical devices		55,700	55,700
				Article 33, Paragraph 6, Item 3 (b)-(4)	
	Unregistered			76,100	76,100
				Article 33, Paragraph 5, Item 3 (b)-(5) and Paragraph 11, Item 2 (e) and Paragraph 12, Item 2	
		MAHs of class II medical devices		53,200	53,200
				Article 33, Paragraph 6, Item 3 (b)-(5)	
Options	Micro machine			47,500	47,500
				Article 33, Paragraph 7, Item 1	
		MAHs of class II medical devices		33,200	33,200
				Article 33, Paragraph 8	
	Nano materials			47,500	47,500
				Article 33, Paragraph 7, Item 2	
		MAHs of class II medical devices		33,200	33,200
				Article 33, Paragraph 8	
	Others (including reprocessed single-use medical devices)			47,500	47,500
				Article 33, Paragraph 7, Item 3	
		MAHs of class II medical devices		33,200	33,200
				Article 33, Paragraph 8	
Travel expenses for on-site inspection (per day)		In Japan		212,400	212,400
				Article 33, Paragraph 9, Item 1 and Paragraph 13	
		Overseas		179,500 + overseas travel expenses	179,500 + overseas travel expenses
				Article 33, Paragraph 9, Item 2 (a) and (b)	
Re-issue/renewal of compliance certification				11,000	11,000
				Article 33, Paragraph 17	

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.

(Yen)

Classification				User fees		
				Review	Inspection	Total
GLP inspection of medical devices						
	GLP	In Japan			2,482,600	2,482,600
					Article 33, Paragraph 4, Item 1 (a)	
		Overseas			3,146,100 + overseas travel expenses	3,146,100 + overseas travel expenses
					Article 33, Paragraph 4, Item 1 (b)	
GCP inspection of medical devices						
	GCP	In Japan			875,500	875,500
					Article 33, Paragraph 4, Item 2 (a)	
		Overseas			1,265,800 + overseas travel expenses	1,265,800 + overseas travel expenses
					Article 33, Paragraph 4, Item 2 (b)	
Use-results evaluation of medical devices and *in vitro* diagnostics						
	Target medical devices			673,600	860,800 (+ overseas travel expenses *2)	1,534,400 (+ overseas travel expenses *2)
				Article 33, Paragraph 14, Item 1 (a)	Article 33, Paragraph 15, Item 1	
	Child items with multiple brand names of the target medical device			47,700		47,700
				Article 33, Paragraph 14, Item 1 (b)		
	Target *in vitro* diagnostics			673,600	860,800 (+ overseas travel expenses *2)	1,534,400 (+ overseas travel expenses *2)
				Article 33, Paragraph 14, Item 2	Article 33, Paragraph 15, Item 1	
	GLP for use-results evaluation of medical devices	In Japan			2,842,600	2,842,600
					Article 33, Paragraph 15, Item 2 (a)-(1)	
		Overseas			3,146,100 (+ overseas travel expenses *2)	3,146,100 (+ overseas travel expenses *2)
					Article 33, Paragraph 15, Item 2 (a)-(2)	
	GPSP	Medical devices	In Japan		841,700	841,700
					Article 33, Paragraph 15, Item 2 (b)-(1)	
			Overseas		1,307,900 (+ overseas travel expenses *2)	1,307,900 (+ overseas travel expenses *2)
					Article 33, Paragraph 15, Item 2 (b)-(2)	
		In vitro diagnostics	In Japan		841,700	841,700
					Article 33, Paragraph 15, Item 2 (b)-(1)	
			Overseas		1,307,900 (+ overseas travel expenses *2)	1,307,900 (+ overseas travel expenses *2)
					Article 33, Paragraph 15, Item 2 (b)-(2)	

(*2) Overseas travel expenses (Article 33, Paragraph 16) are added to the user fees if an inspection is conducted overseas.

Revised on December 30, 2018

Table 14-2. List of User Fees for Medical Devices and In Vitro Diagnostics

List of user fees for reviews etc. of medical devices and in vitro diagnostics under the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Act No. 145 of 1960)

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.

(Yen)

Classification				User fees		
				Review	Inspection	Total
Review for approval of medical devices and *in vitro* diagnostics (new approval)						
New medical devices (Class IV)				14,581,400 Article 33, Paragraph 1, Item 1 (a)-(1)	1,144,700 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 1 (a)	15,726,100 (+ overseas travel expenses *1)
New medical devices (Class II/III)				10,406,700 Article 33, Paragraph 1, Item 1 (a)-(3)	1,144,700 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 1 (a)	11,551,400 (+ overseas travel expenses *1)
Improved medical devices with clinical data (Class IV)				8,325,300 Article 33, Paragraph 1, Item 1 (a)-(2)	915,800 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 1 (b)	9,241,100 (+ overseas travel expenses *1)
Improved medical devices with clinical data (Class II/III)				4,986,300 Article 33, Paragraph 1, Item 1 (a)-(4)	915,800 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 1 (b)	5,902,100 (+ overseas travel expenses *1)
Improved medical devices without clinical data, without approval standards (Class IV)				2,779,300 Article 33, Paragraph 1, Item 1 (a)-(7)	83,100 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 1 (c)	2,862,400 (+ overseas travel expenses *1)
Generic medical devices without clinical data, without approval standards (Class IV)				2,085,800 Article 33, Paragraph 1, Item 1 (a)-(8)	83,100 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 1 (c)	2,168,900 (+ overseas travel expenses *1)
Improved/generic medical devices without clinical data, without approval standards (Class II/III)				1,663,600 Article 33, Paragraph 1, Item 1 (a)-(9)	83,100 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 1 (c)	1,746,700 (+ overseas travel expenses *1)
Generic medical devices with approval standards (Class IV)				506,400 Article 33, Paragraph 1, Item 1 (a)-(5)	83,100 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 1 (c)	589,500 (+ overseas travel expenses *1)
Generic medical devices with approval standards (Class II/III)				406,000 Article 33, Paragraph 1, Item 1 (a)-(6)	83,100 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 1 (c)	489,100 (+ overseas travel expenses *1)
Re-processed single-use medical devices		(Class IV)		8,325,300 Article 33, Paragraph 1, Item 1 (a)-(2)	915,800 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 1 (b)	9,241,100 (+ overseas travel expenses *1)
		(Class II/III)		4,986,300 Article 33, Paragraph 1, Item 1 (a)-(4)	915,800 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 1 (b)	5,902,100 (+ overseas travel expenses *1)
In vitro diagnostics	New products	Excluding companion diagnostics		2,534,000 Article 33, Paragraph 1, Item 1 (b)-(2)		2,534,000
		Companion diagnostics		4,295,000 Article 33, Paragraph 1, Item 1 (b)-(3)		4,295,000
	Out of scope of approval standards	With clinical data	Excluding companion diagnostics	2,534,000 Article 33, Paragraph 1, Item 1 (b)-(2)		2,534,000
			Companion diagnostics	4,295,000 Article 33, Paragraph 1, Item 1 (b)-(3)		4,295,000
		Without clinical data		2,362,200 Article 33, Paragraph 1, Item 1 (b)-(4)		2,362,200
	Nonconformity with approval standards	With clinical data	Excluding companion diagnostics	2,534,000 Article 33, Paragraph 1, Item 1 (b)-(2)		2,534,000
			Companion diagnostics	4,295,000 Article 33, Paragraph 1, Item 1 (b)-(3)		4,295,000
		Without clinical data		1,096,500 Article 33, Paragraph 1, Item 1 (b)-(6)		1,096,500
	Conformity with approval standards	Without clinical data		380,100 Article 33, Paragraph 1, Item 1 (b)-(5)		380,100
	Addition of series			63,300 Article 33, Paragraph 1, Item 1 (b)-(1)		63,300
Change of brand name				37,300 Article 33, Paragraph 1, Item 1 (c)		37,300

(*1) Overseas travel expenses (Article 33, Paragraph 3) are added to the user fees if an inspection is conducted overseas.

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.

(Yen)

Classification				User fees		
				Review	Inspection	Total
Review for approval of medical devices and *in vitro* diagnostics (approval for partial changes to approved matters)						
New medical devices (Class IV)				7,298,400 Article 33, Paragraph 1, Item 2 (a)-(1)	1,144,700 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (a)	8,443,100 (+ overseas travel expenses *1)
New medical devices (Class II/III)				5,208,900 Article 33, Paragraph 1, Item 2 (a)-(3)	1,144,700 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (a)	6,353,600 (+ overseas travel expenses *1)
Improved medical devices with clinical data (Class IV)				4,167,100 Article 33, Paragraph 1, Item 2 (a)-(2)	915,800 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (b)	5,082,900 (+ overseas travel expenses *1)
Improved medical devices with clinical data (Class II/III)				2,509,000 Article 33, Paragraph 1, Item 2 (a)-(4)	915,800 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (b)	3,424,800 (+ overseas travel expenses *1)
Improved medical devices without clinical data, without approval standards (Class IV)				1,393,800 Article 33, Paragraph 1, Item 2 (a)-(7)	45,000 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (c)	1,438,800 (+ overseas travel expenses *1)
Generic medical devices without clinical data, without approval standards (Class IV)				1,043,300 Article 33, Paragraph 1, Item 2 (a)-(8)	45,000 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (c)	1,088,300 (+ overseas travel expenses *1)
Improved/generic medical devices without clinical data, without approval standards (Class II/III)				837,200 Article 33, Paragraph 1, Item 2 (a)-(9)	45,000 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (c)	882,200 (+ overseas travel expenses *1)
Generic medical devices with approval standards (Class IV)				256,700 Article 33, Paragraph 1, Item 2 (a)-(5)	45,000 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (c)	301,700 (+ overseas travel expenses *1)
Generic medical devices with approval standards (Class II/III)				204,800 Article 33, Paragraph 1, Item 2 (a)-(6)	45,000 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (c)	249,800 (+ overseas travel expenses *1)
Others (medical devices)				169,300 Article 33, Paragraph 1, Item 2 (a)-(10)	45,000 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (c)	214,300 (+ overseas travel expenses *1)
Reprocessed single-use medical devices		With design/ manufacturing data for reprocessing	(Class IV)	4,167,100 Article 33, Paragraph 1, Item 2 (a)-(2)	915,800 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (b)	5,082,900 (+ overseas travel expenses *1)
			(Class II/III)	2,509,000 Article 33, Paragraph 1, Item 2 (a)-(4)	915,800 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (b)	3,424,800 (+ overseas travel expenses *1)
		Without design/ manufacturing data for reprocessing	(Class IV)	1,043,300 Article 33, Paragraph 1, Item 2 (a)-(8)	45,000 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (c)	1,088,300 (+ overseas travel expenses *1)
			(Class II/III)	837,200 Article 33, Paragraph 1, Item 2 (a)-(9)	45,000 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (c)	882,200 (+ overseas travel expenses *1)
		Others		169,300 Article 33, Paragraph 1, Item 2 (a)-(10)	45,000 (+ overseas travel expenses *1) Article 33, Paragraph 2, Item 2 (c)	214,300 (+ overseas travel expenses *1)
In vitro diagnostics	Out of scope of approval standards	With clinical data	Excluding companion diagnostics	1,048,200 Article 33, Paragraph 1, Item 2 (b)-(2)		1,048,200
			Companion diagnostics	1,996,600 Article 33, Paragraph 1, Item 2 (b)-(3)		1,996,600
		Without clinical data	Excluding companion diagnostics	528,700 Article 33, Paragraph 1, Item 2 (b)-(4)		528,700
			Companion diagnostics	1,007,200 Article 33, Paragraph 1, Item 2 (b)-(5)		1,007,200
	Nonconformity with approval standards	With clinical data	Excluding companion diagnostics	1,048,200 Article 33, Paragraph 1, Item 2 (b)-(2)		1,048,200
			Companion diagnostics	1,996,600 Article 33, Paragraph 1, Item 2 (b)-(3)		1,996,600
		Without clinical data	Excluding companion diagnostics	528,700 Article 33, Paragraph 1, Item 2 (b)-(4)		528,700
			Companion diagnostics	1,007,200 Article 33, Paragraph 1, Item 2 (b)-(5)		1,007,200
	Conformity with approval standards	Without clinical data		216,500 Article 33, Paragraph 1, Item 2 (b)-(6)		216,500
	Addition of series			33,400 Article 33, Paragraph 1, Item 2 (b)-(1)		33,400
Others (*in vitro* diagnostics)				150,600 Article 33, Paragraph 1, Item 2 (b)-(7)		150,600

(*1) Overseas travel expenses (Article 33, Paragraph 3) are added to the user fees if an inspection is conducted overseas.

Revised on December 30, 2018

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.

(Yen)

Classification				User fees		
				Review	Inspection	Total
QMS inspection of medical devices and *in vitro* diagnostics						
	Issuance fee for certification of conformity with approval standards				50,400	50,400
					Article 33, Paragraph 5, Item 1 (a), Item 2 (a), and Item 3 (a); and Paragraph 6, Item 1 (a), Item 2 (a), and Item 3 (a)	
Fee paid by MAH	New	New medical devices			386,600	386,600
					Article 33, Paragraph 5, Item 1 (a)-(2)	
			MAHs of class II medical devices		386,600	386,600
					Article 33, Paragraph 6, Item 1 (a)-(2)	
		Class IV			374,500	374,500
					Article 33, Paragraph 5, Item 1 (a)-(3)	
		Biological products			398,500	398,500
					Article 33, Paragraph 5, Item 1 (a)-(1)	
			MAHs of class II medical devices		398,500	398,500
					Article 33, Paragraph 6, Item 1 (a)-(1)	
		Other medical devices			374,500	374,500
					Article 33, Paragraph 5, Item 1 (a)-(4)	
			MAHs of class II medical devices		262,100	262,100
					Article 33, Paragraph 6, Item 1 (a)-(3)	
		In vitro diagnostics			272,900	272,900
					Article 33, Paragraph 5, Item 1 (a)-(5)	
	Partial change	Class IV			134,000	134,000
					Article 33, Paragraph 5, Item 2 (a)-(2)	
		Biological products			145,600	145,600
					Article 33, Paragraph 5, Item 2 (a)-(1)	
			MAHs of class II medical devices		145,600	145,600
					Article 33, Paragraph 6, Item 2 (a)-(1)	
		Other medical devices			127,800	127,800
					Article 33, Paragraph 5, Item 2 (a)-(3)	
			MAHs of class II medical devices		89,400	89,400
					Article 33, Paragraph 6, Item 2 (a)-(2)	
		In vitro diagnostics			93,200	93,200
					Article 33, Paragraph 5, Item 2 (a)-(4)	
	Renewal	Class IV			167,600	167,600
					Article 33, Paragraph 5, Item 3 (a)-(2)	
		Biological products			176,900	176,900
					Article 33, Paragraph 5, Item 3 (a)-(1)	
			MAHs of class II medical devices		176,900	176,900
					Article 33, Paragraph 6, Item 3 (a)-(1)	
		Other medical devices			149,200	149,200
					Article 33, Paragraph 5, Item 3 (a)-(3)	
			MAHs of class II medical devices		104,400	104,400
					Article 33, Paragraph 6, Item 3 (a)-(2)	
		In vitro diagnostics			129,700	129,700
					Article 33, Paragraph 5, Item 3 (a)-(4)	

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.

(Yen)

Classification				User fees		
				Review	Inspection	Total
	New	Design			86,100	86,100
					Article 33, Paragraph 5, Item 1 (b)-(1) and Paragraph 11, Item 1 (a)	
			MAHs of class II medical devices		60,200	60,200
					Article 33, Paragraph 6, Item 1 (b)-(1)	
		Sterilization			91,200	91,200
					Article 33, Paragraph 5, Item 1 (b)-(3) and Paragraph 11, Item 1 (c)	
			MAHs of class II medical devices		63,800	63,800
					Article 33, Paragraph 6, Item 1 (b)-(3)	
		Assembly/Cleaning			104,100	104,100
					Article 33, Paragraph 5, Item 1 (b)-(2) and Paragraph 11, Item 1 (b)	
			MAHs of class II medical devices		72,800	72,800
					Article 33, Paragraph 6, Item 1 (b)-(2)	
		Others			90,500	90,500
					Article 33, Paragraph 5, Item 1 (b)-(4) and Paragraph 11, Item 1 (d)	
			MAHs of class II medical devices		63,200	63,200
					Article 33, Paragraph 6, Item 1 (b)-(4)	
		Unregistered			87,500	87,500
					Article 33, Paragraph 5, Item 1 (b)-(5) and Paragraph 11, Item 1 (e) and Paragraph 12, Item 1	
			MAHs of class II medical devices		61,200	61,200
					Article 33, Paragraph 6, Item 1 (b)-(5)	

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Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.

(Yen)

Classification			User fees		
			Review	Inspection	Total
QMS inspection of medical devices and *in vitro* diagnostics					
Partial change	Design			64,400	64,400
				Article 33, Paragraph 5, Item 2 (b)-(1)	
		MAHs of class II medical devices		45,000	45,000
				Article 33, Paragraph 6, Item 2 (b)-(1)	
	Sterilization			75,900	75,900
				Article 33, Paragraph 5, Item 2 (b)-(3)	
		MAHs of class II medical devices		53,100	53,100
				Article 33, Paragraph 6, Item 2 (b)-(3)	
	Assembly/Cleaning			87,700	87,700
				Article 33, Paragraph 5, Item 2 (b)-(2)	
		MAHs of class II medical devices		61,300	61,300
				Article 33, Paragraph 6, Item 2 (b)-(2)	
	Others			75,800	75,800
				Article 33, Paragraph 5, Item 2 (b)-(4)	
		MAHs of class II medical devices		53,000	53,000
				Article 33, Paragraph 6, Item 2 (b)-(4)	
	Unregistered			75,900	75,900
				Article 33, Paragraph 5, Item 2 (b)-(3)	
		MAHs of class II medical devices		53,100	53,100
				Article 33, Paragraph 6, Item 2 (b)-(3)	
Renewal	Design			68,800	68,800
				Article 33, Paragraph 5, Item 3 (b)-(1) and Paragraph 11, Item 2 (a)	
		MAHs of class II medical devices		48,100	48,100
				Article 33, Paragraph 6, Item 3 (b)-(1)	
	Sterilization			80,100	80,100
				Article 33, Paragraph 5, Item 3 (b)-(3) and Paragraph 11, Item 2 (c)	
		MAHs of class II medical devices		56,000	56,000
				Article 33, Paragraph 6, Item 3 (b)-(3)	
	Assembly/Cleaning			97,400	97,400
				Article 33, Paragraph 5, Item 3 (b)-(2) and Paragraph 11, Item 2 (b)	
		MAHs of class II medical devices		68,100	68,100
				Article 33, Paragraph 6, Item 3 (b)-(2)	
	Others			79,600	79,600
				Article 33, Paragraph 5, Item 3 (b)-(4) and Paragraph 11, Item 2 (d)	
		MAHs of class II medical devices		55,700	55,700
				Article 33, Paragraph 6, Item 3 (b)-(4)	
	Unregistered			76,100	76,100
				Article 33, Paragraph 5, Item 3 (b)-(5) and Paragraph 11, Item 2 (e) and Paragraph 12, Item 2	
		MAHs of class II medical devices		53,200	53,200
				Article 33, Paragraph 6, Item 3 (b)-(5)	
Options	Micro machine			47,500	47,500
				Article 33, Paragraph 7, Item 1	
		MAHs of class II medical devices		33,200	33,200
				Article 33, Paragraph 8	
	Nano materials			47,500	47,500
				Article 33, Paragraph 7, Item 2	
		MAHs of class II medical devices		33,200	33,200
				Article 33, Paragraph 8	
	Others (including reprocessed single-use medical devices)			47,500	47,500
				Article 33, Paragraph 7, Item 3	
		MAHs of class II medical devices		33,200	33,200
				Article 33, Paragraph 8	
Travel expenses for on-site inspection (per day)		In Japan		212,400	212,400
				Article 33, Paragraph 9, Item 1 and Paragraph 13	
		Overseas		179,500 + overseas travel expenses	179,500 + overseas travel expenses
				Article 33, Paragraph 9, Item 2 (a) and (b)	
Re-issue/renewal of compliance certification				11,000	11,000
				Article 33, Paragraph 17	

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Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.

(Yen)

Classification				User fees		
				Review	Inspection	Total
GLP inspection of medical devices						
	GLP	In Japan			2,482,600	2,482,600
					Article 33, Paragraph 4, Item 1 (a)	
		Overseas			3,146,100 + overseas travel expenses	3,146,100 + overseas travel expenses
					Article 33, Paragraph 4, Item 1 (b)	
GCP inspection of medical devices						
	GCP	In Japan			875,500	875,500
					Article 33, Paragraph 4, Item 2 (a)	
		Overseas			1,265,800 + overseas travel expenses	1,265,800 + overseas travel expenses
					Article 33, Paragraph 4, Item 2 (b)	
Use-results evaluation of medical devices and *in vitro* diagnostics						
	Target medical devices			673,600	860,800 (+ overseas travel expenses *2)	1,534,400 (+ overseas travel expenses *2)
				Article 33, Paragraph 14, Item 1 (a)	Article 33, Paragraph 15, Item 1	
	Child items with multiple brand names of the target medical device			47,700		47,700
				Article 33, Paragraph 14, Item 1 (b)		
	Target *in vitro* diagnostics			673,600	860,800 (+ overseas travel expenses *2)	1,534,400 (+ overseas travel expenses *2)
				Article 33, Paragraph 14, Item 2	Article 33, Paragraph 15, Item 1	
	GLP for use-results evaluation of medical devices	In Japan			2,842,600	2,842,600
					Article 33, Paragraph 15, Item 2 (a)-(1)	
		Overseas			3,146,100 (+ overseas travel expenses *2)	3,146,100 (+ overseas travel expenses *2)
					Article 33, Paragraph 15, Item 2 (a)-(2)	
	GPSP	Medical devices	In Japan		841,700	841,700
					Article 33, Paragraph 15, Item 2 (b)-(1)	
			Overseas		1,307,900 (+ overseas travel expenses *2)	1,307,900 (+ overseas travel expenses *2)
					Article 33, Paragraph 15, Item 2 (b)-(2)	
		In vitro diagnostics	In Japan		841,700	841,700
					Article 33, Paragraph 15, Item 2 (b)-(1)	
			Overseas		1,307,900 (+ overseas travel expenses *2)	1,307,900 (+ overseas travel expenses *2)
					Article 33, Paragraph 15, Item 2 (b)-(2)	
Assessment of registered certification bodies for medical devices and *in-vitro* diagnostics						
	Medical devices	Registration of new certification bodies	In Japan		1,520,300	1,520,300
					Article 34, Paragraph 1, Item 1	
			Overseas		1,578,900 + overseas travel expenses	1,578,900
					Article 34, Paragraph 1, Item 2	
		Renewal of registration of certification bodies	In Japan		609,300	609,300
					Article 34, Paragraph 2, Item 1	
			Overseas		670,700 + overseas travel expenses	670,700
					Article 34, Paragraph 2, Item 2	
	In vitro diagnostics	Registration of new certification bodies	In Japan		1,520,300	1,520,300
					Article 34, Paragraph 1, Item 1	
			Overseas		1,578,900 + overseas travel expenses	1,578,900
					Article 34, Paragraph 1, Item 2	
		Renewal of registration of certification bodies	In Japan		609,300	609,300
					Article 34, Paragraph 2, Item 1	
			Overseas		670,700 + 0overseas travel expenses	670,700
					Article 34, Paragraph 2, Item 2	

(*2) Overseas travel expenses (Article 33, Paragraph 16) are added to the user fees if an inspection is conducted overseas.

Revised on April 1, 2018

Table 15-1. List of User Fees for Regenerative Medical Products

List of user fees for reviews etc. of regenerative medical products based on the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Act No. 145 of 1960)

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. (Yen)

Classification			User fees		
			Review	Inspection	Total
Assessment for manufacturing license of regenerative medical products					
	New license	On-site		159,900	159,900
				Article 34, Paragraph 1, Item 1 (a)	
		Document		120,400	120,400
				Article 34, Paragraph 1, Item 1 (b)	
	Renewal of existing license	On-site		105,200	105,200
				Article 34, Paragraph 1, Item 2 (a)	
		Document		59,700	59,700
				Article 34, Paragraph 1, Item 2 (b)	
	Change/addition of classification	On-site		105,200	105,200
				Article 34, Paragraph 1, Item 3 (a)	
		Document		59,700	59,700
				Article 34, Paragraph 1, Item 3 (b)	
Assessment for foreign manufacturers accreditation of regenerative medical products					
	New accreditation	On-site		143,900 + overseas travel expenses	143,900 + overseas travel expenses
				Article 34, Paragraph 2, Item 1 (a)	
		Document		62,600	62,600
				Article 34, Paragraph 2, Item 1 (b)	
	Renewal of accreditation	On-site		69,700 + overseas travel expenses	69,700 + overseas travel expenses
				Article 34, Paragraph 2, Item 2 (a)	
		Document		42,900	42,900
				Article 34, Paragraph 2, Item 2 (b)	
	Change/addition of classification	On-site		69,700 + overseas travel expenses	69,700 + overseas travel expenses
				Article 34, Paragraph 2, Item 3 (a)	
		Document		42,900	42,900
				Article 34, Paragraph 2, Item 3 (b)	
Review for approval of regenerative medical products (new approval)					
	New regenerative medical products		14,690,200	1,153,300 (+ overseas travel expenses *1)	15,843,500 (+ overseas travel expenses *1)
			Article 35, Paragraph 1, Item 1 (a)	Article 35, Paragraph 2, Item 1	
	Regenerative medical products in case of new application for approval after the conditional time-limited authorization		7,352,900	1,153,300 (+ overseas travel expenses *1)	8,506,200 (+ overseas travel expenses *1)
			Article 35, Paragraph 1, Item 1 (b)	Article 35, Paragraph 2, Item 1	
	Application for change of brand name		37,300		37,300
			Article 35, Paragraph 1, Item 1 (c)		
Review for approval of regenerative medical products (approval of partial changes to approved matters)					
	Regenerative medical products (change of indications, etc.)		7,352,900	1,153,300 (+ overseas travel expenses *1)	8,506,200 (+ overseas travel expenses *1)
			Article 35, Paragraph 1, Item 2 (a)	Article 35, Paragraph 2, Item 2 (a)	
	Regenerative medical products (other changes)		1,594,700	51,500 (+ overseas travel expenses *1)	1,646,200 (+ overseas travel expenses *1)
			Article 35, Paragraph 1, Item 2 (b)	Article 35, Paragraph 2, Item 2 (b)	

(*1) Overseas travel expenses (Article 35, Paragraph 3) are added to the user fees if an inspection is conducted overseas.

Revised on April 1, 2018

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. (Yen)

Classification					User fees		
					Review	Inspection	Total
GCTP inspection of regenerative medical products							
	Approval/partial change	Manufacturing sites other than those conducting only packaging, labelling, or storage		In Japan		875,000	875,000
						Article 35, Paragraph 5, Item 1 (a)	
				Overseas		1,104,200 (+ overseas travel expenses)	1,104,200 (+ overseas travel expenses)
						Article 35, Paragraph 5, Item 1 (b) and (Article 35, Paragraph 7)	
		Packaging, labelling, or storage		In Japan		75,400	75,400
						Article 35, Paragraph 5, Item 2 (a)	
				Overseas		100,200 (+ overseas travel expenses)	100,200 (+ overseas travel expenses)
						Article 35, Paragraph 5, Item 2 (b) and (Article 35, Paragraph 7)	
		Testing institutions		In Japan		75,400	75,400
						Article 35, Paragraph 6, Item 1 (a)	
				Overseas		100,200 (+ overseas travel expenses)	100,200 (+ overseas travel expenses)
						Article 35, Paragraph 6, Item 1 (b) and (Article 35, Paragraph 7)	
	Renewal	Manufacturing sites other than those conducting only packaging, labelling, or storage	Basic	In Japan		875,000	875,000
						Article 35, Paragraph 5, Item 3 (a)-(1)	
				Overseas		1,104,200 (+ overseas travel expenses)	1,104,200 (+ overseas travel expenses)
						Article 35, Paragraph 5, Item 3 (a)-(2) and (Article 35, Paragraph 7)	
			Addition of products	In Japan		36,100	36,100
						Article 35, Paragraph 5, Item 3 (a)-(1)	
				Overseas		36,100	36,100
						Article 35, Paragraph 5, Item 3 (a)-(2)	
		Packaging, labelling, or storage	Basic	In Japan		305,700	305,700
						Article 35, Paragraph 5, Item 3 (b)-(1)	
				Overseas		399,900 (+ overseas travel expenses)	399,900 (+ overseas travel expenses)
						Article 35, Paragraph 5, Item 3 (b)-(2) and (Article 35, Paragraph 7)	
			Addition of products	In Japan		7,900	7,900
						Article 35, Paragraph 5, Item 3 (b)-(1)	
				Overseas		7,900	7,900
						Article 35, Paragraph 5, Item 3 (b)-(2)	
		Testing institutions	Basic	In Japan		305,700	305,700
						Article 35, Paragraph 6, Item 2 (a)	
				Overseas		399,900 (+ overseas travel expenses)	399,900 (+ overseas travel expenses)
						Article 35, Paragraph 6, Item 2 (b) and (Article 35, Paragraph 7)	
			Addition of products	In Japan		7,900	7,900
						Article 35, Paragraph 6, Item 2 (a)	
				Overseas		7,900	7,900
						Article 35, Paragraph 6, Item 2 (b)	
GLP inspection of regenerative medical products							
	GLP			In Japan		2,863,800	2,863,800
						Article 35, Paragraph 4, Item 1 (a)	
				Overseas		3,169,600 + overseas travel expenses	3,169,600 + overseas travel expenses
						Article 35, Paragraph 4, Item 1 (b)	
GCP inspection of regenerative medical products							
	GCP			In Japan		882,000	882,000
						Article 35, Paragraph 4, Item 2 (a)	
				Overseas		1,275,300 + overseas travel expenses	1,275,300 + overseas travel expenses
						Article 35, Paragraph 4, Item 2 (b)	

Revised on April 1, 2018

Note: The lower rows in the “User fees” column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. (Yen)

Classification			User fees		
			Review	Inspection	Total
GPSP inspection of regenerative medical products					
	GPSP	In Japan		848,400	848,400
				Article 35, Paragraph 4, Item 3 (a)	
		Overseas		1,317,700 + overseas travel expenses	1,317,700 + overseas travel expenses
				Article 35, Paragraph 4, Item 3 (b)	
Re-examination of regenerative medical products					
	Regenerative medical products		680,900	867,200 (+ overseas travel expenses)	1,548,100 (+ overseas travel expenses)
			Article 35, Paragraph 9	Article 35, Paragraph 10, Item 1 and (Article 35, Paragraph 11)	
	GLP for re-examination	In Japan		2,863,800	2,863,800
				Article 35, Paragraph 10, Item 2 (a)-(1)	
		Overseas		3,169,600 (+ overseas travel expenses)	3,169,600 (+ overseas travel expenses)
				Article 35, Paragraph 10, Item 2 (a)-(2) and (Article 35, Paragraph 11)	
	GPSP	In Japan		848,200	848,200
				Article 35, Paragraph 10, Item 2 (b)-(1)	
		Overseas		1,317,700 (+ overseas travel expenses)	1,317,700 (+ overseas travel expenses)
				Article 35, Paragraph 10, Item 2 (b)-(2) and (Article 35, Paragraph 11)	

Revised on December 30, 2018

Table 15-2. List of User Fees for Regenerative Medical Products

List of user fees for reviews etc. of regenerative medical products based on the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Act No. 145 of 1960)

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. (Yen)

Classification			User fees		
			Review	Inspection	Total
Assessment for manufacturing license of regenerative medical products					
	New license	On-site		159,900	159,900
				Article 35, Paragraph 1, Item 1 (a)	
		Document		120,400	120,400
				Article 35, Paragraph 1, Item 1 (b)	
	Renewal of existing license	On-site		105,200	105,200
				Article 35, Paragraph 1, Item 2 (a)	
		Document		59,700	59,700
				Article 35, Paragraph 1, Item 2 (b)	
	Change/addition of classification	On-site		105,200	105,200
				Article 35, Paragraph 1, Item 3 (a)	
		Document		59,700	59,700
				Article 35, Paragraph 1, Item 3 (b)	
Assessment for foreign manufacturers accreditation of regenerative medical products					
	New accreditation	On-site		143,900 + overseas travel expenses	143,900 + overseas travel expenses
				Article 35, Paragraph 2, Item 1 (a)	
		Document		62,600	62,600
				Article 35, Paragraph 2, Item 1 (b)	
	Renewal of accreditation	On-site		69,700 + overseas travel expenses	69,700 + overseas travel expenses
				Article 35, Paragraph 2, Item 2 (a)	
		Document		42,900	42,900
				Article 35, Paragraph 2, Item 2 (b)	
	Change/addition of classification	On-site		69,700 + overseas travel expenses	69,700 + overseas travel expenses
				Article 35, Paragraph 2, Item 3 (a)	
		Document		42,900	42,900
				Article 35, Paragraph 2, Item 3 (b)	
Review for approval of regenerative medical products (new approval)					
	New regenerative medical products		14,690,200	1,153,300 (+ overseas travel expenses *1)	15,843,500 (+ overseas travel expenses *1)
			Article 36, Paragraph 1, Item 1 (a)	Article 36, Paragraph 2, Item 1	
	Regenerative medical products in case of new application for approval after the conditional time-limited authorization		7,352,900	1,153,300 (+ overseas travel expenses *1)	8,506,200 (+ overseas travel expenses *1)
			Article 36, Paragraph 1, Item 1 (b)	Article 36, Paragraph 2, Item 1	
	Application for change of brand name		37,300		37,300
			Article 36, Paragraph 1, Item 1 (c)		
Review for approval of regenerative medical products (approval of partial changes to approved matters)					
	Regenerative medical products (change of indications, etc.)		7,352,900	1,153,300 (+ overseas travel expenses *1)	8,506,200 (+ overseas travel expenses *1)
			Article 36, Paragraph 1, Item 2 (a)	Article 36, Paragraph 2, Item 2 (a)	
	Regenerative medical products (other changes)		1,594,700	51,500 (+ overseas travel expenses *1)	1,646,200 (+ overseas travel expenses *1)
			Article 36, Paragraph 1, Item 2 (b)	Article 36, Paragraph 2, Item 2 (b)	

(*1) Overseas travel expenses (Article 36, Paragraph 3) are added to the user fees if an inspection is conducted overseas.

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.

(Yen)

Classification					User fees		
					Review	Inspection	Total
GCTP inspection of regenerative medical products							
	Approval/partial change	Manufacturing sites other than those conducting only packaging, labelling, or storage		In Japan		875,000 Article 36, Paragraph 5, Item 1 (a)	875,000
				Overseas		1,104,200 (+ overseas travel expenses) Article 36, Paragraph 5, Item 1 (b) and (Article 36, Paragraph 7)	1,104,200 (+ overseas travel expenses)
		Packaging, labelling, or storage		In Japan		75,400 Article 36, Paragraph 5, Item 2 (a)	75,400
				Overseas		100,200 (+ overseas travel expenses) Article 36, Paragraph 5, Item 2 (b) and (Article 36, Paragraph 7)	100,200 (+ overseas travel expenses)
		Testing institutions		In Japan		75,400 Article 36, Paragraph 6, Item 1 (a)	75,400
				Overseas		100,200 (+ overseas travel expenses) Article 36, Paragraph 6, Item 1 (b) and (Article 36, Paragraph 7)	100,200 (+ overseas travel expenses)
	Renewal	Manufacturing sites other than those conducting only packaging, labelling, or storage	Basic	In Japan		875,000 Article 36, Paragraph 5, Item 3 (a)-(1)	875,000
				Overseas		1,104,200 (+ overseas travel expenses) Article 36, Paragraph 5, Item 3 (a)-(2) and (Article 36, Paragraph 7)	1,104,200 (+ overseas travel expenses)
			Addition of products	In Japan		36,100 Article 36, Paragraph 5, Item 3 (a)-(1)	36,100
				Overseas		36,100 Article 36, Paragraph 5, Item 3 (a)-(2)	36,100
		Packaging, labelling, or storage	Basic	In Japan		305,700 Article 36, Paragraph 5, Item 3 (b)-(1)	305,700
				Overseas		399,900 (+ overseas travel expenses) Article 36, Paragraph 5, Item 3 (b)-(2) and (Article 36, Paragraph 7)	399,900 (+ overseas travel expenses)
			Addition of products	In Japan		7,900 Article 36, Paragraph 5, Item 3 (b)-(1)	7,900
				Overseas		7,900 Article 36, Paragraph 5, Item 3 (b)-(2)	7,900
		Testing institutions	Basic	In Japan		305,700 Article 36, Paragraph 6, Item 2 (a)	305,700
				Overseas		399,900 (+ overseas travel expenses) Article 36, Paragraph 6, Item 2 (b) and (Article 36, Paragraph 7)	399,900 (+ overseas travel expenses)
			Addition of products	In Japan		7,900 Article 36, Paragraph 6, Item 2 (a)	7,900
				Overseas		7,900 Article 36, Paragraph 6, Item 2 (b)	7,900
GLP inspection of regenerative medical products							
	GLP		In Japan			2,863,800 Article 36, Paragraph 4, Item 1 (a)	2,863,800
			Overseas			3,169,600 + overseas travel expenses Article 36, Paragraph 4, Item 1 (b)	3,169,600 + overseas travel expenses
GCP inspection of regenerative medical products							
	GCP		In Japan			882,000 Article 36, Paragraph 4, Item 2 (a)	882,000
			Overseas			1,275,300 + overseas travel expenses Article 36, Paragraph 4, Item 2 (b)	1,275,300 + overseas travel expenses

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.

(Yen)

Classification			User fees		
			Review	Inspection	Total
GPSP inspection of regenerative medical products					
	GPSP	In Japan		848,400	848,400
				Article 36, Paragraph 4, Item 3 (a)	
		Overseas		1,317,700 + overseas travel expenses	1,317,700 + overseas travel expenses
				Article 36, Paragraph 4, Item 3 (b)	
Re-examination of regenerative medical products					
	Regenerative medical products		680,900	867,200 (+ overseas travel expenses)	1,548,100 (+ overseas travel expenses)
			Article 36, Paragraph 9	Article 36, Paragraph 10, Item 1 and (Article 36, Paragraph 11)	
	GLP for re-examination	In Japan		2,863,800	2,863,800
				Article 36, Paragraph 10, Item 2 (a)-(1)	
		Overseas		3,169,600 (+ overseas travel expenses)	3,169,600 (+ overseas travel expenses)
				Article 36, Paragraph 10, Item 2 (a)-(2) and (Article 36, Paragraph 11)	
	GPSP	In Japan		848,200	848,200
				Article 36, Paragraph 10, Item 2 (b)-(1)	
		Overseas		1,317,700 (+ overseas travel expenses)	1,317,700 (+ overseas travel expenses)
				Article 36, Paragraph 10, Item 2 (b)-(2) and (Article 36, Paragraph 11)	

Table 16. List of User Fees for Inspections

List of user fees for PMDA's inspections based on the Act on Securing Safety of Regenerative Medicine (Act No. 85 of 2013)

Note: The lower rows in the "User fees" column indicate the applicable articles of the Cabinet Order on Fees related to the Act on Securing Safety of Regenerative Medicine (Cabinet Order No. 278). (Yen)

Classification			Inspection	Total
Inspection concening license for manufacturing specified cellular products				
	New license	On-site	144,000	144,000
			Article 8, Paragraph 1, Item 1	
		Document	98,200	98,200
			Article 8, Paragraph 1, Item 2	
	Renewal of license	On-site	97,100	97,100
			Article 8, Paragraph 2, Item 1	
		Document	48,600	48,600
			Article 8, Paragraph 2, Item 2	
Inspection concerning accreditation for manufacturing specified cellular products				
	New accreditation	On-site	120,500 +overseas travel expenses	120,500 +overseas travel expenses
			Article 8, Paragraph 3, Item 1	
		Document	54,200	54,200
			Article 8, Paragraph 3, Item 2	
	Renewal of accreditation	On-site	56,500 +overseas travel expenses	56,500 +overseas travel expenses
			Article 8, Paragraph 4, Item 1	
		Document	37,100	37,100
			Article 8, Paragraph 4, Item 2	

Table 17. Classification of user fees, etc.

Revised on June 1, 2018

(Yen)

		User fees				Timing of payment
Consultations						
Drugs/Quasi drugs	Procedural consultation for drugs	per consultation	150,900			Payment by the date of consultation application after arrangement of the consultation date
	Consultation before the start of expanded clinical trials for drugs	per consultation	261,500			
	Consultation for electronic study data submission (with recording)	per consultation	99,300			
	Consultation on bioequivalence testing, etc. for drugs	per consultation	600,400			
	Consultation for safety of drugs	per consultation	1,925,300			
	Consultation for quality of drugs	per consultation	1,596,500			
	Consultation before start of phase I study for drugs (non-orphan drugs)	per consultation	4,578,500			
	Consultation before start of phase I study for drugs (orphan drugs)	per consultation	3,441,000			
	Consultation before start of early phase II study for drugs (non-orphan drugs)	per consultation	1,752,800			
	Consultation before start of early phase II study for drugs (orphan drugs)	per consultation	1,320,200			
	Consultation before start of late phase II study for drugs (non-orphan drugs)	per consultation	3,737,800			
	Consultation before start of late phase II study for drugs (orphan drugs)	per consultation	2,807,000			
	Consultation after completion of phase II study for drugs (non-orphan drugs)	per consultation	7,419,900			
	Consultation after completion of phase II study for drugs (orphan drugs)	per consultation	5,573,700			
	Pre-application consultation for drugs (non-orphan drugs)	per consultation	7,419,900			
	Pre-application consultation for drugs (orphan drugs)	per consultation	5,570,400			
	Consultation on protocols of post-marketing clinical trials of drugs	per consultation	1,997,700			
	Consultation at completion of post-marketing clinical trials of drugs (preparation of application data, etc.)	per consultation	1,997,700			
	Consultation at completion of post-marketing clinical trials of drugs (review of conditions of approval, etc.)	per consultation	992,100			
	Additional consultation for drugs (non-orphan drugs)	per consultation	2,889,700			
	Additional consultation for drugs (orphan drugs)	per consultation	2,171,200			
	Consultation on epidemiological survey procedures for drugs	per consultation	150,900			
	Consultation on epidemiological survey plan for drugs	per consultation	3,007,900			
	Additional consultation on epidemiological survey of drugs	per consultation	1,505,900			
	Consultation on prior confirmation of revision of package inserts for drugs	per consultation	99,200			
	Consultation on revision of package inserts for drugs	per consultation	4,987,400			
	Consultation on GLP/GCP/GPSP compliance assessment for drugs	per consultation	3,549,200			
	Consultation on re-examination data compliance assessment for drugs	per consultation	1,797,200		+ overseas travel expenses	
	Consultation on compliance inspections of supporting data for revision of package inserts for drugs	per consultation	1,797,200	(Conducted at the Kansai branch)** +280,000 yen	+ overseas travel expenses	
	Prior assessment consultation for drugs (quality)	per consultation	3,763,800			
	Prior assessment consultation for drugs (non-clinical: toxicity)	per consultation	2,544,000			
	Prior assessment consultation for drugs (non-clinical: pharmacology)	per consultation	2,544,000			
	Prior assessment consultation for drugs (non-clinical: pharmacokinetics)	per consultation	2,544,000			
	Prior assessment consultation for drugs (phase I study)	per consultation	4,301,100			
	Prior assessment consultation for drugs (phase II study)	per consultation	5,551,000			
	Prior assessment consultation for drugs (phase II / III study)	per consultation	8,622,300			
	Consultation on drug product eligibility for priority review	per consultation	1,016,100			
	Consultation on drug product eligibility for priority review (with pre-application consultation for drugs)	per consultation	208,200			
	Consultation on drug product eligibility for conditional early approval	per consultation	1,016,100			
	Consultation on drug product eligibility for conditional early approval (with pre-application consultation for drugs)	per consultation	208,200			
	Consultation on pharmacogenomics/biomarkers (qualification)	per consultation	3,270,600			
	Consultation on pharmacogenomics/biomarkers (key points of clinical trial protocols)	per consultation	1,199,900			
	Additional consultation on pharmacogenomics/biomarkers (qualification)	per consultation	995,700			
	Additional consultation on pharmacogenomics/biomarkers (key points of clinical trial protocols)	per consultation	435,300			
	Consultation on PACMP quality for drugs	per consultation	319,900			
	Consultation on PACMP qualityfor generic drugs	per consultation	319,900			
	Consultation on PACMP GMP	per consultation	201,000		+ overseas travel expenses	
	Consultation on bioequivalence of generic drugs	per consultation	1,077,300			
	Consultation for quality of generic drugs	per consultation	531,100			
	Consultation before minor change notification	per consultation	319,900			
	Pre-application consultation for switch OTC drugs	per consultation	1,621,200			
	Consultation on key points of clinical trial protocols for OTC drugs	per consultation	542,600			
	Consultation on appropriateness of development of new OTC drugs	per consultation	215,000			
	Consultation for human study plan confirmation for quasi drugs	per consultation	499,800			
	Consultation on new excipient development for quasi drugs	per consultation	249,800			
	Post-consultation for drugs (with recording)	per consultation	99,200			
	Consultation on GCP/GLP/GPSP for drugs	per consultation	347,000			

Revised on June 1, 2018

(Yen)

			User fees			Timing of payment
Consultations						
Medical devices	Preliminary interview of consultation for medical devices		per consultation	29,400		Payment by the date of consultation application after arrangement of the consultation date
	Consultation before the start of expanded clinical trials for medical devices		per consultation	249,000		
	Pre-development consultation for medical devices		per consultation	294,100		
	Pre-development consultation for medical devices (preliminary interview completed)		per consultation	264,700		
	Pre-development consultation for medical devices (additional consultation)		per consultation	147,000		
	Consultation on finalization of application dossiers for medical devices		per consultation	390,100		
	Consultation on finalization of application dossiers for medical devices (additional consultation)		per consultation	196,000		
	Consultation on necessity of clinical trials for medical devices		per consultation	980,300		
	Consultation on necessity of clinical trials for medical devices (preliminary interview completed)		per consultation	950,600		
	Consultation on necessity of clinical trials for medical devices (additional consultation)		per consultation	490,200		
	Consultation on necessity of clinical trials for medical devices (assessed by referring to clinical literature, etc.)		per consultation	1,960,900		
	Consultation on necessity of clinical trials for medical devices (assessed by referring to clinical literature, etc.) (preliminary interview completed)		per consultation	1,931,500		
	Consultation on necessity of clinical trials for medical devices (assessed by referring to clinical literature, etc.) (additional consultation)		per consultation	980,300		
	Consultation on protocol for medical devices	Safety (1 test)	per consultation	98,000		
		Safety (1 test) (preliminary interview completed)	per consultation	68,600		
		Safety (1 test) (additional consultation)	per consultation	46,800		
		Safety (2 tests)	per consultation	196,000		
		Safety (2 tests) (preliminary interview completed)	per consultation	166,600		
		Safety (2 tests) (additional consultation)	per consultation	98,000		
		Safety (3 tests)	per consultation	293,800		
		Safety (3 tests) (preliminary interview completed)	per consultation	264,400		
		Safety (3 tests) (additional consultation)	per consultation	147,000		
		Safety (4 or more tests)	per consultation	390,100		
		Safety (4 or more tests) (preliminary interview completed)	per consultation	360,700		
		Safety (4 or more tests) (additional consultation)	per consultation	196,000		
		Quality	per consultation	390,100	(Conducted at the Kansai branch)** +280,000 yen	
		Quality (preliminary interview completed)	per consultation	360,700		
		Quality (additional consultation)	per consultation	196,000		
		Performance (1 test)	per consultation	98,000		
		Performance (1 test) (preliminary interview completed)	per consultation	68,600		
		Performance (1 test) (additional consultation)	per consultation	46,800		
		Performance (2 tests)	per consultation	196,000		
		Performance (2 tests) (preliminary interview completed)	per consultation	166,600		
		Performance (2 tests) (additional consultation)	per consultation	98,000		
		Performance (3 tests)	per consultation	293,800		
		Performance (3 tests) (preliminary interview completed)	per consultation	264,400		
		Performance (3 tests) (additional consultation)	per consultation	147,000		
		Performance (4 or more tests)	per consultation	390,100		
		Performance (4 or more tests) (preliminary interview completed)	per consultation	360,700		
		Performance (4 or more tests) (additional consultation)	per consultation	196,000		
		Exploratory clinical trial	per consultation	1,076,200		
		Exploratory clinical trial (preliminary interview completed)	per consultation	1,046,800		
		Exploratory clinical trial (additional consultation)	per consultation	539,100		
		Clinical trial	per consultation	2,353,100		
		Clinical trial (preliminary interview completed)	per consultation	2,323,700		
		Clinical trial (additional consultation)	per consultation	1,176,500		
	Consultation on data sufficiency/category of application for medical devices		per consultation	134,800		
	Consultation on GLP/GCP/GPSP compliance assessment for medical devices		per consultation	399,700		
	Consultation on GLP/GCP/GPSP compliance assessment for medical devices (preliminary interview completed)		per consultation	370,300		
	Consultation on GLP/GCP/GPSP compliance assessment for medical devices (additional consultation)		per consultation	197,900		
	Evaluation consultation for medical devices	Safety (1 test)	per consultation	98,000		
		Safety (1 test) (preliminary interview completed)	per consultation	68,600		
		Safety (1 test) (unevaluated protocol)	per consultation	147,000		
		Safety (1 test) (unevaluated protocol) (preliminary interview completed)	per consultation	115,500		
		Safety (1 test) (additional consultation)	per consultation	46,800		

Revised on June 1, 2018

(Yen)

			User fees				Timing of payment
Consultations							
Medical devices	Evaluation consultation for medical devices	Safety (2 tests)	per consultation	196,000	(Conducted at the Kansai branch)** +280,000 yen		Payment by the date of consultation application after arrangement of the consultation date
		Safety (2 tests) (preliminary interview completed)	per consultation	166,600			
		Safety (2 tests) (unevaluated protocol)	per consultation	293,800			
		Safety (2 tests) (unevaluated protocol) (preliminary interview completed)	per consultation	264,400			
		Safety (2 tests) (additional consultation)	per consultation	98,000			
		Safety (3 tests)	per consultation	293,800			
		Safety (3 tests) (preliminary interview completed)	per consultation	264,400			
		Safety (3 tests) (unevaluated protocol)	per consultation	441,200			
		Safety (3 tests) (unevaluated protocol) (preliminary interview completed)	per consultation	411,800			
		Safety (3 tests) (additional consultation)	per consultation	147,000			
		Safety (4 or more tests)	per consultation	390,100			
		Safety (4 or more tests) (preliminary interview completed)	per consultation	360,700			
		Safety (4 or more tests) (unevaluated protocol)	per consultation	588,200			
		Safety (4 or more tests) (unevaluated protocol) (preliminary interview completed)	per consultation	558,800			
		Safety (4 or more tests) (additional consultation)	per consultation	196,000			
		Quality	per consultation	390,100			
		Quality (preliminary interview completed)	per consultation	360,700			
		Quality (unevaluated protocol)	per consultation	588,200			
		Quality (unevaluated protocol) (preliminary interview completed)	per consultation	558,800			
		Quality (additional consultation)	per consultation	196,000			
		Performance (1 test)	per consultation	98,000			
		Performance (1 test) (preliminary interview completed)	per consultation	68,600			
		Performance (1 test) (unevaluated protocol)	per consultation	147,000			
		Performance (1 test) (unevaluated protocol) (preliminary interview completed)	per consultation	115,500			
		Performance (1 test) (additional consultation)	per consultation	46,800			
		Performance (2 tests)	per consultation	196,000			
		Performance (2 tests) (preliminary interview completed)	per consultation	166,600			
		Performance (2 tests) (unevaluated protocol)	per consultation	293,800			
		Performance (2 tests) (unevaluated protocol) (preliminary interview completed)	per consultation	264,400			
		Performance (2 tests) (additional consultation)	per consultation	98,000			
		Performance (3 tests)	per consultation	293,800			
		Performance (3 tests) (preliminary interview completed)	per consultation	264,400			
		Performance (3 tests) (unevaluated protocol)	per consultation	441,200			
		Performance (3 tests) (unevaluated protocol) (preliminary interview completed)	per consultation	411,800			
		Performance (3 tests) (additional consultation)	per consultation	147,000			
		Performance (4 or more tests)	per consultation	390,100			
		Performance (4 or more tests) (preliminary interview completed)	per consultation	360,700			
		Performance (4 or more tests) (unevaluated protocol)	per consultation	588,200			
		Performance (4 or more tests) (unevaluated protocol) (preliminary interview completed)	per consultation	558,800			
		Performance (4 or more tests) (additional consultation)	per consultation	196,000			
		Exploratory clinical trial	per consultation	980,300			
		Exploratory clinical trial (preliminary interview completed)	per consultation	950,900			
		Exploratory clinical trial (unevaluated protocol)	per consultation	1,519,700			
		Exploratory clinical trial (unevaluated protocol) (preliminary interview completed)	per consultation	1,488,100			
		Exploratory clinical trial (additional consultation)	per consultation	490,200			
		Clinical trial	per consultation	1,470,700			
		Clinical trial (preliminary interview completed)	per consultation	1,441,300			
		Clinical trial (unevaluated protocol)	per consultation	2,647,200			
		Clinical trial (unevaluated protocol) (preliminary interview completed)	per consultation	2,617,700			
		Clinical trial (additional consultation)	per consultation	733,000			
	Consultation on GCP/GLP/GPSP for medical devices		per consultation	196,000			
	Consultation on GCP/GLP/GPSP for medical devices (preliminary interview completed)		per consultation	166,600			
	Consultation on GCP/GLP/GPSP for medical devices (additional consultation)		per consultation	98,000			
	Consultation on the evaluation of reprocessed single-use medical devices (QMS compliance confirmation)		per consultation	1,498,600		+ overseas travel expenses	

Revised on June 1, 2018

(Yen)

			User fees			Timing of payment
Consultations						
In vitro diagnostics	Preliminary interview of consultation for *in vitro* diagnostics		per consultation 29,400			Payment by the date of consultation application after arrangement of the consultation date
	Pre-development consultation for *in vitro* diagnostics		per consultation 196,000			
	Pre-development consultation for *in vitro* diagnostics (preliminary interview completed)		per consultation 166,600			
	Pre-development consultation for *in vitro* diagnostics (additional consultation)		per consultation 98,000			
	Pre-development consultation for companion diagnostics		per consultation 293,800			
	Pre-development consultation for companion diagnostics (preliminary interview completed)		per consultation 264,400			
	Pre-development consultation for companion diagnostics (additional consultation)		per consultation 147,000			
	Consultation on the development program of companion diagnostics		per consultation 1,541,600			
	Consultation on the development program of companion diagnostics (preliminary interview completed)		per consultation 1,512,200			
	Consultation on protocol for *in vitro* diagnostics	Quality	per consultation 127,400			
		Quality (preliminary interview completed)	per consultation 89,100			
		Quality (additional consultation)	per consultation 60,800			
		Performance (other than quality) (1 test)	per consultation 127,400			
		Performance (other than quality) (1 test) (preliminary interview completed)	per consultation 89,100			
		Performance (other than quality) (1 test) (additional consultation)	per consultation 60,800			
		Performance (other than quality) (2 tests)	per consultation 254,800			
		Performance (other than quality) (2 tests) (preliminary interview completed)	per consultation 216,500			
		Performance (other than quality) (2 tests) (additional consultation)	per consultation 127,400			
		Performance (other than quality) (3 or more tests)	per consultation 381,900			
		Performance (other than quality) (3 or more tests) (preliminary interview completed)	per consultation 343,700			
		Performance (other than quality) (3 or more tests) (additional consultation)	per consultation 191,100			
		Correlation	per consultation 254,800			
		Correlation (preliminary interview completed)	per consultation 216,500			
		Correlation (additional consultation)	per consultation 127,400			
		Clinical performance studies	per consultation 735,300			
		Clinical performance study (preliminary interview completed)	per consultation 688,000	(Conducted at the Kansai branch)** +280,000 yen		
		Clinical performance study (additional consultation)	per consultation 367,600			
		Clinical performance study for companion diagnostics	per consultation 2,353,100			
		Clinical performance study for companion diagnostics (preliminary interview completed)	per consultation 2,323,700			
		Clinical performance study for companion diagnostics (additional consultation)	per consultation 1,176,500			
	Application procedure consultation for *in vitro* diagnostics		per consultation 78,300			
	Consultation on evaluation for*in vitro* diagnostics	Quality	per consultation 127,400			
		Quality (preliminary interview completed)	per consultation 89,100			
		Quality (unevaluated protocol)	per consultation 191,100			
		Quality (unevaluated protocol) (preliminary interview completed)	per consultation 150,100			
		Quality (additional consultation)	per consultation 60,800			
		Performance (other than quality) (1 test)	per consultation 127,400			
		Performance (other than quality) (1 test) (preliminary interview completed)	per consultation 89,100			
		Performance (other than quality) (1 test) (unevaluated protocol)	per consultation 191,100			
		Performance (other than quality) (1 test) (unevaluated protocol) (preliminary interview completed)	per consultation 150,100			
		Performance (other than quality) (1 test) (additional consultation)	per consultation 60,800			
		Performance (other than quality) (2 tests)	per consultation 254,800			
		Performance (other than quality) (2 tests) (preliminary interview completed)	per consultation 216,500			
		Performance (other than quality) (2 tests) (unevaluated protocol)	per consultation 381,900			
		Performance (other than quality) (2 tests) (unevaluated protocol) (preliminary interview completed)	per consultation 343,700			
		Performance (other than quality) (2 tests) (additional consultation)	per consultation 127,400			
		Performance (other than quality) (3 or more tests)	per consultation 381,900			
		Performance (other than quality) (3 or more tests) (preliminary interview completed)	per consultation 343,700			
		Performance (other than quality) (3 or more tests) (unevaluated protocol)	per consultation 573,500			
		Performance (other than quality) (3 or more tests) (unevaluated protocol) (preliminary interview completed)	per consultation 535,300			
		Performance (other than quality) (3 or more tests) (additional consultation)	per consultation 191,100			

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			User fees			Timing of payment
Consultations						
In vitro diagnostics	Consultation on evaluation for *in vitro* diagnostics	Correlation	per consultation	254,800		Payment by the date of consultation application after arrangement of the consultation date
		Correlation (preliminary interview completed)	per consultation	216,500		
		Correlation (unevaluated protocol)	per consultation	381,900		
		Correlation (unevaluated protocol) (preliminary interview completed)	per consultation	343,700		
		Correlation (additional consultation)	per consultation	127,400		
		Clinical performance studies	per consultation	440,700		
		Clinical performance study (preliminary interview completed)	per consultation	396,600		
		Clinical performance study (unevaluated protocol)	per consultation	808,600		
		Clinical performance study (unevaluated protocol) (preliminary interview completed)	per consultation	764,500	(Conducted at the Kansai branch)** +280,000 yen	
		Clinical performance study (additional consultation)	per consultation	220,500		
		Clinical performance study for companion diagnostics	per consultation	1,470,700		
		Clinical performance study for companion diagnostics (preliminary interview completed)	per consultation	1,441,300		
		Clinical performance study for companion diagnostics (unevaluated protocol)	per consultation	2,647,200		
		Clinical performance study for companion diagnostics (unevaluated protocol) (preliminary interview completed)	per consultation	2,617,700		
		Clinical performance study for companion diagnostics (additional consultation)	per consultation	733,000		
Regenerative medical products	Procedural consultation for regenerative medical products		per consultation	141,600		
	Consultation before the start of expanded clinical trials for regenerative medical products		per consultation	261,400		
	Pre-development consultation for regenerative medical products		per consultation	314,700		
	Pre-development consultation for regenerative medical products (additional consultation)		per consultation	157,300		
	Non-clinical consultation for regenerative medical products (effectiveness)		per consultation	944,400		
	Non-clinical consultation for regenerative medical products (effectiveness) (additional consultation)		per consultation	472,100		
	Non-clinical consultation for regenerative medical products (safety)		per consultation	993,500		
	Non-clinical consultation for regenerative medical products (safety) (additional consultation)		per consultation	496,800		
	Consultation for quality of regenerative medical products		per consultation	993,500		
	Consultation for quality of regenerative medical products (additional consultation)		per consultation	496,800		
	Consultation on qualification of materials for regenerative medical products		per consultation	496,800		
	Consultation before therapeutic exploratory study for regenerative medical products		per consultation	1,153,400		
	Consultation before therapeutic exploratory study for regenerative medical products (additional consultation)		per consultation	577,100		
	Consultation after therapeutic exploratory study for regenerative medical products		per consultation	1,318,200		
	Consultation after therapeutic exploratory study for regenerative medical products (additional consultation)		per consultation	659,600		
	Prior assessment consultation for regenerative medical products (safety, quality, effectiveness)		per consultation	2,878,300	(Conducted at the Kansai branch)** +280,000 yen	
	Prior assessment consultation for regenerative medical products (therapeutic exploratory study)		per consultation	1,318,200		
	Prior assessment consultation for regenerative medical products (confirmatory clinical study)		per consultation	2,878,300		
	Pre-application consultation for regenerative medical products		per consultation	2,878,300		
	Pre-application consultation for regenerative medical products (additional consultation)		per consultation	1,439,100		
	Consultation on protocols of clinical trials for regenerative medical products after the conditional time-limited authorization (with protocol)		per consultation	1,318,200		
	Consultation on protocols of clinical trials for regenerative medical products after the conditional time-limited authorization (with protocol) (additional consultation)		per consultation	659,600		
	Consultation on protocols of clinical trials for regenerative medical products after the conditional time-limited authorization (only for investigation)		per consultation	989,400		
	Consultation on protocols of clinical trials for regenerative medical products after the conditional time-limited authorization (only for inspection) (additional consultation)		per consultation	494,600		
	Consultation at completion of clinical trials for regenerative medical products after the conditional time-limited authorization (with protocol)		per consultation	1,318,200		
	Consultation at completion of clinical trials for regenerative medical products after the conditional time-limited authorization (with protocol) (additional consultation)		per consultation	659,600		
	Consultation at completion of clinical trials for regenerative medical products after the conditional time-limited authorization (only for inspection)		per consultation	989,400		
	Consultation at completion of clinical trials for regenerative medical products after the conditional time-limited authorization (only for inspection) (additional consultation)		per consultation	494,600		

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		User fees				Timing of payment
Consultations						
Regenerative medical products	Consultation on protocols of post-marketing clinical trials for regenerative medical products (with protocol)	per consultation	1,318,200	(Conducted at the Kansai branch)** +280,000 yen		Payment by the date of consultation application after arrangement of the consultation date
	Consultation on protocols of post-marketing clinical trials for regenerative medical products (with protocol) (additional consultation)	per consultation	659,600			
	Consultation on protocols of post-marketing clinical trials for regenerative medical products (only for inspection)	per consultation	989,400			
	Consultation on protocols of post-marketing clinical trials for regenerative medical products (only for inspection) (additional consultation)	per consultation	494,600			
	Consultation at completion of post-marketing clinical trials for regenerative medical products (with protocol)	per consultation	1,318,200			
	Consultation at completion of post-marketing clinical trials for regenerative medical products (with protocol) (additional consultation)	per consultation	659,600			
	Consultation at completion of post-marketing clinical trials for regenerative medical products (only for inspection)	per consultation	989,400			
	Consultation at completion of post-marketing clinical trials for regenerative medical products (only for inspection) (additional consultation)	per consultation	494,600			
	Consultation on GLP/GCP (including GCTP) compliance assessment for regenerative medical products	per consultation	479,600			
	Consultation on GLP/GCP (including GCTP) compliance assessment for regenerative medical products (additional consultation)	per consultation	237,500			
	Preliminary interview for regenerative medical products (with recording)	per consultation	99,200			
	Post-consultation for regenerative medical products (with recording)	per consultation	99,200			
SAKIGAKE comprehensive evaluation consultation	SAKIGAKE comprehensive evaluation consultation for drugs (quality)	per consultation	3,597,200	(Conducted at the Kansai branch)** +280,000 yen		
	SAKIGAKE comprehensive evaluation consultation for drugs (non-clinical)	per consultation	5,999,500			
	SAKIGAKE comprehensive evaluation consultation for drugs (clinical)	per consultation	7,193,800			
	SAKIGAKE comprehensive evaluation consultation for drugs (GLP/GCP)	per consultation	3,589,000			
	SAKIGAKE comprehensive evaluation consultation for drugs (GMP)	per consultation	3,586,800		+ overseas travel expences	
	SAKIGAKE comprehensive evaluation consultation for medical devices (quality)	per consultation	1,499,700			
	SAKIGAKE comprehensive evaluation consultation for medical devices (non-clinical)	per consultation	2,497,800			
	SAKIGAKE comprehensive evaluation consultation for medical devices (clinical)	per consultation	2,998,800			
	SAKIGAKE comprehensive evaluation consultation for medical devices (GCP/GLP)	per consultation	1,498,600			
	SAKIGAKE comprehensive evaluation consultation for medical devices (QMS)	per consultation	1,498,600		+ overseas travel expences	
	SAKIGAKE comprehensive evaluation consultation for *in vitro* diagnostics (quality)	per consultation	299,100			
	SAKIGAKE comprehensive evaluation consultation for *in vitro* diagnostics (performance)	per consultation	999,500			
	SAKIGAKE comprehensive evaluation consultation for *in vitro* diagnostics (clinical performance)	per consultation	1,599,300			
	SAKIGAKE comprehensive evaluation consultation for *in vitro* diagnostics (QMS)	per consultation	599,000		+ overseas travel expences	
	SAKIGAKE comprehensive evaluation consultation for regenerative medical products (quality)	per consultation	1,799,600			
	SAKIGAKE comprehensive evaluation consultation for regenerative medical products (non-clinical)	per consultation	2,997,300			
	SAKIGAKE comprehensive evaluation consultation for regenerative medical products (clinical)	per consultation	3,598,500			
	SAKIGAKE comprehensive evaluation consultation for regenerative medical products (GLP/GCP)	per consultation	1,798,300			
	SAKIGAKE comprehensive evaluation consultation for regenerative medical products (GCTP)	per consultation	1,798,300		+ overseas travel expences	
Regulatory Science (RS) Strategy Consultation (R&D)	RS Strategy Consultation (R&D) for drugs	per consultation	1,541,600	(Conducted at the Kansai branch)** +280,000 yen		
	RS Strategy Consultation (R&D) for drugs (universities/research institutions and venture companies meeting requirements specified separately*)	per consultation	154,100			
	Consultation on quality and safety for regenerative medical products	per consultation	1,541,600			
	Consultation on quality and safety for regenerative medical products (universities/research institutions and venture companies meeting requirements specified separately*)	per consultation	154,100			
	RS Strategy Consultation (R&D) for medical devices	per consultation	874,000			
	RS Strategy Consultation (R&D) for medical devices (universities/research institutions and venture companies meeting requirements specified separately*)	per consultation	87,400			
	RS Strategy Consultation (R&D) for regenerative medical products	per consultation	874,000			
	RS Strategy Consultation (R&D) for regenerative medical products (universities/research institutions and venture companies meeting requirements specified separately*)	per consultation	87,400			
	RS Strategy Consultation (R&D) for development plans, etc.	per consultation	73,600			

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(Yen)

				User fees		Timing of payment
Consultations						
Simple consultations	Generic drugs			per consultation	22,600	Payment by the date of consultation application after arrangement of the consultation date
	OTC drugs			per consultation	22,600	
	Quasi-drugs (including pest control agents)			per consultation	22,600	
	Medical devices or *in vitro* diagnostics			per consultation	39,400	
	Simple consultations on the prior confirmation of minor change notifications for medical devices			per consultation	39,400	Payment by the date of written consultation application
	Simple consultations on the prior confirmation of minor change notifications for drugs			per consultation	39,400	
	Simple consultations on the prior confirmation of minor change notifications for generic drugs			per consultation	39,400	
	New drugs			per consultation	22,600	Payment by the date of consultation application after arrangement of the consultation date
	Regenerative medical products			per consultation	22,600	
	GCP/GLP/GPSP for drugs			per consultation	20,300	
	GCP/GLP/GPSP for medical devices			per consultation	19,400	
	GCP/GLP/GPSP for regenerative medical products			per consultation	20,400	
	GMP/QMS inspection			per consultation	25,400	
	GCTP inspection			per consultation	26,700	
GLP inspection of test facilities						
All test items	Basic fee		With animal house facility	per facility	1,364,500	Request to PMDA after advanced payment
			Without animal house facility	per facility	839,400	
	Additional fee for target tests		General toxicity studies	per study	419,600	
			Reproduction toxicity studies	per study	209,800	
			Safety pharmacology core battery (only for drugs)	per study	209,800	
			Hemocompatibility studies (only for medical devices)	per study	209,800	
			In vitro studies	per study	209,800	
			Other studies (dependence, TK, pathology, etc.)	per study	209,800	
	Additional fee for target category		Drugs	per facility	209,800	
			Medical devices	per facility	209,800	
			Regenerative medical products	per facility	209,800	
Additional compliance accreditation				per facility	1,007,200	
Additional inspection				per inspection for the second and subsequent inspections	416,300	
Confirmation of certification on drugs, etc.						
GMP certification on investigational products (with on-site inspection)				per product of one facility	798,900	Request to PMDA after advanced payment
GMP certification on investigational products (without on-site inspection)				per product of one facility	16,200	
Certification of drug products				per product	16,200	
Other certifications (including GMP/QMS certification)				per matter of one product	9,100	
Fee for the video conference system at the Kansai Branch (consultations on safety measures)						
				per consultation	70,000	Payment by the date of consultation application after scheduling
Use of document storage rooms						
				per day per room	3,000	Payment upon invoice sent from PMDA after the end of the period of use

* Universities/research institutions and venture companies meeting requirements specified separately.
All of the following requirements should be met in principle:

For universities/research institutions

- Having not received not more than the following amount from the national government, to proceed with the research on the seed-stage resource
  - For the RS strategy consultation (R&D) for drugs or consultation on quality and safety for regenerative medical products, 90 million yen or more
  - For the RS strategy consultation (R&D) for medical devices or RS strategy consultation (R&D) for regenerative medical products, 50 million yen or more
- Having not received a research fund from a pharmaceutical company, medical device company, etc. under a joint research agreement, etc., for practical application of the seed-stage resource

For venture companies

- Being a small or medium-sized company (with 300 employees or less, or capitalized at 300 million yen or less)
- Any other corporation does not hold half or more of the total number of shares or investments
- Two or more other corporations do not hold two thirds or more of the total number of shares or investments
- For the preceding fiscal year, profits of the term have not been reported, or profits of the term have been reported but without operating revenue

**** When a video conference consultation is conducted at the Kansai branch, a user fee of 280,000 yen is required uniformly.**
(Excluding simple consultations and consultations on safety measures)

Appendix 1

Mid-term Targets of the Pharmaceuticals and Medical Devices Agency (PMDA)
(Provisional Translation)

** This translation of the original Japanese text is for information purposes only (in the event of inconsistency, the Japanese text shall prevail).*

Instruction No. 0307-73 (dated March 7, 2014) of
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare (MHLW)

Targets to be achieved by the Pharmaceuticals and Medical Devices Agency in its operation management shall be established as below, based on the provision of Article 29, Paragraph 1 of the Act on General Rules for Incorporated Administrative Agency for Incorporated Administrative Agency (Act No. 103, 1999),.

March 7, 2014

Minister of Health, Labour and Welfare
Norihisa Tamura

Part 1
Effective Period for Mid-term Targets

The effective period for Mid-term Targets according to Article 29, Paragraph 2, Item 1 of the Act on General Rules for Incorporated Administrative Agency (Act No. 103, 1999) shall be 5 years, from April 2014 through March 2019.

Part 2
Matters Regarding Improvement in Operation Management of the Overall Corporation and Matters Regarding Improvement in the Quality of Services and Other Operations Rendered to the Public

The targets related to the overall corporation regarding improvement in efficiency of operations, as stipulated in Article 29, Paragraph 2, Item 2 of the Act on General Rules for Incorporated Administrative Agency, and the targets regarding improvement in the quality of services and other operations rendered to the public, as stipulated in Article 29, Paragraph 2, Item 3 of the Act on General Rules for Incorporated Administrative Agency, shall be as follows.

1) Efficient and Flexible Management of Operations

a) The Pharmaceuticals and Medical Devices Agency (hereinafter referred to as the “PMDA”) shall establish an efficient and flexible system for managing operations, confirm the way of operational control and methods for implementing operations through external evaluation, and improve the management of operations based on the following points.
   - Improve internal controls including the way of implementing duties in accordance with instructions from accounting auditors, and proactively disclose measures taken.
   - Examine the way of internal control by utilizing professional knowledge from experts of third-parties.
   - PMDA shall refer to the matters that were notified to each evaluation committee of the incorporated administrative agencies of the government ministries, which are opinions on the report (*Internal Control and Evaluation in Incorporated Administrative Agencies*) released by the Study Group on Internal Control and Evaluation in Incorporated Administrative Agencies held by the Ministry of Internal Affairs and Communications, and opinions on evaluation results of the operating performance in incorporated administrative agencies from the Ministry of Internal Affairs and Communications and the Evaluation Committee of Incorporated Administrative Agencies.

b) Promote computerization of the operations to increase efficiency of the operation management system.

c) Based on a re-examination of systems control operation of the common information and the review operation, PMDA shall control costs by re-examining the system configuration of the overall PMDA and its procurement method, in order to reduce system costs, to ensure transparency of system procurement, and to streamline operation management.
   For this reason, PMDA shall promote approaches to optimize operations and systems by integrating the individual review systems and by establishing a system to promote information sharing among review services, post-marketing safety measures, and relief services for adverse health effects, based on the Optimization Plan for Operations and Systems established at the end of FY 2007.

2) Improvement of Operation Management

a) By continuously improving the operation and increasing efficiency in management, the following reduction in the budget for the Mid-term Plan is expected to have been achieved by the end of the effective period for Mid-term Targets, regarding general administrative expenses (excluding personnel expenses) in which the administrative subsides are to be applied.
   - No less than 15% as compared to FY 2014.
   - Appropriately utilize outsourcing (outsource when possible to prevent increase in personnel, etc.).

b) By increasing efficiency in operations, the following reduction, regarding operating expenses (excluding personnel expenses, and single fiscal-year expenses, etc., that were paid for the establishment of operations) in which the administrative subsidies are to be applied, is expected to be made by the end of the effective period for Mid-term Targets.
   - No less than 5% as compared to FY 2014.
   - Appropriately utilize outsourcing (outsource when possible to prevent increase of personnel, etc.).

c) Yearly administrative subsidies are to be rigorously calculated with consideration of its debt balance.

d) Promote efficiency and improvements of operations by consolidating the management of the marketing authorization holder’s product data, etc. of contributions for adverse drug reaction (ADR), contributions for relief for infections, and contributions for post-marketing safety measures.

e) As a general rule, contracts shall be concluded through open competitive bidding, etc., and the following approaches shall be made.
   - Fully secure competitiveness and transparency even when contracts are not concluded by open competitive bidding such as planning competition and invitation to bids.

- Conduct bids and conclude contracts appropriately, by having them thoroughly checked by auditors and accounting auditors as well as by utilizing opinions of experts.

f) Provide and disseminate genuinely useful information from the public perspective

Let the public be aware of the services and role of PMDA by disseminating and providing information from the public's perspective, which enables the public and patients to readily access to the information they need. Enhance the consultation system and ensure transparency of operations and its details in order to improve the services rendered to the public.

g) Analyze issues of the operation system

Analyze the issues of the operation system appropriately and revise them if necessary.

h) Considerations related to financial base

Consider a financial base that is appropriate for the role of PMDA and take necessary measures.

Part 3

Matters Regarding Improvement in Operation Management of Each Division and Matters Regarding Improvement in the Quality of Services and Other Operations Rendered to the Public

1. Relief Fund Services for Adverse Health Effects

With regard to the relief fund services for Adverse Health Effects (hereinafter referred to as "relief services"), it is important not only to fully disseminate more people the Adverse Drug Reaction Relief System and the Relief System for Infections Acquired through Biological Products (hereinafter referred to as "relief systems") and appropriately operate them, but also adequately and promptly provide relief for those suffering from ADR and infections acquired through biological products or regenerative medical products (hereinafter, including cellular and tissue-based products and gene therapy products).
Based on this concept, the following targets shall be achieved.

1) Enhance Public Relations and Dissemination of Information Regarding the Relief Systems

a) Conduct proactive public relations so that the relief systems are definitely utilized when necessary.

b) Make more efficient operations by reducing the number of cases where inadequate operations of claim documents, etc., result in need of extra processing time.

2) Promptly Process Relief Benefit Claims by Investigating and Organizing the Facts of the Claims

a) Promptly process relief benefit claims

b) Set up standard administrative processing times* and steadily achieve those standards.

* Standard administrative processing time includes a certain period for medical and pharmaceutical judgments of the Ministry of Health, Labour and Welfare. However, administrative processing time shall exclude the period when processing could not be continued because additional or supplementary documents and investigations of the claimant or medical institutions were required to make medical and pharmaceutical judgments.

3) Promote Appropriate Information Transmission in cooperation with Divisions

Cooperation shall be promoted among the divisions of PMDA, and information especially regarding cases of relief payment shall be appropriately disseminated to the Review Divisions and the Safety Measures Divisions, with attention to ensuring protection of personal information.

4) Implement Appropriate Health and Welfare Services

Steadily implement health and welfare services.

5) Appropriately Provide Healthcare Allowances to SMON Patients and Patients infected with HIV through Blood Products

Appropriately conduct services regarding healthcare allowances to SMON patients and HIV-positive patients infected with blood products.

6) Appropriately Pay Benefits to Assist Individuals Affected by Hepatitis C through Specified Fibrinogen Products and Specified Blood Coagulation Factor IX Products Contaminated by Hepatitis C Virus

Appropriately conduct services regarding 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.

2. Reviews and Related Services

In the review services and post-marketing safety measures, PMDA shall enable better pharmaceuticals and medical devices, etc., to be provided to medical settings more promptly and safely, so that the public can use global standard pharmaceuticals and medical devices, etc., at ease. It is important to ensure that pharmaceuticals and medical devices, etc., are appropriately used, prevent health hazards from occurring while accurately and promptly taking measures in cases where health hazards occur, and make pharmaceuticals and medical devices, etc., fulfill their mission in the long term.

Along with this conception, and based on the Japan Revitalization Strategy (adopted by the Cabinet on June 14,2013) and the Healthcare and Medical Strategy (an agreement among the Chief Cabinet Secretary, Minister of Health, Labour and Welfare, and Minister of Internal Affairs and Communications on June 14, 2013) , Act to Ensure Quality, Efficacy, and Safety of Pharmaceuticals and Medical Devices (Act No. 145, 1960) that were revised as a result of the Act for Partial Revision of the Pharmaceutical Affairs Act, (Act No. 84, 2013) , as well as the Act to Ensure Safety of Regenerative Medicine (Act No. 85, 2013), etc. , PMDA shall accelerate reviews speed for s and medical devices, aim to achieve elimination of review lag*, and aim to improve the quality of the reviews, etc. Pharmaceutical Affairs Consultation on R&D Strategy, etc., shall also be enhanced as a support to eliminate the developmental lag*.

In order to achieve these targets, PMDA's financial resources shall be utilized in enhancing the system.

*Drug lag and device lag are defined as delay of approvals of pharmaceuticals and medical devices, respectively, from United States in Japan. Drug lag or device lag can be divided into review lag, which are

differences in review time (time from application to approval) between the United States and Japan, and development lag, which are differences in time at which the companies submit applications to the regulatory agencies of the United States and Japan (from the Japan Revitalization Strategy [approved by the Cabinet on June 14, 2013]).

The overall lag shall be eliminated by eliminating the review lag and development lag.

Following measures shall be promoted in order for the above mentioned measures to be implemented appropriately and smoothly, while maintaining cooperation with MHLW.

1) Make pharmaceuticals, medical devices, etc. accessible by the public more quickly

Efforts shall be made to enable the public and healthcare professionals to promptly gain advantage of advanced and safe pharmaceuticals and medical devices, etc., based on their needs so that they can receive the maximum benefit from them.

PMDA shall proactively support and cooperate with MHLW and its approaches, including acceleration of clinical trials, to promote development of pharmaceuticals and medical devices that are still unapproved in Japan but are of high medical need, in order to reduce development lag.

a) Conduct various measures, while evaluating and verifying their state of progress, and take additional measures when necessary.

b) In order to achieve reduce review lag while improving the quality of reviews, PMDA shall improve the services by setting time reduction targets (targets at ordinary times without any exceptional cases such as substantial changes in the systems or social conditions) for the processing time of applications (regulatory review time for products approved in the respective years) that were submitted after April 1, 2004. PMDA shall develop a review system to achieve these targets.

c) Promote multiregional clinical trials by cooperating with the United States, Europe, and Asian countries.

d) Prioritize clinical trial consultations for pharmaceuticals and medical devices that are expected to be highly useful by enhancing pre-application consultations, so as to reduce review period. Correctly understand the accurate needs of companies at the stage of development and reevaluate system of the consultation service whenever necessary.

e) Improve PMDA's own scientific levels for skills of consultations and reviews, with consideration of the rapid development of the latest technologies such as biotechnology, genomics, and regenerative medicine, and shall take necessary measures for the consultations and reviews along with the development of new pharmaceuticals, new medical devices, and regenerative medical products that utilize the latest technologies.

f) Take necessary measures to accelerate reviews for generic drugs, etc., as in the case of new pharmaceuticals.

g) Take measures to accelerate reviews for behind-the-counter (BTC) drugs*, over-the-counter (OTC) drugs, and quasi-drugs as with new pharmaceuticals.

*Behind-the counter (BTC) drugs are defined as switch OTC drugs and powerful OTC drugs which require pharmacist's intervention.

h) Set targets to aim for eliminating review lag for medical devices, as with new pharmaceuticals, and take measures to accelerate reviews. Develop a review system to achieve these targets.
Regarding reviews of improved medical devices and generic medical devices, PMDA shall take measures to systematically and intensively review items which had taken long time for the reviews after submission, and shall make efforts to reduce the applicant's time (the time within the review time that is necessary for the applicants to reply to inquiries from the regulatory side).

i) Take measures to accelerate reviews for regenerative medical products by enhancing the relevant review divisions necessary to conduct accurate and prompt reviews, while introducing conditional and time-limited approval system as well as setting target review times.

j) Appropriately and efficiently conduct conformity inspections.

k) Conduct appropriate and efficient GMP/QMS/GCTP (Good gene, Cellular and Tissue Practice) etc. inspections.

2) Provide Support to be the First in the World to Facilitate Practical Use of Innovative Pharmaceuticals, Medical Devices, and Regenerative Medical Products

Make the following approaches in order to be first in the world to facilitate practical use of innovative pharmaceuticals, medical devices, and regenerative medical products.

a) Establish and update review standards for innovative products.

b) Proactively conduct Pharmaceutical Affairs Consultation on R&D Strategy, etc.

c) Operate the approval system based on the characteristics of regenerative medical products.

3. Safety Measures

In the review services and post-marketing safety measures, PMDA shall promptly and safely provide superior pharmaceuticals and medical devices, etc., to medical settings in order to enable the public to use global standard pharmaceuticals and medical devices, etc., at ease. It is important to ensure that pharmaceuticals and medical devices, etc., are appropriately used, prevent health hazards from occurring while accurately and promptly taking measures in cases where health hazards occur, and make pharmaceuticals and medical devices, etc., fulfill their mission in the long term.

In accordance with this concept, utilize finances including PMDA's own financial resource and enhance the system when necessary to improve post-marketing safety measures of pharmaceuticals and medical devices, etc., based on the Act for Partial Revision of the Pharmaceutical Affairs Act that reflects the details of Japan Revitalization Strategy, the Healthcare and Medical Strategy, the final recommendation of the Committee for Investigation of Pharmaceutical-induced Hepatitis Cases and Appropriate Regulatory Administration to Prevent Similar Sufferings, etc.

a)Systematically and continuously conduct comprehensive evaluations of information on ADR, Malfunction, and Adverse Reaction (here in after ADR, etc.), by substantially enhancing assemble of information on ADR, etc., and its evaluation analysis system in order to accurately respond to the advanced and specialized evaluation of information on ADR, etc. Furthermore, find out new relationships among

multiple ADR information, and establish an efficient and effective evaluation system for safety information such as researching and utilizing methods to identify and analyze new safety information, and improved it when necessary, by using IT technology.

b) Have healthcare professionals and companies increase utilization of feedback information on the analysis results of collected safety information, etc., and enhance methods of disseminating information on appropriate use to the patients, in order to enhance the rigorous system for disseminating safety information to improve safety measures at medical institutions. At the same time, PMDA shall also establish standards that enable the accomplishments of safety measures to be more accurately understood in a manner in which the public are able to understand easily.

c) Conduct appropriate post-marketing safety measures based on the Risk Management Plan of pharmaceuticals.

d) Cooperation shall be promoted among the relief services and the review services to enable appropriate assessment of safety.

e) Establish a system that enables confirmation of the current status and effectiveness of post-marketing safety measures taken by PMDA in companies and medical institutions, etc.

f) Appropriately collect information on Adverse Reaction reports regulated in the Preventive Vaccination Act and appropriately conduct investigations and analyses.

4. Promotion of Regulatory Science, Globalization, etc.

Note: Regulatory science = Science for coordinating results of science and technology into the most desirable form for harmonizing people and society, by conducting accurate and evidence-based estimations, evaluations, and decisions in order for the results of science and technology to be used for people and society. (from the Science and Technology Basic Plan, adopted by the Cabinet on August 19, 2011)

a) Enhance regulatory science research

Develop an environment and system for conducting regulatory science research (hereinafter referred to as the “RS research”) aimed at improving the quality of the services provided by PMDA. Make efforts to train human resources to be experts in RS research through conducting it, and make efforts to contribute to increase the efficiency of development of pharmaceuticals, etc., through establishment of guidelines, etc.

b) Response to globalization

Reinforce partnerships with foreign regulatory agencies, promote global harmonization activity to proactively collect foreign information, and make efforts to promote dissemination of information in English.

Furthermore, enhance the English website of PMDA, and enhance measures in order for Asian countries to increase their understanding of Japanese regulations and standards regarding pharmaceutical applications, etc.

c) Enhance staff training

By enhancing staff training, PMDA shall establish a group of engineering supervisors that have a global level in review services and post-marketing safety measures so as to increase the quality of the services, and shall make efforts to train human resources to be experts in RS research.

d) Promote interaction with external researchers and investigative research

Promote investigative research by proactively interacting with external researchers in order to contribute to activate development and to establish guidelines regarding innovative seed-stage resources.

e) Promptly facilitate practical use of pharmaceuticals for intractable diseases and orphan diseases.

f) Promote further transparency of review services and post-marketing safety measures such as revealing in public review reports.

g) Develop an information system basis that ensures reliability and increases efficiency of review services and post-marketing safety measures.

Part 4
Matters Regarding Improvement in Financial Affairs

The following is the target for improving financial affairs specified in Article 29, Paragraph 2, Item 4 of the Act on General Rules for Incorporated Administrative Agency.

For matters specified in Part 2, items 1) and 2) of this Mid-term Targets, a Mid-term budget shall be developed with an estimation of cost reductions, and PMDA shall operate based on this budget.

Part 5
Important Matters Regarding Other Operation Management

The following are important targets regarding other operation management specified in the Article 29, Paragraph 2, Item 5 of the Act on General Rules for Incorporated Administrative Agency.

1) Matters Regarding Personnel Affairs

a) Secure enough personnel necessary to reviews and post-marketing safety measures, based on the Act for Partial Revision of the Pharmaceutical Affairs Act, etc., that reflects the details of Japan Revitalization Strategy, the Healthcare and Medical Strategy, and the final recommendation of the Committee for Investigation of Pharmaceutical-induced Hepatitis Cases and Appropriate Regulatory Administration to Prevent Similar Sufferings, etc.

In order to avoid any suspicion of inappropriate relationships with pharmaceutical companies, etc., PMDA shall take appropriate measures in employment, allocation, post-retirement reemployment, etc., of executives and employees, while thoroughly ensuring its neutrality, etc.

PMDA shall make efforts to adjust the salary levels of the employees to achieve an appropriate and efficient level, taking into consideration competitiveness for stable securement of excellent human resources.

b) Appropriately develop personnel capacities by having them interact with external institutions to increase their expertise, and appropriately conduct personnel evaluations based on their work performance. PMDA shall also increase motivation of the personnel through these measures, etc.

2) Ensure Security

Ensure security of the offices, etc. and take all measures to thoroughly manage information, in order to thoroughly protect information of personal, corporate, etc.

3) Matters Regarding Disposition of the Reserve Funds Specified in Article 31, Paragraph 1 of the Act on the Pharmaceuticals and Medical Devices Agency

Appropriately dispose the reserve funds that are still left even after adjusting profit and loss according to Article 44 of the Act on General Rules for Incorporated Administrative Agency at the end of the last fiscal-year of the effective period for the Second Mid-term Targets.

4) Other Matters

Steadily conduct approaches based on the government policy indicated in past Cabinet decisions, etc.

Appendix 2

Mid-term Plan of the Pharmaceuticals and Medical Devices Agency (PMDA)
(Provisional Translation)

** This translation of the original Japanese text is for information purposes only (in the event of inconsistency, the Japanese text shall prevail).*

Notification No. 0331-44 (dated March 31, 2014) of
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

To achieve the Mid-term Targets of the Pharmaceuticals and Medical Devices Agency assigned on March 7, 2014 by the Minister of Health, Labour and Welfare based on the provisions of Article 29, Paragraph 1 of the Act on General Rules for Incorporated Administrative Agency (Act No. 103, 1999), the Pharmaceuticals and Medical Devices Agency (PMDA) has developed the following Mid-term Plan based on the provisions of Article 30, Paragraph 1 of the same act.

March 7, 2014

Tatsuya Kondo, Chief Executive,
Pharmaceuticals and Medical Devices Agency

Development toward global PMDA based on the PMDA Philosophy

PMDA was established in April 2004, after several times of reorganization by integrating the services of review and post-marketing safety measures, and has its roots in the “Fund for Relief Services for Adverse Drug Reactions”, which was established following tragic pharmaceutical-induced sufferings caused by pharmaceuticals such as thalidomide and diseases such as subacute myelo-optical neuropathy (SMON). Based on this history, and in order to carry out its mission to promptly provide the public with more effective and safer pharmaceuticals and medical devices, PMDA has been dedicating itself to improve its services for review, post-marketing safety measures, and relief services for adverse health effects. Essential targets have been accomplished by accelerating reviews and enhancing post-marketing safety measures in its efforts during the first and second terms. PMDA will need to further strengthen and enhance its system to aim to be a world-class institution responsible for reviews and post-marketing safety measures, in order to equal the United States and Europe in the future.

PMDA will promote comprehensive risk management through “Safety Triangle”, a system based on three major services, which are the review, post-marketing safety measures for pharmaceuticals and medical devices, and relief services for adverse health effects, to secure safety and efficacy, based on the following organizational philosophy of action (PMDA Philosophy).

1) 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.
2) We will be the bridge between the patients and their wishes for faster access to safer and more effective pharmaceuticals and medical devices.
3) 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.
4) We play an active role within the global community by promoting global harmonization.
5) We conduct services in a way that is trusted by the public based on our experiences from the past.

In promoting its risk management, PMDA will especially make efforts to develop an environment that enables judgments from an ethical perspective based on regulatory science, and to proactively contribute in improving public health and safety. PMDA will also promote cooperation with the United States, Europe, and Asian countries, etc., and approach issues from a global perspective in order to further improve health of people not only in Japan but also in the world.

Based on the Japan Revitalization Strategy (adopted by the Cabinet on June 14, 2013), the Healthcare and Medical Strategy (an agreement among the Chief Cabinet Secretary, Minister of Health, Labour and Welfare, and Minister of Internal Affairs and Communications, etc., on June 14, 2013), the Act to Ensure Quality, Efficacy, and Safety of Pharmaceuticals and Medical Devices (Act No. 145, 1960; hereinafter referred to as the “Pharmaceutical and Medical Devices Act”), and the Act to Ensure Safety of Regenerative Medicine (Act No. 85, 2013; hereinafter referred to as the “The Act of the Safety of Regenerative Medicine”), etc., PMDA will further accelerate and improve the review services in order to promote to be the first in the world in practical use of innovative pharmaceuticals, medical devices, and regenerative medical products, while taking post-marketing safety measures, such as ensuring quality of post-marketing products and preventing occurrence and spread of health hazards.

In order to achieve these goals, the review and post-marketing safety measures in this term shall be improved by further enhancing the system and by introducing new review methods, etc., while pursuing elimination of review lag. Efforts will be made to have the public be aware of the relief services to ensure utilization of them. With these targets, the Third Mid-term Plan is to be established and implemented as follows:

Part 1

Measures to be taken in Order to Achieve Targets Related to Matters Regarding Improvement in Operation Management of the Overall Corporation and Matters Regarding Improvement in the Quality of Services and Other Operations Rendered to the Public

The following are the measures to be taken in order to achieve targets regarding improvement in efficiency of operations, as stipulated in Article 30, Paragraph 2, Item 1 of the Act on General Rules for Incorporated Administrative Agency (Act No. 103, 1999; hereinafter referred to as the "Act on General Rules"), and to achieve targets regarding improvement in the quality of services and other operations rendered to the public, as stipulated in Article 30, Paragraph 2, Item 2 of the Act on General Rules.

1) Efficient and Flexible Management of Operations

a) Manage transparent and appropriate operations through thorough compliance risk management
- Clarify the operational targets and responsibilities of each division, and identify and resolve problems by managing the operational progress on a daily basis.
- Develop and appropriately utilize internal control processes to achieve efficacy and efficiency of operations, reliability of financial reports, compliance with acts related to operational activities, and maintenance of assets, and proactively disclose the details of those measures that were taken.
- Gather opinions on operational performance for each fiscal year and utilize them in managing the operations.
- Hold advisory councils as an opportunity to exchange opinions with experts from various fields, and seek proposals and improvement measures for operations and the management system, in order to increase efficiency as well as to ensure fairness and transparency of the operations.
- Efficiently manage the operations by flexibly allocating personnel according to situations and by effectively utilizing external experts.
- Utilize manuals for emergency management appropriately by reviewing them from time to time in response to particular situations, in order to thoroughly manage risks in the management of operations.

- Develop a system necessary to support the operations of the review, post-marketing safety measures, and relief service in order to respond to the expansion of the organization due to system reinforcement, and to enable reviewers to concentrate on technical and specialized operations.

b) Standardize operation procedures
- Standardize the procedures of each operation so that they can be conducted appropriately, which will enable utilization of non-regular staff, and as a result limit the number of regular staff members.

c) Develop materials and information databases
- Utilize an electronic format for documentary information whenever possible, and promote the development of databases that enable the information to be systematically organized and stored, as well as to enable material and information to be collected and analyzed.

d) Optimize the system to improve efficiency of operations
- Continue operations based on the basic policies of the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as the "Agency") for developing the system environment.
- Based on the Optimization Plan for Operations and Systems that was established at the end of FY 2007, a system shall be developed to promote information sharing in the operations of review, post-marketing safety measures, and relief services for adverse health effects, and further approaches shall be promoted for the optimization of operations and systems, which was revised in FY 2012 for the purpose of enhancing the accounting and personnel management functions to respond to changes such as increase in personnel. Expenses for system development and improvement shall be invested systematically and efficiently by comprehensively judging at the Committee on Investment in Information Systems from such perspectives as appropriateness, cost-effectiveness, and technical difficulty.
- Along with the Optimization Plan for Operations and Systems, increase efficiency of operations by revising the information system according to the actual status of the operations in each division.

2) Rationalize Operation Management

a) Retrench general administrative expenses (management divisions)
- By continuously improving the operation and increasing efficiency in management, the following reduction in the budget for the Mid-term Plan is expected to have been achieved by the end of the effective period for Mid-term Targets, regarding general administrative expenses (excluding personnel expenses) in which the administrative subsidies are to be applied.
- No less than 15% as compared to FY 2014
- Appropriately utilize consolidation and outsourcing for management operations such as payroll accounting, fund balancing, and calculation of travel expenses.

b) Retrench operating expenses for efficient operation management
- By increasing efficiency in operations such as promoting computerization, the following reduction in the budget for the Mid-term Plan is expected to have been made by the end of the effective period for Mid-term Targets, regarding operating expenses (excluding personnel expenses, and single fiscal-year expenses that were paid for the establishment of operations) in which the administrative subsidies are to be applied.
- No less than 5% as compared to FY 2014
- Appropriately utilize consolidation and outsourcing for management operations such as payroll accounting, fund balancing, and calculation of travel expenses.

c) Calculate administrative subsidies
- Yearly administrative subsidies are to be rigorously calculated with consideration of its debt balance.

d) Stable collection of contributions
- Have the marketing authorization holders (MAHs) of pharmaceuticals and medical devices understand the significance of the contribution system for adverse drug reaction (ADR) fund, relief for infections, and contributions to post-marketing safety measures, in order for contributions to be appropriately declared and paid, and to ensure stable collection of each contribution.
- The collection rate for the contributions of ADR fund, relief for infections, and contributions to post-marketing safety measures shall be no less than 99%.

e) Secure contract competitiveness and transparency
- Contracts shall be concluded through open competitive bidding as a principle, and the following approaches shall be made.
- Fully secure competitiveness and transparency even when contracts are not concluded by general competitive bidding such as planning competition and invitation to bids.

- To conduct biddings and conclusion of contracts appropriately, contracts should be pre-inspected, etc., by the Contract Review Committee and thoroughly checked by auditor and accounting auditor.

f) Provide and disseminate genuinely useful information from the public perspective
- Take the following measures to steadily implement the PMDA Public Relations Strategic Plan.
  1. Enhance dissemination of information by improving the website so that it can be easily understood in order for the public and patients to be able to readily access information regarding safety and efficacy of pharmaceuticals and medical devices.
  2. Conduct public relations using newsletters related to PMDA.
  3. Provide and publish information regarding PMDA in television and magazines.
  4. Create newsletters in English and disseminate information to Foreign Correspondents' Club of Japan and to foreign media.
  5. Enhance and improve the system for responding to consultations and complaints from the public.
- Enhance dissemination of information to the general public by disclosing the details of PMDA's services and achievements when appropriate, through various media including its website in order for the public to better understand the safety of pharmaceuticals and medical devices, as well as the overall services of PMDA.
- Conduct external audit in accordance with the incorporated administrative agencies system, together with systematic internal audit and accounting audit, and disclose those results.
- Disclose PMDA's overall financial standing as well as its financial standing for each account and segment in order to ensure transparency of the expenditures.

g) Analyze issues of the operation system
- Quantitatively analyze and examine issues of each division regarding the current operation processes as well as their systems as much as possible by the midpoint of the effective period for the Third Mid-term Targets, based on the understanding of the past operating performances of the relief service, review, and safety divisions, and those processes and systems shall be revised if necessary in order to confirm whether the personnel are allocated appropriately for the system enhancement and whether the operations are conducted efficiently.

h) Considerations related to financial base
- Consider a financial base that is appropriate for the role of PMDA, and take necessary measures based on the current situation where PMDA's revenue such as user fees from companies accounts for the majority of the financial base of PMDA, because the review and safety services of pharmaceuticals and medical devices greatly influence the life and safety of the public.

Part 2

Measures to be taken in Order to Achieve Targets Related to Matters Regarding Improvement in Operation Management of Each Division and Matters Regarding Improvement in the Quality of Services and Other Operations Rendered to the Public

- Make all efforts to promote the safety triangle of review, safety, and relief as a mission of PMDA -

1. Relief Fund Services for Adverse Health Effects

The Relief System for ADR and the Relief System for Infections Acquired through Biological Products (hereinafter referred to as the "relief systems") are systems unique to Japan, which, along with reviews and post-marketing safety measures, are responsible for being part of the safety triangle. The following measures shall be taken for the necessity of having the relief systems to be definitely utilized through consultations with physicians and pharmacists in case of emergencies of health damage due to ADR of pharmaceuticals or regenerative medical products, or due to infections through biological products or regenerative medical products, as well as for the necessity of continuing appropriate operations, such as prompt processing of relief benefit claims.

1) Enhance Public Relations and Dissemination of Information Regarding the Relief Systems

a) Proactively develop public relations in order for the relief systems to be definitely utilized.
- Consider and proactively conduct effective public relations regarding the relief systems.
- Continue informing more of the public regarding the relief systems by utilizing such media as websites and newspapers.
- Current measures, including dissemination of thorough information with the cooperation of relevant organizations, etc., shall be promoted, and the following measures shall be focused in order to increase the awareness by the end of the effective period for the Mid-term Targets, in order to further gain awareness and understanding from the public, health care professionals and MAHs, etc., regarding the relief systems. Surveys shall be conducted every fiscal year to find out the degree of their awareness, and those results shall be examined.
  1. Public relations activities shall be proactively conducted by utilizing the opportunities of training at medical institutions for health care professionals and opportunities of informing pharmacists regarding the systems, in order to properly make patients know the existence of relief systems by healthcare professionals including physicians and pharmacists, in case health damage occurs due to ADR or infections through biological products.
  2. Develop public relations nationwide through professional medical organizations.
  3. Conduct public relations for the general public using such media as websites, television, and newspapers.
  4. Develop effective public relations through other media aside from the above that is appropriate for promoting the relief systems.

b) Announce cases of benefit payment
- Further understanding of the current situation of benefit payment and dissemination of the relief systems to the public, healthcare professionals shall be promoted, by announcing cases of benefit payment and operational statistics on the website.

c) Disseminate information regarding the relief systems
- Review the methods of disseminating information from the perspective of making it user-friendly and easy to be understood, by revising the pamphlets and claim guidelines, by improving the content of information disseminated through the Internet, etc.

d) Ensure an efficient system for the consultation services
- Allocate regular staff for the consultation services, and ensure a system where specialized consultations can be received regarding use of the relief systems as well as the procedures to process benefit payments for ADR and infections.

2) Accelerate the Processing of Relief Benefit Claims

a) Investigate and organize the facts of the claim
- In order for relief benefit claims to be promptly processed, the facts of the claims shall be investigated and organized when received, before requesting the Minister of Health, Labour and Welfare for medical and pharmaceutical judgment.

b) Promptly process within the standard administrative processing time
- The target administrative processing time from receipt of the claim until the decision of payment (within 6 months, more than 60%) shall be maintained even in situations where the number of claims is expected to increase, by taking appropriate measures such as by enhancing the system for receiving and investigating claims, further enhancing and improving instructions for filling medical certificates, and accurately managing the time to use a system.
- Administrative processing time shall exclude the period when processing could not be continued because additional or supplementary documents and investigations of the claimant or medical institutions were necessary in order to make medical and pharmaceutical judgments.

c) Promote efficient operation with the use of databases
- Data of information related to the operation of relief services of ADR, especially information on the causative pharmaceutical, etc., and health damages shall be accumulated on the database, and those accumulated data shall be statistically processed so that they can be analyzed from various perspectives, in order to operate a system that enables prompt and efficient payment of relief benefits using those results.
- Upgrade the systems, develop operation support tools, and enhance systems if necessary, in order to respond to increases in relief benefit claims and to operational situations accordingly.

3) Promote Cooperation with the Review Divisions and the Safety Divisions

- Cooperate with each division of PMDA and appropriately disseminate information, especially regarding cases of relief payment to the divisions of review and the post-marketing safety measures, with attention to ensuring protection of personal information.

4) Implement Appropriate Health and Welfare Services

- Based on the results of a survey that investigated the current situation of health damages due to ADR, investigative research shall be continued in order to obtain information for considering measures to improve QOL of patients suffering from serious and rare health damages.
- Steadily conduct consultations regarding mental issues.

5) Provide Healthcare Allowances for SMON Patients and HIV-positive Patients Infected with Blood Products Appropriately

- In providing healthcare allowances to SMON patients and HIV-positive patients infected with blood products, appropriate services shall be implemented based on the details of the consignment contract, with special attention to ensuring protection of personal information.

6) Pay Benefits to Assist Individuals Affected by Hepatitis C through Specified Fibrinogen Products and Specified Blood Coagulation Factor IX Products Contaminated by Hepatitis C virus Appropriately

- In providing benefits to assist individuals affected by hepatitis C through specified fibrinogen products and specified blood coagulation factor IX products contaminated by hepatitis C virus, appropriate operations shall be implemented, with special attention to ensure protection of personal information.

2. Reviews and Related Services

Based on the Japan Revitalization Strategy and the Healthcare and Medical Strategy, as well as the Pharmaceutical and Medical Devices Act and the Regenerative Medicine Act that were revised as a result of the Act for Partial Revision of the Pharmaceutical Affairs Act, (Act No. 84, 2013), reviewing speed shall be accelerated, aiming to reduce review lag*, and the quality of the reviews shall be improved through approaches according to the characteristic of each pharmaceutical, medical device, and regenerative medical product (hereinafter, including cellular and tissue-based product and gene therapy product). Pharmaceutical Affairs Consultation on R&D Strategy shall also be enhanced as a support to eliminate the development lag*.

In order to achieve these targets, PMDA's financial resources shall be utilized in enhancing the system.

* Drug lag and device lag are defined as delay of approvals of pharmaceuticals and medical devices, respectively, from United States in Japan. Drug lag or device lag can be divided into review lag, which are differences in review time (time from application to approval) between the United States and Japan, and development lag, which are the differences in time at which the companies submit application to the regulatory agencies of the United States and Japan (from the Japan Revitalization Strategy [approved by the Cabinet on June 14, 2013]). The overall lag shall be eliminated by eliminating the review lag and development lag.

Following measures shall be promoted in order for the above mentioned measures to be implemented appropriately and smoothly, while maintaining cooperation with MHLW.

Note: The organization responsible for implementing the following measures is PMDA unless otherwise stated as MHLW, or other corporations.

1) Make pharmaceuticals, medical devices, etc. accessible by the public more quickly

New pharmaceuticals

a) Conduct accurate and prompt reviews
- Enhance system in order to improve quality of the reviews by utilizing the Science Board and by enhancing training, with aiming to achieve elimination of review lag.
- Steadily implement the project management system in order to improve the progress management function of the review services and to increase transparency of the progress and outlook of reviews for applicants as well.
- Continue considering the efficiency and transparency of the review services and processes through exchange of opinions with the industry.
- Strengthen cooperation with academia and healthcare professionals in order to conduct consultations and reviews based on the latest medical care trends and needs, and to promote cooperation toward appropriate use of pharmaceuticals.

- Proactively support and cooperate in discussions and in requesting development for unapproved pharmaceuticals etc., at the Study Group on Unapproved and Off-label Pharmaceuticals of High Medical Need organized by MHLW.
- Continue making approaches to reduce unapproved pharmaceuticals and off-label pharmaceuticals by enhancing database for the current status of pharmaceutical approval in major overseas nations.
- Secure consistency between clinical trial consultations and reviews by maintaining cooperation between these two services, and flexibly organize groups to conduct accurate and prompt reviews and consultations.
- Conduct accurate and prompt re-examinations for new pharmaceuticals. Take appropriate measures for re-evaluations as well.
- Promote establishment of standards regarding quality of pharmaceuticals, such as the Japanese Pharmacopoeia established by MHLW, in order to conduct accurate and prompt reviews.

b) Introduce new methods for reviews and others
- Systematically enhance the system for prior assessment consultations and respond to all consultations that were requested regarding superior pharmaceuticals of high medical need by the FY 2018.
- Develop a system in PMDA that enables to accept electronic submission of clinical study data regarding new pharmaceutical applications after FY 2016.
- Improve the quality of reviews and consultations by conducting PMDA-initiated analyses using the clinical trial data and by giving indications and suggestions based on those analyses results. Consider a system that enables cross-sectional analyses of products using advanced methods of analysis and prediction evaluation, and further improve reviews and consultation by establishing guidelines, etc., and increase efficiency of pharmaceutical development.

c) Targets to aim for eliminating review lag in pharmaceuticals
- Regarding pharmaceuticals which new pharmaceutical applications were submitted after April 1, 2004, the percentile of the standard total review time from application to approval for the items approved in respective fiscal years, shall rise in stages as shown in the following table. The review time of 9 months for priority review products and 12 months for standard review products shall be achieved at 80th percentile by FY 2018.
  The review services shall be enhanced to achieve these targets.

1. Review time for new pharmaceuticals (priority review products)

Fiscal year	Percentile	Review time
FY 2014	60%	9 months
FY 2015	60%	9 months
FY 2016	70%	9 months
FY 2017	70%	9 months
FY 2018	80%	9 months

2. Review time for new pharmaceuticals (standard review products)

Fiscal year	Percentile	Review time
FY 2014	60%	12 months
FY 2015	70%	12 months
FY 2016	70%	12 months
FY 2017	80%	12 months
FY 2018	80%	12 months

- Regarding re-examination of new pharmaceuticals, the review time shall be reduced in stages regarding pharmaceuticals that are to be submitted for re-examination after FY 2014, with review results issued in respective fiscal years, and the total review time of 18 months shall be achieved at 50th percentile (median) by FY 2018. Products re-examined before FY 2014 shall also be sequentially processed.
- Regarding re-evaluations, evaluation and confirmation shall be conducted without delay by setting the appropriate standard review time to each pharmaceutical, based on the points of the application.

d) Promote multi-regional clinical trials
- In order to promote multi-regional clinical trials, appropriately respond to requests for consultations related to multi-regional clinical trials, based on the guidance regarding study design, etc.
- In order to promote multi-regional clinical trials especially in Asian countries, PMDA shall support the approaches of the Multi Regional Clinical Trial Roadmap led by MHLW at APEC RHSC, and develop an environment for conducting multi-regional clinical trials in Asian countries.
- PMDA shall promote multi-regional clinical trials in clinical trial consultations, etc., including information sharing with foreign regulatory agencies so as to increase the rate of conducting multi-regional clinical trials that Japan will participate amongst foreign clinical trials by FY 2018, to eliminate pharmaceutical development lag.

e) Conduct smooth clinical trial consultations, etc.
- Priority consultations and advance confirmation of application documents shall be continued, in order to increase opportunities to provide guidance and consultations before applications.
- Firmly maintain the time it currently takes from request for clinical trial consultation of new pharmaceuticals to direct consultation (about 2 months), while at any time accepting requests for priority clinical trial consultations so as to accelerate procedures for clinical trial consultations on new pharmaceuticals.
- Regarding categories such as prior assessment consultations, Pharmaceutical Affairs Consultation on R&D Strategy, and simple consultations, categories shall be added or altered according to the needs of the applicants by exchanging opinions with relevant industries and by analyzing the content of consultations, so as to enhance clinical trial consultations.

f) Promote evaluation of new technologies, etc.
- For pharmaceuticals developed using new technologies, concepts regarding development and evaluation shall be established in cross-sectional projects, along with guidelines if necessary, by using the knowledge of the Science Board and opinions of external experts.
- PMDA shall increase its scientific knowledge in order to lead the development of pharmaceuticals using latest technologies such as iPS cells.
- Cooperate with MHLW in establishing guidelines for evaluating products using the latest technologies, and proactively disclose the points to consider for evaluations.
- For preliminary reviews regarding the Act Concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (hereinafter referred to as the “Cartagena Act”), the regulatory review time shall be 6 months for approval of first-class use and 2 months for confirmation of second-class use, with a target of achieving 50th percentile (median) for each class.
- Enhance the Pharmaceutical Affairs Consultation on R&D Strategy by conducting consultations where suggestions can be made on development processes (roadmap) as well as confirmatory trial protocols, and by conducting consultations for pharmaceutical companies on developmental strategies.

Generic drugs, etc.

The following measures shall be taken to promote wide use of generic drugs, etc.

a) Conduct accurate and prompt reviews

1. Establish a new office for generic drugs, etc.
- Enhance and accelerate reviews by appropriately increasing and allocating members for the generic drug, etc. group and by establishing a new office.

2. Ensure efficient and transparent reviews
- Strengthen cooperation with academia and healthcare professionals, etc. to conduct consultations and reviews based on the latest medical care trends and needs, and to promote cooperation toward appropriate use of pharmaceuticals.
- Promote establishment of standards regarding quality of pharmaceuticals, etc., such as the Japanese Pharmacopoeia, etc., established by MHLW, in order to conduct accurate and prompt reviews.
- Recommend application by CTD/eCTD format in order to increase efficiency in reviews.
- Ensure transparency of the reviews by preparing and disclosing review reports on new generic drugs.
- Establish guidelines for bioequivalence testing in order to respond to the increased complexity of bioequivalence assessments and the diverse pharmaceutical products that are being developed.
- Cooperate with relevant offices to take appropriate measures to steadily implement the risk management plan.

b) Targets for reducing review time
- Regarding pharmaceuticals which applications were submitted after April 1, 2004, the target review times for the items approved in respective fiscal years, shall be as shown in the following table. The regulatory authority shall make efforts to achieve these targets with the cooperation of the applicants.
The review system shall be enhanced to achieve these targets.

1. Review time for new application of generic drugs
The following targets shall be achieved at 50th percentile (median) by FY 2018.

Product	Regulatory review time
New generic drugs	10 months

2. Review time of application for partial change approval in generic drugs, etc. (standard review products)
Targets shall be achieved at 50th percentile (median) by FY 2018, based on the following plan.

Fiscal year	Total review time
FY 2014	15 months
FY 2015	14 months
FY 2016	13 months
FY 2017	12 months
FY 2018	10 months

3. Review time of application for partial change approval in generic drugs, etc. (products other than standard review products)
The following targets shall be achieved at 50th percentile (median) by FY 2018.

Products	Total review time
Products applied for partial change approval (change in procedure of study, etc.)	6 months
Products applied for partial change approval (prompt review)	3 months

c) Conduct smooth clinical study consultations, etc.
- All consultations shall be conducted for those requested for quality consultation or bioequivalence consultation (face to face consultation).
- Enhance consultation services by considering whether setting up new consultation categories are necessary to meet the needs of the applicants.

Behind-the-counter (BTC) drugs*, over-the-counter (OTC) drugs, and quasi-drugs

The following measures shall be taken to promote public self-medication.

a) Conduct accurate and prompt reviews
- In order to conduct accurate and prompt reviews for BTC drugs, OTC drugs, and quasi-drugs, etc., the following measures shall be taken to enhance the review system, etc., including safety assessments.

1. Enhance system for BTC drugs and OTC drugs, etc.
- In order to respond to the establishment of BTC drugs system, etc., that was newly developed by the Act for Partial Revision of the Pharmaceutical Affairs Act and the Pharmacists Act (Act No. 103 of 2013), the review system shall be enhanced by allocating reviewers for toxicity and clinical matters (including biostatistics), and by securing human resources who have experience in post-marketing safety measures and conformity assessment.
- Strengthen cooperation with academia and healthcare professionals, etc., in order to conduct consultations and reviews based on the latest medical care trends and needs, and to promote cooperation toward appropriate use of BTC drugs and OTC drugs.
- Conduct accurate and prompt reviews by establishing standards regarding quality of pharmaceuticals, such as the Japanese Pharmacopoeia as well as official specification for excipients.
- Increase efficiency and enhance the review service for Chinese herbal medicines and crude drugs.

2. Enhance system for quasi-drugs, etc.
- Increase the number of reviewers in order to accelerate reviews for innovative products.
- Increase efficiency of the reviews by establishing standards for quasi-drugs, such as the Japanese Standards of Quasi-drug Ingredients established by MHLW, as well as establishing quality standards for excipients, etc.
- Improve quality of the reviewers through training, etc.
- Strengthen cooperation with academia and healthcare professionals, etc., in order to conduct consultations and reviews based on the latest medical care trends and needs, and to promote cooperation toward appropriate use of quasi-drugs.

*Behind-the-counter (BTC) drugs are defined as switch OTC drugs and powerful OTC drugs which require pharmacist's intervention.

b) Targets for reducing review time

- Regarding BTC drugs, OTC drugs and quasi-drugs which applications were submitted after April 1, 2004, and were approved in respective fiscal years, the target review times shall be as shown in the following table. Approaches shall be made to achieve these targets.

1. Review time for BTC drugs and OTC drugs

The following target shall be achieved at 50th percentile (median) by FY 2018.

Product	Regulatory review time
BTC drugs and OTC drugs	7 months

2. Review time for quasi-drugs

The following target shall be continuously achieved at 50th percentile (median) by FY 2018.

Product	Regulatory review time
Quasi-drugs	5.5 months

c) Conduct smooth consultation services

- For BTC drugs and OTC drugs, conduct consultations on the appropriateness of developing new OTC drugs, etc., pre-application consultations for switch OTC drugs, and consultations on confirming the key points of the protocols.
- For quasi-drugs, develop and conduct pre-application consultations.

Medical devices

a) Conduct accurate and prompt reviews

- Systematically enhance the review system for new medical devices in order to accelerate the reviews for innovative medical devices.
- Accelerate reviews by making efforts to conduct rational reviews based on the characteristic of medical devices which constantly being improved, etc.
- Strengthen cooperation with academia and healthcare professionals in order to conduct consultations and reviews based on the latest medical care trends and needs, and to promote cooperation toward appropriate use of medical devices.
- Proactively support and cooperate in requesting development for medical devices, including unapproved medical devices, at the Study Group on the Early Introduction of Medical Devices, etc. with High Medical Need held by MHLW.
- Make efforts to smoothly operate and implement the new use-results evaluation system for medical devices.
- For new medical devices, improved medical devices, and generic medical devices, thoroughly manage the timeline for the standard review process so as to be conducted adequately.

b) Clarify review standards, etc.

- Compile and disclose the concept regarding clinical evaluation.
- In order to accelerate the reviews, cooperate with MHLW in establishing approval standards, certification standards, and review guidelines for medical devices, and disclose those standards and guidelines on the website, etc.
- Clarify, share, and establish the concept of substantial equivalence for generic medical devices.

c) Smoothly transfer specially controlled medical devices to the third party certification system

- Transfer to the third party certification system sequentially from the products whose standards have been established among specially controlled medical devices (class III).

d) Targets to aim for eliminating review lag in medical devices

- Regarding medical devices which applications were submitted after April 1, 2004, the percentile of the standard total review time from application to approval for the items approved in respective fiscal years, shall be raised in stages as shown in the following table, in order for the targets to be achieved by FY 2018. Approaches shall be made to achieve these targets by systematically and intensively completing processing of the devices that were submitted for application in the past as soon as possible, and the regulatory authority shall make efforts to improve the lag with the cooperation of the applicants.

1. Review time for new medical devices (priority review products)

Achieve 10 months at 80th percentile by FY 2018 based on the following plan.

Fiscal year	Percentile	Review time
FY 2014	60%	10 months
FY 2015	60%	10 months
FY 2016	70%	10 months
FY 2017	70%	10 months
FY 2018	80%	10 months

2. Review time for new medical devices (standard review products)

Achieve 14 months at 80th percentile by FY 2018 based on the following plan.

Fiscal year	Percentile	Review time
FY 2014	60%	14 months
FY 2015	60%	14 months
FY 2016	70%	14 months
FY 2017	70%	14 months
FY 2018	80%	14 months

3. Review time for improved medical devices (with clinical data)

Achieve 10 months at 60th percentile by FY 2018 based on the following plan.

Fiscal year	Percentile	Review time
FY 2014	52%	10 months
FY 2015	54%	10 months
FY 2016	56%	10 months
FY 2017	58%	10 months
FY 2018	60%	10 months

4. Review time for improved medical devices (without clinical data)

Achieve 6 months at 60th percentile by FY 2018 based on the following plan.

Fiscal year	Percentile	Review time
FY 2014	52%	6 months
FY 2015	54%	6 months
FY 2016	56%	6 months
FY 2017	58%	6 months
FY 2018	60%	6 months

5. Review time for generic medical devices

Achieve 4 months at 60th percentile by FY 2018 based on the following plan.

Fiscal year	Percentile	Review time
FY 2014	52%	4 months
FY 2015	54%	4 months
FY 2016	56%	4 months
FY 2017	58%	4 months
FY 2018	60%	4 months

e) Conduct smooth clinical trial consultations, etc.

- Reconsider the consultation category and improve consultation methods in order for the consultation service to be easier to utilize, and to be efficient and effective.
- Address the relevant industries to proactively utilize the consultation service, in order to eliminate review lag and development lag.

f) Promote evaluation of new technologies, etc.

- For medical devices using new technologies, guidelines, etc., shall be established if necessary, utilizing knowledge of the Science Board and opinions of external experts.
- Make efforts to accumulate relevant knowledge, etc., in order to appropriately respond to the development of medical devices using the latest technologies.
- Cooperate with MHLW in establishing guidelines for evaluating products that were developed using the latest technologies, and proactively disclose the points to consider for evaluations.
- For preliminary reviews regarding the Cartagena Act, the regulatory review time shall be 6 months for approval of first-class use and 2 months for confirmation of second-class use, with a target of achieving 50th percentile (median) for each class.
- Enhance the Pharmaceutical Affairs Consultation on R&D Strategy by conducting consultations where suggestions can be made on development processes (roadmap) and confirmatory trial protocol, and by conducting consultations for medical devices related companies on developmental strategies.

***In vitro* diagnostics**

a) Conduct accurate and prompt reviews

- Appropriately increase and allocate members for the *in vitro* diagnostics group, in order to accelerate and increase transparency of the reviews.
- Strengthen cooperation with the academia and healthcare professionals, etc., to conduct consultations and reviews based on the latest medical care trends and needs, and to promote cooperation toward appropriate use of *in vitro* diagnostics.
- Proactively support and cooperate in requesting development of *in vitro* diagnostics, including those that are still unapproved, that were discussed at the Study Group on the Early Introduction of Medical Devices, etc., with High Medical Need held by MHLW.

b) Enhance consultation service

- Reconsider the consultation category and improve consultation methods in order for the consultation service to be easier to utilize, and to be efficient and effective.

Regenerative medical products

a) Conduct accurate and prompt reviews

- Enhance the services of the division of Pharmaceutical Affairs Consultation and its relevant divisions, as well as the division of biologics reviews. Strengthen cooperation with academia such as the Japanese Society for Regenerative Medicine, the National Institute of Health Sciences, and the Center for iPS Cell Research and Application (CiRA), etc., in order to conduct consultations and reviews based on the latest medical care trends and needs.
- Conduct consultations.

b) Introduce new review methods

- With the implementation of the Act for Partial Revision of the Pharmaceutical Affairs Act, respond appropriately to conditions related to regenerative medical products and to the introduction of time-limited approvals. Develop a system for this, along with its review process, and conduct them accurately.

c) Target review time

- For regenerative medical products which applications were submitted based on the Pharmaceutical Medical Devices Act, standard review time (regulatory time) for the items approved in respective fiscal years shall be set to 9 months.

  The review system shall be enhanced to achieve this target.

d) Conduct smooth clinical study consultations, etc.

- Make efforts to conduct thorough consultations so as to be understood easily, since regenerative medical products are a new field.
- Conduct high-quality consultations by utilizing the Science Board for considering evaluation methods, etc., and highly-qualified external experts, etc., to obtain the latest knowledge.
- PMDA shall make efforts to have applications of regenerative medical products after going through consultations such as the Pharmaceutical Affairs Consultation on R&D Strategy (as the substitute of pre-confirmation application) and pre-application consultations, and develop a system necessary to conduct prompt and smooth reviews considering the current situation of consultations and reviews.
- In order to enable the academia and ventures to consult easily, the target details, etc., of the Pharmaceutical Affairs Consultation on R&D Strategy shall be considered for regenerative medical products, based on the current situation.

e) Promote evaluation of new technologies, etc.

- Conduct appropriate evaluations for regenerative medical products, by utilizing the Science Board for considering evaluation methods, etc., and highly-qualified external experts.
- Make efforts to accumulate relevant knowledge, etc., in order to be able to appropriately respond to the development of regenerative medical products using the latest technologies, such as iPS cells, etc.
- Clarify and rationalize the review standards by promoting the initiative to facilitate development and designated research.
- Enhance the post-marketing surveillance, considering especially the surveillance methods for those conducted after conditional and time-limited approvals, cooperating with the safety division.
- Cooperate with the MHLW in establishing evaluation guidelines regarding products using the latest technologies, and proactively disclose the points to consider for evaluations.

- Enhance consultations to enable proactive utilization of Pharmaceutical Affairs Consultation on R&D Strategy as the substitute of preliminary reviews conducted before clinical trials regarding regenerative medical products and gene therapy products.
- For preliminary reviews regarding the Cartagena Act, the regulatory review time shall be 6 months for approval of first-class use and 2 months for confirmation of second-class use, with a target of achieving 50th percentile (median) for each class.

Promotion of conformity assessments and clinical trials, etc.

The following measures shall be taken to enhance, with strengthening the organization, studies related to the application such as clinical trials, and to ensure reliability of submitted application documents, with focus on an importance of ensuring the reliability of clinical trial data, etc., at the application of pharmaceuticals and medical devices.

a) Implement smooth and efficient conformity assessments for new pharmaceuticals, etc.
- Strengthen the organization to conduct timely assessments which will not affect the time of approval. New assessment methods with efficiency and effectiveness shall also be introduced.
- As for the items concurrently submitted with the applications in the world, etc., strengthen the coordination on partnership with foreign regulatory agencies and strengthen the organization, for example, considering the assessment in collaboration with them.
- Make clear policy on the procedure for clinical trials in which CDISC was introduced from data gathering step.

b) Implement smooth and efficient conformity assessments for medical devices
- Strengthen the organization to conduct timely assessments which will not affect the time of approval.
- Strengthen the organization conduct GCP on-site assessment, in particular, focus on innovative medical devices and multi-regional clinical trials, etc.
- Establish and disseminate detailed requirements that are necessary for applications, in order to implement conformity assessments smoothly and promptly.

c) Implement smooth and efficient conformity assessments for regenerative medical products
- Cope with the introduction of a conditional and time-limited approval system.
- In order to implement appropriate conformity assessments, coordinate with the division of biologics review sufficiently considering assessment methods and processes that are based on the characteristics of regenerative medical products.

d) Implement smooth and efficient GLP compliance assessment
- Train GLP inspectors that has global competency.
- Examine how to establish a smooth operation of the GLP regulation considering global consistency, and implement the GLP compliance assessment more appropriately and efficiently.

e) Implement smooth and efficient conformity assessment for re-examinations (including conformity assessment on use-results evaluation)
- Implement efficient and effective GPSP on-site assessments and document-based conformity assessments.
- To enable high quality post-marketing surveillances, examine to establish such as consultation to provide guidance and advices regarding the compliance for GPSP, etc., during the re-examination period.
- Examine and disseminate effective assessment methods, to enable smooth and prompt conformity assessments for re-examination, etc.

f) Promote appropriate clinical trials, etc.
- Enlighten the further promotion for implementation of appropriate clinical trials, etc., through the conformity assessment at medical institutions and sponsors, and training course, etc., in the period of the Mid-term targets, to ensure the quality of clinical trials, etc. in Japan.
- Examine the establishment of advice system that enables individual cases on GCP, etc.

Promotion of GMP/QMS/GCTP inspection

In order for manufacturers to appropriately maintain and control manufacturing processes and the quality management system for pharmaceuticals, medical devices, and regenerative medical products, the following improvements shall be made to improve inspectional quality.

a) Conduct efficient GMP inspections
- In response to accelerated reviews and increased numbers of bio-products, methods to improve GMP inspection efficiency shall be considered and conducted. This includes system enhancements to conduct timely inspections and clarify application time, while not affecting the time of approval.
- Increase the efficiency of inspections by using the assessment results of other regulatory agencies under PIC/S etc., in risk evaluation to decide if inspections shall be conducted on-site or off-site.
- In response to globalization of active pharmaceutical ingredients supply, partnerships with foreign regulatory agencies shall be reinforced and inspectional information shall be exchanged. A system to enhance on-site inspections at manufacturers overseas, especially in Asian countries, shall be developed.
- Quality of inspections shall be improved by having reviewers accompany the GMP inspection team and by promoting cooperation between GMP inspectors and reviewers.
- Enhance staff training for GMP inspectors by letting them proactively participate in training and meetings conducted overseas. Overseas training will increase staff with knowledge of global GMP harmonization and practices.

b) Conduct smooth and efficient QMS inspections
- QMS inspection and related operations streamlined by the Act for Partial Revision shall be established.
- Promote cooperation between the review groups and the QMS inspection group.
- Standardize inspection methods with other domestic and overseas inspection agencies, such as registered certification bodies.
- Build expertise in global QMS harmonization and practices, through enhancing training for QMS inspectors and let them proactively participate in training and meetings conducted overseas, etc.
- Share inspection information with relevant domestic authorities to efficiently use resources.

c) Conduct smooth GCTP inspections
- For accurate and prompt GCTP (Good gene, Cellular and Tissue Practice) inspections by PMDA that will start after enactment of the Act for Partial Revision, appropriate inspection methodology and necessary resources shall be established and secured.
- For buildings/facilities conformity assessments and relevant on-site inspections by PMDA into establishments that are processing cell/tissue products, that will start after enactment of the Regenerative Medicines Safety Act. Necessary resources shall be immediately secured and managed

and current domestic and overseas situation regarding production of such products shall be figured out.

d) Increase efficiency of inspectional efficiency by utilizing the Kansai Branch and by conducting GMP inspections.

Establishment of control function for the registered certification bodies

1) Improve the quality of certification bodies by ensuring the quality of the inspectors and by conducting appropriate training, etc., for those bodies.

2) Provide Support to be the First in the World to Facilitate Practical Use of Innovative Pharmaceuticals, Medical Devices, and Regenerative Medical Products

a) Establish and update review standards regarding innovative products
- Utilize the Science Board, the initiative to facilitate practical use of innovative pharmaceuticals, medical devices, and regenerative medical products, and regulatory science research (hereinafter referred to as the "RS research"), etc., in order to establish guidelines and guidance and to consider RS research, etc., that PMDA shall make approaches on.
- Establish guidelines and guidance, etc., in cross-sectional projects regarding development and evaluation of pharmaceuticals, etc., that uses new technologies, and make necessary approaches in order to smoothly implement them.

b) Proactively conduct Pharmaceutical Affairs Consultation on R&D Strategy, etc.
- Conduct consultations where suggestions can be made on development processes (roadmap) and confirmatory trial protocol. Conduct consultations for pharmaceutical companies on developmental strategies as well.
- Promote medical innovations by utilizing the Kansai Branch to fully educe technological capacity of Japan regarding biopharmaceuticals, medical devices, and regenerative medical products, etc.
- Regarding PMDA's function to mediate between clinical study and practical use, support, etc., shall be proactively provided through Pharmaceutical Affairs Consultation on R&D Strategy, etc., in establishing exit strategies, with the cooperation of the Japan National Institutes of Health, etc.

c) Operation of approval system based on the characteristics of regenerative medical products
- In order to appropriately cope with conditions related to regenerative medical products as well as the system for time-limited approval that were both introduced by the enforcement of the Act for Partial Revision of the Pharmaceutical Affairs Act, information dissemination and utilization of the consultations shall be promoted, by enhancing Pharmaceutical Affairs Consultation on R&D Strategy and by cooperating with relevant academia and industry.

3. Safety Measures

Utilize finances including PMDA's own financial resource and enhance system necessary to improve post-marketing safety measures of pharmaceuticals, medical devices, etc., based on the Act for Partial Revision of the Pharmaceutical Affairs Act that reflects the details of Japan Revitalization Strategy, the Healthcare and Medical Strategy, the final recommendation by the Committee for Investigation of Pharmaceutical-induced Hepatitis Cases and Appropriate Regulatory Administration to Prevent Similar Sufferings, the discussions held by the Investigational Sub-committee on Revision of Pharmaceutical Regulatory Systems of the Health Science Council, etc.

The following measures shall be taken in order to promote appropriate and efficient approaches mentioned above, with close cooperation with MHLW.

Note: The organization responsible for implementing the following measures is PMDA unless otherwise stated to be MHLW, etc., or other corporations, etc.

1) Enhance Collection of ADR and Malfunction Information
- Establish a system in which patients can easily report ADR, based on opinions, etc., from the patients and patients' families, etc., who have reported them, and officially commence accepting and evaluating ADR reports, including reports on OTC drugs and Switch OTC and powerful drugs.
- Accept reports from MAHs as well as healthcare professionals, and take measures to increase reports from healthcare professionals with the cooperation of MHLW.
- Enhance and improve the systems to report information on ADR and malfunctions, etc., based on the current situation of global development such as ICH E2B and on the advancement of information technology, etc., and promote efficient and effective collection of safety information, etc.
- Enhance measures to collect information on ADR of quasi-drugs and cosmetics.

2) Systematize Information of ADR, etc., and Its Evaluation Analysis
- In order to appropriately respond to the evaluation approach for ADR which is increasingly sophisticated and specialized, substantially enhance current framework to assemble and analyze information on ADR. For this purpose, it is necessary to increase the number of staff members in each group organized according to pharmaceutical effect classification and area of medical practice that correspond to the review divisions. Measures, such as utilizing IT technology, shall also be taken to carefully investigate the overall domestic reports on ADR and infections.
- Modify a PMDA-initiated system step-by-step to follow-up on ADR reported from medical institutions, and ensure its application for all reports that needs investigation by FY 2018.
- Standardize and increase transparency of the process from obtaining information of ADR to take post-marketing safety measures including revision of package inserts, and increase accuracy and expediting of the process.
- Steadily accelerate the process taken to prepare post-marketing safety measures by setting a target time, and by increasing efficiency of the process with standardization. For the target time, consider, reducing the current median time from the first meeting with the MAHs until notification of investigation results.
- Modify submission process for package inserts to enable MAHs to smoothly submit package inserts.
  Establish a system to check contents of submitted package inserts and ensure that the submitted information is based on the latest knowledge.
- Respond promptly to consultations from MAHs when it voluntarily develop or revise either package inserts or communication tools for healthcare professionals and patients.
- Respond promptly to medical safety consultations from MAHs regarding safer use of pharmaceuticals and medical devices at clinical practice.

3) Establish Database, etc., for Medical Information
- Conduct pharmacoepidemiological analyses using electronic medical information, such as the Medical Information Database Network, and improve those analysis methods to promote its utilization for risk/benefit assessments of pharmaceuticals and for post-marketing safety measures.

- Promote MAHs to utilize the Medical Information Database Network for post-marketing safety measures, with its conditions of utilization determined by MHLW for post-marketing surveillance, etc., based on results of utilization obtained through pilot studies.
- Data accumulation shall be promoted in order to improve the quantity and quality of the Medical Information Database Network as well as to improve post-marketing safety measures.
- In order to promptly and safely provide useful medical devices and regenerative medical products, discussions up to the previous effective period for the Mid-term Targets shall be put into consideration to enhance the system of collecting post-marketing information, for example, by establishing a patient registry system for confirming long-term safety, with the cooperation of relevant academia and companies, etc.
- Promote investigational research regarding utilization of pharmacogenomics in post-marketing safety measures.

4) Establish a System for Post-marketing Safety Measures by Providing Information Feedback, etc.
- Regarding line listing of ADR, the time from ADR reporting to disclosure shall remain as within 4 months.
- ADR reports from medical institutions shall be promptly disclosed in the line listing for those that have been investigated by PMDA.
- The instructions for revising the package inserts shall be published on the website within 2 days after issuance of those instructions.
- Disseminate information related to cases of ADR and malfunction, etc., for those that served as the basis for revising package inserts for prescription pharmaceuticals and medical devices, etc.
- Consider with MHLW about measures to enable medical institutions to discern the urgency and importance of the disseminated information more easily.
- Enhance dissemination of information to promote appropriate use of generic drugs.
- Regularly disseminate medical safer information so that pharmaceuticals and medical devices, etc., will be used safely at clinical settings.
- Collect medical safety information from vocational groups, etc., and enhance dissemination of the information.
- Aim for a wider use of the Pharmaceuticals and Medical Devices Information E-Mail Alert Service by enhancing the content of the service and by increasing the number of registries at an early period before the end of FY 2018 by more than 1.5 times that at the end of FY 2013, by means of strongly promoting registry of healthcare professionals working at medical institutions and pharmacies with the cooperation of relevant organizations, and so on.
- Let healthcare professionals, including physicians and pharmacists, etc., increase understanding of the information that PMDA provides.

5) Enhance Dissemination of Information to the Public Regarding Safety of Pharmaceuticals and Medical Devices, etc.
- Improve the method of disseminating information on the website regarding safety of pharmaceuticals and medical devices, etc., in order to respond to changes in the environment in which pharmaceuticals, medical devices, and regenerative medical products are provided, such as internet marketing of OTC drugs.
- Promptly release important safety information in a manner that is easy to understand from the patients' perspective.
- Enhance dissemination of information to patients by further increasing patient's awareness of the Pharmaceutical Guide for Patients and by increasing its convenience.
- Enhance dissemination of information that can be used for medication instructions for patients.
- Conduct consultations services for general consumers and patients for a safe and secure use of pharmaceuticals and medical devices, etc.
- Further improve the contents of information to the public, etc.

6) Conduct Appropriate Post-marketing Safety Measures Based on the Risk Management Plan of Pharmaceuticals
- Consultation and instruction systems shall be strengthened and enhanced to appropriately conduct pharmacovigilance activities and risk minimization activities, based on the new Risk Management Plan (RMP) of pharmaceuticals.
- The new pharmaceuticals review divisions and the safety divisions shall cooperate together through discussions with the applicant in confirming RMP before reviews of new pharmaceuticals concludes.
- Regarding generic drugs, the generic drugs review division and the safety divisions shall cooperate together in order to confirm in the reviews the pharmacovigilance activity and the risk minimization activity that the MAHs are required to conduct.

7) Enhance Safety Measures in Response to the Introduction of New Review Service, and a Safety Management System Consistent from the Review Stage
- Safety management system shall strengthen cooperation with the relief services and maintain consistency from the review stage. Information from the relief services shall be utilized in the post-marketing safety measure operation, with special attention to ensuring protection of personal information.
- The safety divisions and the review divisions shall share information on adverse reactions caused by regenerative medical products (including time during conditional and time-limited approvals), and shall cooperate in taking post-marketing safety measures.
- Information on malfunctions of new medical devices and certified medical devices shall be shared among the safety divisions, the review divisions, and the registered certification body assessment division, for taking post-marketing safety measures.
- The system of safety management shall be enhanced in order to maintain consistency from the review stage, by allocating multiple risk managers for each field according to the number of new pharmaceutical products.
- The management function of the overall post-marketing safety measures shall be enhanced and the groups shall coordinately cooperate, to conduct appropriate operation.
- For products which need investigation on all cases as an approval condition, safety and efficacy information obtained from post-marketing surveillance shall be promptly provided to the public and health care professionals?

8) Enhance Follow-ups of the Safety Measures Conducted
- Conduct investigations to confirm the current status of post-marketing safety measures in MAHs, for example, whether information is definitely conveyed from the MAHs to medical institutions, and to confirm whether information from MAHs is conveyed and utilized within medical institutions and pharmacies. Based on the investigation results, information regarding methods of utilizing safety information in medical institutions and pharmacies shall be disseminated as best practices to use pharmaceuticals and medical devices safely.
- Investigate the status of whether the information provided from PMDA is utilized by general consumers and healthcare professionals, and analyze their needs and satisfaction level, to reflect them in the information service improvement.

9) Data Collection, Investigation, and Analysis on Adverse Reactions Reports in Accordance with the Preventive Vaccination Act

- Adverse reactions shall be promptly disclosed on the website for those that were reported from medical institutions and were investigated by PMDA.
- Details of adverse reactions reports shall be investigated in accordance with the Preventive Vaccination Act, with special attention to ensuring protection of personal information, and investigations and analyses shall be conducted in order to ensure safety of vaccination.

4. Promotion of Regulatory Science and Globalization, etc.

In order to promptly provide clinical settings with necessary pharmaceuticals and medical devices, etc., it is essential for the quality, efficacy, and safety of pharmaceuticals and devices to be accurately estimated, evaluated, and determined based on scientific rationale and to be ascertained from an ethical perspective on whether to allow the public to use them. Regulatory science (RS) pursue this, and it has become increasingly important to be promoted, and research needs to be conducted on establishing prompt and accurate evaluation methods, etc., based on the latest results of technology, by utilizing external experts and by improving PMDA's capability.

In the midst of global development, manufacturing, distribution, and marketing of pharmaceuticals and medical devices, the services of PMDA have increasingly become globalized. Under these circumstances, improvement in medical services as well as establishment of PMDA's global standing shall be made by cooperating with MHLW, the United States, Europe, and Asian countries, etc., and by proactively promoting global activities based on the PMDA International Strategic Plan, PMDA International Vision, and Road map for the PMDA International Vision.

Note: Regulatory science = Science for coordinating results of science and technology into the most desirable form for harmonizing people and the society, by conducting accurate and evidence-based estimations, evaluations, and decisions in order for the results of science and technology to be used for the people and the society (from the Science and Technology Basic Plan, adopted by the Cabinet on August 19, 2011).

1) Promotion of Regulatory Science

1. Utilize the Science Board

- Proactively utilize the Science Board comprising external experts from the fields of medical science, dentistry, pharmaceutics, and engineering, to strengthen cooperation and communication with universities, research institutions, etc., and clinical settings regarding evaluation methods for innovative pharmaceuticals, medical devices, and regenerative medical products, and to make approaches to advanced technology products more adequately, for example, by utilizing Pharmaceutical Affairs Consultation on R&D Strategy.

2. Enhance regulatory science research

- Establish a system in PMDA to enable electronic submission of clinical study data for new pharmaceuticals that are to be submitted after FY 2016.

  Conduct PMDA-initiated cross-sectional analyses on cross-sectional clinical study data, etc., using advanced methods of analysis and prediction evaluation, and consider a system that increases the efficiency of pharmaceutical development through establishment of guidelines, etc.
- As a part of RS research aimed at improving the quality of PMDA's services, a system and environment shall be developed by cooperating with external organizations (NIHS, academia, etc.) when necessary, so PMDA can take initiative in reaching solutions for issues that become evident through its services and issues of making practical use of the latest technologies.
- Develop an environment to easily engage in RS research, to promote and enhance designated research.
- Promote RS research, and encourage those results to be presented at conferences or to be submitted to scientific journals. Through RS research, train human resources to be experts in it.
- As for cross-sectional activities, establish the concept of developing and evaluating pharmaceuticals to enable exchange of opinions between industry, government, and academia, and to establish guidelines and GRP, etc.

3. Enhance staff training

- Besides improving the quality of review, etc., and post-marketing safety measures, from the perspective of developing experts in RS research, status of the current training programs shall be evaluated for their implementation status, and their content shall be improved and conducted steadily.
- Enhance staff training to raise staff members with abilities to take the initiative in discussions at global negotiations and conferences, and to cooperate with foreign countries in establishing standards and guidelines, etc.
- Enhance on-site training at clinical settings and at manufacturing sites of companies, etc., as it is necessary, when conducting reviews, etc., and post-marketing safety measures, to have experience in clinical settings and increase in knowledge of manufacturing processes and quality controls for pharmaceuticals and medical devices.

4. Promote Interaction and investigative research with external researchers

- Proactively accept personnel from universities and research institutions in the field to facilitate practical use of innovative pharmaceuticals, medical devices, and regenerative medical products conducted by MHLW, while also dispatching staff from PMDA in order to help promote the development of innovative seed-stage resources and to establish guidelines.
- Develop and enhance education and research guidance systems that are conducted by directors and staff members at joint graduate school program, including regulations for those systems. These approaches will target increasing staff members who have a doctoral degree, etc.

2) Response to Globalization

1. Reinforce partnerships with the United States, Europe, Asian countries, and global organizations, etc.

- Cooperation with the United States FDA, the European Commission, EMA, and Swissmedic, etc., in promoting bilateral conferences based on confidentiality agreement and promoting exchange of information.
- Establish partnerships with other countries in America, Europe, and Asia, and global organizations.
- Continue dispatching liaison personnel to the United States, Europe, and Switzerland as much as possible, while promoting further dispatches to other countries in America, Europe, and Asia, etc., and global organizations, etc., as well.
- Utilize the liaison personnel dispatched to foreign countries to proactively collect information from their dispatched country, and to strengthen cooperation with those countries.
- Regarding GLP, GCP, GMP, and QMS inspections, further strengthen cooperation with foreign countries by proactively exchanging information on inspection notifications and investigation reports, etc.
- Respond to globalization of pharmaceutical distribution by enhancing globalization measures, for example, by promoting support in issuing an English version of the Japanese Pharmacopoeia as soon as possible, by disseminating information in English, and by promoting partnerships with the pharmacopoeias of Europe, the United States and Asia, etc.

- Reinforce partnerships with regulatory agencies in the United States and Europe in order to conduct accurate reviews and consultations based on the latest science and technology, and to take post-marketing safety measures based on the latest information.
- Promote cooperation necessary to deepen mutual understanding regarding pharmaceutical regulations with the regulatory agencies in Asian countries, which are becoming increasingly important as sites of clinical development and manufacturing of pharmaceuticals, etc.
- Make necessary efforts for the pharmaceuticals and medical devices approved in Japan to be accepted by regulatory agencies in foreign countries, by enhancing information dissemination regarding review and post-marketing safety measures in Japan, etc.

2. Enhance approaches toward global harmonization
- Contribute to the establishment of global standards and provide cooperation at global conferences regarding establishment of standards, such as at ICH and International Medical Device Regulators Forum (hereinafter referred to as “IMDRF”), etc., by proposing new topics, taking the initiative in establishing global standards, and proactively stating opinion on topics initiated by other countries. Promote harmonization with other global standards, such as standards for establishing application data that were defined in these conferences, and the ISO and others.
- For medical devices, continue promoting activities of the Harmonization by Doing (HBD) conducted with the United States and promote exchange of information.
- Promote globalization of the Japanese Pharmacopoeia through global harmonization of pharmacopoeia, etc., at the Pharmacopoeial Discussion Group (PDG).
- Participate in discussions at IGDRP, where global collaboration is held for generic drugs, and promote cooperation with foreign countries regarding reviews for generic drugs.
- Cooperate with MHLW in discussions at the International Cooperation on Cosmetics Regulation (ICCR) in order to promote cooperation with foreign countries.
- Participate in and contribute to global cooperation activities such as WHO and OECD.
- Consider accepting a wider range of submission data for new pharmaceutical applications that are in English.

3. Promote interaction of personnel
- In order to promote establishment of networks with foreign regulatory agencies, have staff members proactively participate in global academic meetings and conferences, and increase opportunities to dispatch staff to organizations other than FDA, EMA, and Swissmedic.
- Promote personnel interactions through PMDA training seminars with Asian countries, etc., and global organizations, etc., and accepting trainees, etc., in order to establish a system to regularly exchange information related to reviews and post-marketing safety measures. Also have Asian countries, etc., increase their understanding of Japanese regulations, etc., and standards regarding pharmaceutical applications, etc., through symposiums co-hosted by multiple countries, etc.

4. Train and enhance human resources to acquire global perspectives and communication skills
- In order to train human resources to be globally involved in establishing guidelines such as ICH and IMDRF, staff training programs shall be established and conducted, including attendance at meetings and global conferences where guidelines are established, and research opportunities at foreign institutions and graduate schools, etc.
- Improve linguistic ability by continuing and enhancing English training for executives and staff members, etc.

5. Enhance and improve global public relations and information dissemination
- Enhance system to improve ability of disseminating information globally.
- Enhance and improve the content of PMDA’s website in English to promote exchange of opinions and information with foreign countries. To be more specific, proactively release English versions of pharmaceutical regulations, details of services, review reports, and safety information, etc. Make certain that review reports are translated into English especially for products having significance in disseminating information, such as products that are the first in the world to be approved. (Forty products per year by the end of FY 2014. Thereafter, targets will be set in each fiscal year plan, with consideration of the utilization status of relevant people and the application status of pharmaceuticals and medical devices, etc.)
- Continuously conduct lectures and present booth exhibits, etc., at global conferences.

3) Measures for Intractable Diseases and Orphan Diseases, etc.
- Develop review guidelines and enhance consultation services regarding pharmaceuticals for intractable diseases and orphan diseases.
- Take necessary measures to operate notifications and guidance regarding companion diagnostics pharmaceuticals, etc., smoothly.
- Take necessary measures through discussions with foreign regulatory agencies regarding points to be considered in developments, etc., using biomarkers.
- In order to promote utilization of pharmacogenomics in pharmaceutical development, PMDA shall take initiative in establishing evaluation guidelines at ICH, cooperate and share information with foreign regulatory agencies to establish a system that enables the 3 regions, including FDA and EMA, to make recommendations together, and thereby contributing to the development of global methods.

4) Provide Information Including Review Reports, etc.
- In order to promote transparency of the services, PMDA shall proactively promote efforts to enhance disclosure of information by cooperating with MHLW to promptly provide information related to review reports, including results of priority reviews, and other review services, in an easily accessible manner for the public and healthcare professionals, and by enhancing the content of information related to review.
- Both the regulatory authority and the applicants shall make efforts to reveal in public review reports of new pharmaceuticals and new medical devices under the concept of rational use on the website immediately after approval, and also take appropriate measures to release re-examination reports of pharmaceuticals, etc. The outlines of the documents related to new pharmaceuticals and new medical devices shall also be released on the website within three months after approval.
- In addition to the integration of the services of releasing information, such as the service of information disclosure based on the Act on Access to Information Held by Independent Administrative Agencies, and the service of revealing in public review reports, so that PMDA can cope with the yearly increasing disclosure requests of documents, PMDA shall further improve efficiency of the services with the cooperation of relevant divisions.

5) Ensuring Fairness when Utilizing External Experts
- Utilize external experts with relevant knowledge. When utilizing external experts, PMDA shall ensure neutrality and fairness in both the review, etc., and post-marketing safety measures services based on fair rules, and shall review those rules when necessary.

6) Improving the Quality of Review and Safety Services by Enhancing the Information System

- Improve the quality of services by enhancing the function of information system to cope with the changes in review and post-marketing safety measures services where increase of the amount of information to be handled and deepening of the correlation and accuracy of information are expected.
- Consider Enhancing computerization of review procedures, including eCTD, and improving the IT literacy of the staff.

Part 3
Budget, Income and Expenditure Plan and Cash Flows Plan

1. Budget: see Attachment 1

2. Income and expenditure plan: see Attachment 2

3. Cash flows plan: see Attachment 3

Part 4
Limit of Short-term Borrowing

1) Limit of Borrowing

2.2 billion yen

2) Expected Reasons for Short-term Borrowing

a) Shortage of funds due to delayed receipt of administrative subsidies, subvention, and agent service fees, etc.

b) Unexpected retirement payments.

c) Shortage of funds due to other unexpected situations.

Part 5
Plans for Transferring or Mortgaging Important Property if Applicable

None

Part 6
Use of Surplus Funds

Surplus funds can be allocated to the review account for the following purposes.

- Resources for expenditure related to operational improvement.
- Financial resources for training and research, etc., to improve personnel qualifications and service quality.

Regarding the ADR relief account and the infection relief account, surplus funds shall be adjusted as reserve funds, as specified in the provision of Article 31, Paragraph 4 of the Act on the Pharmaceuticals and Medical Devices Agency (Act No. 192, 2002).

Part 7
Other Matters Regarding Operation Management Specified in the Ordinance of the Competent Ministry, etc.

The following measures shall be taken for matters regarding operation management, etc., specified in Article 4 of the Ministerial Ordinance Regarding Operation Management, Finance, and Accounting of the Pharmaceuticals and Medical Devices Agency (MHLW Ministerial Ordinance No. 55, 2004), etc.

1) Matters Regarding Personnel Affairs

a) Plans regarding personnel affairs of staff members

- In order to increase regular staff, PMDA shall employ highly specialized and capable human resources, mainly through open recruitment based on the Act for Partial Revision of the Pharmaceutical Affairs Act that reflects the final proposals of the Japan Revitalization Strategy, the Healthcare and Medical Strategy, and the Committee for Investigation of Pharmaceutical-induced Hepatitis Cases and Appropriate Regulatory Administration to Prevent Similar Sufferings.

  Note: Standards regarding personnel affairs
  The number of regular staff at the end of the term shall not exceed 141.9% of that at the beginning of the term.

  Reference 1) Number of regular staff members at the beginning of the term: 751
  Number of regular staff members at the end of the term: 1,065

  Reference 2) Total personnel expenses for effective period for the Mid-term Targets: 36,535 million yen (estimate)
  Note that the above amount is equivalent to the expenses for the executive compensation and basic pay, miscellaneous allowances, and overtime work pay for staff members.

- Improve qualification and capacity of the staff members by interacting with the government, research institutions, and universities with a consideration of a mobilization of human resources, and reduce proportion of transferees from the government with a consideration of appropriate balance.
  Therefore, PMDA shall strive to make reductions in accordance with the Basic Policy for Review of System/Organization of Incorporated Administrative Agencies (adopted by the Cabinet) established on December 7, 2010, and shall disclose those statuses every year.
  PMDA shall also systematically make approaches to steadily increase staff members, including specialized technical employees, etc., as specified in Part 7-1). Employment terms shall also be revised systematically to make a more attractive work environment.
  To ensure employment of highly specialized human resources, PMDA shall determine strategic methods, including an increase in number of fixed-term staff and introduce an annual salary system.

- In order to avoid any suspicion of inappropriate relationships with pharmaceutical companies, etc., PMDA shall appropriately manage personnel by establishing certain restrictions in employment, allocation, and post-retirement reemployment, etc., for executives and employees.

b) Develop a comfortable working environment

- Consider developing a comfortable working environment for employees by improving working environment such as a promotion of work-life balance. Make approaches that enable a good balance between family life and career and that allows especially the women staff members, accounting for about half of the total employees, to keep fulfilling their abilities.

c) Adjust salary standards

- Based on the Basic Policy Regarding Reform of Incorporated Administrative Agency (adopted by the Cabinet on December 24, 2013), PMDA shall take necessary measures to adjust the salary standards of the employees to achieve an appropriate and efficient level, taking into consideration the salary standards of national government employees as well as its competitiveness to stably securing distinguished human resources.

  PMDA shall also inspect its state of approaches for adjusting salary standards every year from the following perspectives and shall disclose those results.

  1) Appropriateness in salary standards of the employees when compared to the national government employees in view of factors such as their office locations and academic backgrounds, etc.
  2) Room to improve the causes of high salary standards, for example, high proportion of employees dispatched form the government.
  3) Ability to thoroughly explain the appropriateness of the current salary standards when the large government spending, the accumulated losses, and the salary standards of private companies engaged in similar services are pointed out.
  4) Competitive salary standards of PMDA's staff members compared to the standards in the relevant fields, such as pharmaceutical companies and research institutes at universities, etc., when we need to secure human resources with highly specialized knowledge and experience in technical matters.
  5) Other explanations for the salary levels must be rational to gain sufficient public consent.

d) Improve qualifications of the staff members

- In order to improve the quality of the services, PMDA shall improve qualification of the staff members by systematically providing opportunities for training according to targets of the services, etc., by enhancing training conducted with the cooperation of companies, and by interacting with MHLW, as well as domestic and foreign universities and research institutions, etc.
- Training for new staff members shall especially be enhanced in order to ensure effectiveness of enhancing system by increasing staff numbers.
- Enhance staff training programs for administrative staff members who are on main career tracks, so as to improve the quality of staff members at clerical positions supporting the organizational management.
- Implement a personnel evaluation system that allows motivation of the staff members to increase, and appropriately reflect those evaluations and the status of achieving their goals on their salary, pay raise, and promotion.
- Strategically allocate the staff members in view of their future career development to maintain their specialization as well as the continuity of operations.

2) Ensure Security

- Continue enhancing the internal control system for security and confidentiality reasons by thoroughly controlling entrances and exits 24 hours a day, using the entrance and exit control system at the office.
- Continue ensuring security of information related to the information system.
- Continue ensuring the document control system based on the property of the stored documents.

3) Matters Regarding Facilities and Equipment

None

4) Matters Regarding Disposition of the Reserve Funds Specified in Article 31, Paragraph 1 of the Act on the Pharmaceuticals and Medical Devices Agency

In cases where there are still reserve funds for the review account even after adjusting profit and loss according to Article 44 of the Act on General Rules at the end of the last fiscal-year of the effective period for the Second Mid-term Targets, the amount approved by the MHLW out of those reserve funds can be applied to the financial resources of the review service and post-marketing safety measures service, as specified in Article 15 of the Act on Pharmaceuticals and Medical Devices Agency.

5) Other Matters

Steadily conduct approaches based on the government policy indicated in past Cabinet decisions, etc.

Appendix 3

Budget

Budgets for Mid-term Plan (FY 2014 - FY 2018) (Unit: million yen)

Classification	Amount						
	Adverse drug reactions relief account	Infection relief account	Review account	Specified relief account	Commission and loan account	Commissioned payment account	Total
Income							
Administrative subsidies			6,350				6,350
Governmental subsidies	883	707	1,854				3,444
Contributions	20,322	553	16,043	18,390			55,308
User fees			60,151				60,151
Commissioned operations			926		5,410	3,262	9,598
Management income	1,671	312					1,983
Miscellaneous income	7	1	146		8	5	167
Total	22,883	1,572	85,471	18,390	5,418	3,268	137,001
Expenditure							
Operating expenses	16,501	1,300	81,659	18,585	5,380	3,243	126,667
Personnel expenses	1,254	130	38,056	85	188	99	39,813
Administrative expenses	15,247	1,170		18,500	5,192	3,143	43,252
Expenses for reviews and related services			29,533				29,533
Expenses for safety measures, etc.			14,069				14,069
General administrative expenses	541	74	10,526	12	38	25	11,216
Personnel expenses	270		3,626				3,897
Non-personnel expenses	271	74	6,899	12	38	25	7,319
Total	17,043	1,374	92,184	18,597	5,418	3,268	137,883

<Note 1>

Personnel expenses were calculated as expenses based on self-financial resources for increases in and after FY 2015.

<Note 2>

In principle, all figures have been rounded off; therefore, individual totals shown may not coincide with the actual totals.

Appendix 4

Rules of Calculation of the Running Expenses Grant for Accounts for Reviews, etc.

The rules of calculation of the running expenses grant in the target mid-term period (FY 2014 - FY 2018) are as follows.

1. FY 2014

Expenses required for implementation of services are individually estimated and calculated.

2. In or after FY 2015

The following calculation formula is used:

Running expenses grant	=	Service division personnel expenses	+	Expenses	+	Special factor	-	Self-generated income

○ Service division personnel expenses = Basic salaries, etc. (A) + Termination benefits (S)

A: Personnel expenses including basic salaries, various benefits, and contribution to mutual aid association (excluding termination benefits) which are calculated by using the following formula:

$A = [\{P1 \times \alpha \times \beta\} + \{P2 \times \beta\} + P3]$

A: Basic salaries, etc. for the said fiscal year
P1: Those influenced by salary raises and salary revisions among basic salaries in the preceding fiscal year
P2: Those influenced by salary revisions among basic salaries in the preceding fiscal year
P3: Those not influenced by salary raises and salary revisions among basic salaries in the preceding fiscal year
α: Salary raise resource rate in view of running status, etc.
β: Salary revision rate in view of running status, etc.

S: Amount of termination benefits for the said fiscal year corresponding to persons expected to terminate in the said fiscal year and persons expected to terminate in the preceding fiscal year or before

○ Expenses = ((General administrative expenses (B) × γ1 × δ) + (Operating expenses (R) × γ2 × δ))

B: Non-personnel expenses related to the management division in the preceding fiscal year
R: Non-personnel expenses related to services in the preceding fiscal year
γ1: Efficiency coefficient (general administrative expenses)
γ2: Efficiency coefficient (operating expenses)
δ: Consumer price index

○ Special factor = A measure required in association with law/regulation revision, etc. or a demand for fund occurring due to a reason unpredictable at present which is determined in the process of budget-making for every fiscal year.

○ Self-generated income = The estimated mount of an income that may occur from clerical works/projects implemented with the running expenses grant as the financial resource

[Notes]

1. For α, β, δ, γ1, and γ2, concrete discrete values are determined for the said fiscal year in the process of budget-making for the year in view of the followings:
δ (consumer price index): The actual value in the preceding fiscal year is used.
2. Budgets for the overall mid-term plan were estimated,
[1] assuming that the increase rate is 0 for α, β, and δ.
[2] assuming that γ1 (efficiency coefficient) is −3.75% in FY 2015, −3.90% in FY 2016, −4.05% in FY 2017, and −4.23% in FY 2018.
[3] assuming that γ2 (efficiency coefficient) is −1.25% in FY 2015, −1.27% in FY 2016, −1.28% in FY 2017, and −1.30% in FY 2018.

Appendix 5

Income and Expenditure Plan

Income and Expenditure Plan for the Mid-term Plan (FY 2014 - FY 2018) (Unit: million yen)

Classification	Amount						
	Adverse drug reactions relief account	Infection relief account	Review account	Specified relief account	Commission and loan account	Commissioned payment account	Total
Expenditure							
Ordinary expenses	24,163	1,495	93,471	18,600	5,422	3,269	146,420
Operating expenses	16,346	1,233	75,708	18,585	5,383	3,243	120,498
Relief benefits	12,270	155					12,425
Operating expenses for health and welfare	197	621					818
Operating expenses for reviews			29,719				29,719
Operating expenses for safety measures			11,317				11,317
Specified relief benefits				18,390			18,390
Benefits (healthcare allowances, etc.)					5,118		5,118
Benefits (special allowances, etc.)						1,294	1,294
Operating expenses for research and study						1,768	1,768
Administrative expenses	2,619	331		117	93	88	3,249
Personnel expenses	1,260	126	34,673	78	172	92	36,399
General administrative expenses	542	78	10,520	12	38	25	11,214
Personnel expenses	272		3,306				3,577
Non-personnel expenses	270	78	7,214	12	38	25	7,636
Depreciation expenses	241	16	7,243	4	1	1	7,507
Provision for liability reserve	7,030	163					7,192
Miscellaneous losses	5	5					10
Income							
Ordinary income	22,876	1,572	85,713	18,600	5,418	3,268	137,447
Governmental subsidies	883	707	1,854	207			3,651
Contributions	20,322	553	16,043				36,918
User fees			60,151				60,151
Commissioned operations					5,410	3,262	8,672
Other governmental grants			926				926
Administrative subsidies			6,350				6,350
Reversal of asset offset subsidies			89	4			92
Reversal of asset offset administrative subsidies			207				207
Reversal of asset offset gifts received							
Financial income (no operating income)	1,671	312					1,983
Gain on reversal of specified relief fund deposit received				18,390			18,390
Miscellaneous income	△	1	△ 92		△ 8	△ 5	△ 107
Net income (△net loss)	1,287	77	7,759	0	4	1	8,974
Reversal of appropriated surplus	△		△		△	△	△
Gross income (△gross loss)	1,287	77	7,759	0	4	1	8,974

Note 1: Administrative subsidies are assumed to be the financial resource for retirement allowances for staff members in charge of operations financed by administrative subsidies under the review account.
However, this excludes the amount arranged through administrative subsidies as retirement allowances equivalent to tenure, as provided for in Article 8-2 of the supplementary provisions in the Act for Pharmaceuticals and Medical Devices Agency.

Note 2: In principle, all figures have been rounded off; therefore, individual totals shown may not coincide with the actual totals.

Appendix 6

Cash Flows Plan

Cash Flows Plan for the Mid-term Plan (FY 2014 - FY 2018) (Unit: million yen)

Classification	Amount						
	Adverse drug reactions relief account	Infection relief account	Review account	Specified relief account	Commission and loan account	Commissioned payment account	Total
Cash Outflows							
Cash outflows from operating activities	16,462	1,210	86,230	18,599	5,430	3,304	131,234
Relief benefits	12,251	155					12,406
Operating expenses for health and welfare	197	621					818
Operating expenses for reviews			29,012				29,012
Operating expenses for safety measures			10,811				10,811
Specified relief benefits				18,390			18,390
Benefits (healthcare allowances, etc.)					5,131		5,131
Benefits (special allowances, etc.)						1,294	1,294
Operating expenses for research and study						1,768	1,768
Administrative expenses	2,275	243		114	86	119	2,837
General administrative expenses	266	69	6,882	12	31	25	7,286
Personnel expenses	1,472	121	39,525	83	183	97	41,480
Cash outflows from investing activities	20,532	2,664	5,357				28,552
Payments for purchases of investment in securities	20,000	2,500					22,500
Payments for purchases of intangible fixed assets	532	164	5,357				6,052
Cash outflows from financial activities							
Amount carried forward to the next mid-term plan period	438	422	9,440	123	40	96	10,559
Total	37,431	4,296	101,026	18,721	5,471	3,400	170,345
Cash Inflows							
Cash inflows from operating activities	22,906	1,575	86,332	18,423	5,433	3,268	137,937
Governmental subsidies	885	708	1,854				3,447
Administrative subsidies			6,350				6,350
Contributions	20,322	553	16,043	18,422			55,340
User fees			60,975				60,975
Commissioned operations			382		5,423	3,262	9,067
Miscellaneous income	1,698	315	728	1	10	6	2,757
Cash inflows from investing activities	14,100	2,500					16,600
Cash inflows from financial activities							
Amount brought forward at the beginning of the mid-term plan period	426	221	14,694	299	37	132	15,808
Total	37,431	4,296	101,026	18,721	5,471	3,400	170,345

Note: In principle, all figures have been rounded off; therefore, individual totals shown may not coincide with the actual totals.

Appendix 7

Budget for FY 2018

Unit: million yen

Classification	Amount								
			Review account						
	Adverse drug reactions relief account	Infection relief account	Review segment	Safety segment	Total	Specified relief account	Commission and loan account	Commissioned payment account	Total
Income									
Administrative subsidies			1,122	1,002	2,124				2,124
User fees			12,043		12,043				12,043
Contributions	4,151	108		3,422	3,422	3,240			10,921
Usage fees				307	307				307
Commissioned operations			12	40	52		876	640	1,569
Governmental subsidies	179	121	421	362	783				1,083
Management income	282	55	0	0	0				336
Miscellaneous income	1	0	21	5	25	0	1	1	29
Total	4,613	283	13,619	5,138	18,757	3,240	878	641	28,412
Expenditure									
Operating expenses	3,096	203	10,997	3,931	14,929	5,197	866	636	24,926
Personnel expenses	285	30	5,701	1,540	7,241	15	37	18	7,625
Administrative expenses	2,811	173	5,296	2,391	7,688	5,182	830	618	17,301
General administrative expenses	214	16	3,253	753	4,006	2	11	5	4,254
Personnel expenses	56		737	196	933				989
Non-personnel expenses	157	16	2,516	557	3,073	2	11	5	3,265
Total	3,309	219	14,250	4,684	18,934	5,200	878	641	29,181

Note: In principle, all figures have been rounded off; therefore, individual totals shown may not coincide with the actual totals.

Appendix 8

Income and Expenditure Plan for FY 2018

Unit: million yen

Classification	Amount									
			Review account							
	Adverse drug reactions relief account	Infection relief account	Review segment	Safety segment	Adjusted	Total	Specified relief account	Commission and loan account	Commissioned payment account	Total
Ordinary expenses	4,148	382	15,292	5,381	-31	20,642	5,199	875	644	31,890
Relief benefits	2,361	30								2,391
Operating expenses for health and w elfare	31	104								135
Operating expenses for review s			3,744			3,744				3,744
Operating expenses for safety measures				1,888		1,888				1,888
Specified relief benefits							5,160			5,160
Benefits for healthcare allow ances, etc.								809		809
Benefits for special allow ances, etc.									245	245
Investigative research									352	352
Provision of liability reserve	808	150								958
Other operating expenses	728	81	8,177	2,707		10,855	36	52	40	11,823
Personnel expenses	264	27	5,191	1,436		5,197	13	33	17	6,982
Depreciation expenses	33	14	1,137	929		2,066	0	1	4	2,118
Retirement benefit expenses	10	2	223	58		281	1	2	0	296
Provision for accrued bonuses	9	1	301	49		350	1	2	1	364
Other expenses	411	38	1,325	235		1,560	21	15	18	2,063
General administrative expenses	218	17	3,370	784	-31	4,123	3	12	6	4,379
Personnel expenses	53		659	177		836				889
Depreciation expenses	0		145	0		145				145
Retirement benefit expenses	2		5	5		11				12
Provision for accrued bonuses	2		48	13		62				63
Other expenses	162	17	2,513	588	-31	3,070	3	12	6	3,269
Financial expenses	0		0	0		0				0
Miscellaneous losses	1	1	1	1		2		1	1	6
Ordinary income	4,566	278	13,676	5,270	-31	18,914	5,199	877	641	30,476
Administrative subsidies			1,122	982		2,103				2,103
Other governmental grants							39			39
User fees			12,043			12,043				12,043
Contributions	4,151	108		3,422		3,422				7,680
Usage fees				307		307				307
Commissioned operations			12	40		52		876	640	1,569
Governmental subsidies	179	121	421	362		783				1,083
Gain on reversal of specified relief fund deposit received							5,160			5,160
Reversal of assets funded by administrative subsidies, as per contra			0	25		25				25
Reversal of assets funded by subsidies, as per contra			35	132		167	0			167
Reversal of assets funded by donations, as per contra			3			3				3
Donnation of non-current assets, as per contra			0			0				0
Financial income (no operating income)	236	50	0	0		0				286
Miscellaneous income			39	0	-31	8		1	1	10
Ordinary net income or loss	418	-104	-1,617	-111		-1,728	-	3	-3	-1,414
Current net income or loss before tax	418	-104	-1,617	-111		-1,728	-	3	-3	-1,414
Current net income or loss	418	-104	-1,617	-111		-1,728	-	3	-3	-1,414
Reversal of appropriated surplus	-	-	1,337	284		1,622	-	-	-	1,622
Current gross income or loss	418	-104	-279	173		-106	-	3	-3	208

Note: In principle, all figures have been rounded off; therefore, individual totals shown may not coincide with the actual totals.

Appendix 9

Cash Flow Plan for FY 2018

Unit: million yen

Classification	Amount									
			Review account							
	Adverse drug reactions relief account	Infection relief account	Review segment	Safety segment	Adjusted	Total	Specified relief account	Commission and loan account	Commissioned payment account	Total
Cash Outflows										
Cash outflows from operating activities	3,428	217	13,833	5,273	-45	19,062	5,199	900	647	29,452
Relief benefits	2,412	29								2,441
Operating expenses for health and welfare	32	104								136
Operating expenses for reviews			5,061			5,061				5,061
Operating expenses for safety measures				2,980		2,980				2,980
Operating expenses	489	38					21	15	18	581
Specified relief benefits							5,160			5,160
Benefits for healthcare allowances, etc.								815		815
Benefits for special allowances, etc.									245	245
Investigative research									352	352
General administrative expenses	155	16	2,286	559		2,845	2	11	5	3,036
Personnel expenses	328	28	6,171	1,668		7,839	14	35	18	8,263
Repayment money	1	1	1	1		2		1	1	6
Other cash outflow from operating activities	11	1	315	65	-45	335	1	23	7	377
Cash outflow from investing activities	4,007	601	472	266		739	1	4	1	5,352
Amount carried forward to next fiscal year	3,011	641	9,108	3,214		12,323	520	31	137	16,663
Total	10,446	1,459	23,414	8,753	-45	32,123	5,719	935	786	51,467
Cash Inflows										
Cash inflows from operating activities	4,616	283	14,496	5,153	-45	19,604	3,241	874	642	29,260
Administrative subsidies			1,122	1,002		2,124				2,124
User fees			12,801			12,801				12,801
Contributions	4,151	108		3,422		3,422	3,240			10,921
Usage fees				307		307				307
Commissioned operations			12	40		52		873	640	1,566
Governmental subsidies	179	121	421	362		783				1,083
Amount of interests received	282	55	0	0		0				336
Other incomes	4	0	140	20	-45	115	0	1	1	122
Cash inflows from investing activities	3,002	600								3,602
Amount carried forward from previous fiscal year	2,827	575	8,918	3,601		12,519	2,479	61	144	18,605
Total	10,446	1,459	23,414	8,753	-45	32,123	5,719	935	786	51,467

Note: In principle, all figures have been rounded off; therefore, individual totals shown may not coincide with the actual totals.

Appendix 10

Basic Implementation Policy for the Third Mid-term Plan

The Executive Board Decision
November 25, 2014

1. Goals for PMDA to attain by the end of the third mid-term period

In order to meet the public expectations at a higher level in ever-changing business environment, PMDA, as the one and only organization that performs three regulatory operations (review, safety, and relief services) in Japan, aims for the goals described below by the end of the effective period of the mid-term plan, in accordance with the Third Mid-term Plan based on the universally applicable "PMDA Philosophy."

PMDA aims to:

○ Provide fast and high-quality review, safety measures, and relief services for adverse health effects, using the latest scientific knowledge in accordance with the concept of regulatory science;

○ Collaborate with regulatory authorities of other countries and take the lead to promote international harmonization;

○ Contribute to improvement of medical standards in terms of ensuring the efficacy, safety, and quality of medical products and assuring their reliability, in collaboration with academia, etc.;

○ Act and communicate in a way that will earn trust of stakeholders including the general public; and

○ Enhance the standardization, efficiency, and advancement of operations and thereby reduce workload of applicants, persons receiving consultation, and employees of PMDA, while creating a comfortable work environment attracting highly qualified and competent employees and allowing them to pursue long-term careers with PMDA.

2. Basic strategic perspective and policy for implementing the Third Mid-term Plan

○ In order to ensure high-quality and reliable operations, PMDA will:

- Respond to reform of the systems appropriately;
- Improve quality of reviews and enhance transparency of review results;
- Deepen the possessed scientific knowledge and sophisticate the efficiency and efficacy of data analysis; and
- Reinforce the consultation for practical application of promising seed-stage resources in academia and companies.

○ In order to play its expected roles and to increase its presence, PMDA will:

- Enhance its contribution to the international harmonization of regulations and standards and strengthen commitment particularly to Asian countries;
- Strengthen the training function for transferring knowledge and technique/methods of conformity audit and quality control, etc., to stakeholders; and
- Reinforce provision of information about the operations and achievements of PMDA in a clear and transparent manner.

○ In order to make full use of limited resources, PMDA will:

- Promote prioritization/rationalization of operations and systematic implementation while accommodating any situational change in a flexible manner;
- Increase the productivity of individual employees and thereby enhance the performance of PMDA as a whole;
- Work on development or modification of IT systems and cost reduction in order to standardize and streamline operations; and
- Establish appropriate systems for personnel management and training in order to be able to secure competent personnel and to train them.

Appendix 11

Balance Sheet (corporate basis)

(As of March 31, 2019)

Unit: yen

Account item	Amount		Account item	Amount	
Assets			Liabilities		
I Current assets			I Current liabilities		
Cash and deposits		25,222,110,880	Accrued benefits		330,070,530
Securities		3,604,647,059	Accounts payable		2,202,951,125
Expenses for work-in-process reviews, etc.		1,450,137,210	Advances received		9,748,410,613
Prepaid expenses		2,271,588	Deposits received		144,763,108
Accounts due		410,350,887	Lease obligations		144,979,054
Accrued income		40,669,432	Allowance		
Other current assets		368,859	Accrued bonuses	569,955,660	569,955,660
			Total of current liabilities		13,141,130,090
Total of current assets		30,730,555,915	II Fixed liabilities		
			Per contra liabilities for property acquisition		
II Fixed assets			Assets funded by administrative subsidies, as per contra	44,421,941	
Tangible fixed assets			Assets funded by governmental subsidies, etc., as per contra	474,550,893	
Tools, equipment and fixtures	4,658,501,233		Assets funded by donnations, as per contra	24,815,787	
Cumulative total of depreciation	-2,809,502,800	1,848,998,433	Donnation of non-current assets, as per contra	201,217	543,989,838
			Deposits of specified relief funds		
Building and accompanying facilities	183,050,636		Long-term deposit subsidy, etc.	69,791,516	
Cumulative total of depreciation	-12,785,263	170,265,373	Deposit contribution	3,152,336,630	3,222,128,146
			Long-term lease obligations		705,705,573
			Allowances		
Total of tangible fixed assets		2,019,263,806	Allowances for retirement benefits	3,061,400,866	3,061,400,866
			Liability reserve		25,823,369,672
Intangible fixed assets			Total of fixed liabilities		33,356,594,095
Software		2,445,348,768	Total of liabilities		46,497,724,185
Telephone subscription right		286,000	Net assets		
Total of intangible fixed assets		2,445,634,768	I Capital funds		
Investments and other assets			Government investment		1,179,844,924
Investment securities		38,071,573,772	Total of capital funds		1,179,844,924
Rental deposit		13,272,360	II Capital surplus		
Total of investments and other assets		38,084,846,132	Capital reserves		4,670,640
			Cumulative total of depreciation that are not recorded as expenses (-)		-685,406,717
Total of fixed assets		42,549,744,706	Loss on retirement or sale of fixed assets that are not recorded as expenses (-)		-113,407,005
			Total of capital surplus		-794,143,082
			III Retained earnings		26,396,874,594
			Total of net assets		26,782,576,436
Total of assets		73,280,300,621	Total of liabilities and net assets		73,280,300,621

Appendix 12

Profit and Loss Statement (corporate basis)

(From April 1, 2018 to March 31, 2019)

Unit: yen

Account item	Amount		
Ordinary expenses			
Adverse reaction relief benefits		2,353,225,489	
Infection relief benefits		7,837,580	
Operating expenses for health and welfare		124,371,193	
Operating expenses for reviews		3,111,565,431	
Operating expenses for safety measures etc.		1,870,777,001	
Specified relief benefits		1,416,000,000	
Benefits for healthcare allowances, etc.		799,692,059	
Benefits for special allowances, etc.		223,062,000	
Investigative research		280,062,400	
Provision of liability reserve		475,975,331	
Other operating expenses			
Personnel expenses	6,821,788,586		
Depreciation expenses	2,175,813,579		
Retirement benefit expenses	131,560,079		
Provision for accrued bonuses	397,700,290		
Estate rental fees	1,537,900,584		
Other expenses	452,848,862	11,517,611,980	
General administrative expenses			
Personnel expenses	891,548,521		
Depreciation expenses	185,877,553		
Retirement benefit expenses	26,848,300		
Provision for accrued bonuses	71,197,338		
Estate rental fees	240,354,804		
Other expenses	1,682,707,240	3,098,533,756	
Financial expenses			
Interest paid		3,034,688	
Miscellaneous losses		59,109,700	
Total of ordinary expenses			25,340,858,608
Ordinary revenues			
Administrative subsidies		2,112,266,728	
User fees		11,960,259,931	
Contributions		8,109,458,000	
Usage fees		105,307,500	
Commissioned operations for government		47,160,887	
Commissioned operations for others		1,443,158,251	
Revenue from governmental subsidies		948,838,329	
Gain on reversal of provision for deposits of specified relief funds			
Revenues from contributions		1,416,000,000	
Reversal of assets funded by administrative subsidies, as per contra		25,119,668	
Reversal of assets funded by subsidies, etc., as per contra		176,134,367	
Reversal of assets funded by donnations, as per contra		3,234,997	
Donnation of non-current assets, as per contra		256,023	
Financial revenue			
Interest received	894,684		
Interest on securities	290,224,404	291,119,088	
Miscellaneous gains		8,571,126	
Total of ordinary revenues			26,646,884,895
Ordinary profit			1,306,026,287
Extraordinary losses			
Loss on disposal of fixed assets		1,103	1,103
Current net profit			1,306,025,184
Reversal of reserve carried forward from the previous Mid-term target period			1,253,105,094
Current gross profit			2,559,130,278

Appendix 13

Cash Flow Statement (corporate basis)

(From April 1, 2018 to March 31, 2019)

Unit: yen

Account item	Amount
I. Cash flow from operating activities	
Expenditure for adverse reaction relief benefits	-2,347,693,411
Expenditure for infection relief benefits	-7,837,580
Expenditure for operating expenses for health and welfare	-124,252,716
Expenditure for operating expenses for reviews	-3,196,084,340
Expenditure for operating expenses for safety measures	-1,828,378,932
Expenditure for specified relief benefits	-1,416,000,000
Expenditure for benefits for healthcare allowances, etc.	-807,534,698
Expenditure for benefits for special allowances, etc.	-222,758,100
Expenditure for expenses for investigative research	-280,664,200
Expenditure for personnel expenses	-8,285,641,785
Other operating expenditures	-4,259,879,300
Income from administrative subsidies	2,123,524,000
Income from commissioned operations for government	47,761,465
Income from commissioned operations for others	1,452,278,700
Income from user fees	13,594,757,751
Income from contributions	9,689,678,588
Income from usage fees	105,307,500
Income from governmental subsidies	1,165,433,000
Income from subsidies	9,730,000
Other incomes	143,872,833
Subtotal	5,555,618,745
Interest paid	355,944,918
Interest received	-3,034,688
Cash flow from operating activities	5,908,528,975
II. Cash flow from investing activities	
Expenditure for acquisition of investment securities	-4,601,290,000
Income from redemption of investment securities at maturity	3,600,000,000
Expenditure for acquisition of tangible fixed assets	-306,054,072
Expenditure for acquisition of intangible fixed assets	-576,818,541
Cash flow from investing activities	-1,884,162,613
III. Cash flow from financing activities	
Expenditure for repayment of finance lease obligations	-34,929,242
Cash flow from financing activities	-34,929,242
IV. Increase in funds	3,989,437,120
V. Beginning-of-term balance of funds	21,232,673,760
VI. End-of-term balance of funds	25,222,110,880

Appendix 14

Government Service Implementation Cost Statement (corporate basis)

(From April 1, 2018 to March 31, 2019)

Unit: yen

Account item	Amount		
I. Operating expenses			
(1) Expenses in the profit and loss statement			
Adverse reaction relief benefits	2,353,225,489		
Infection relief benefits	7,837,580		
Operating expenses for health and welfare services	124,371,193		
Operating expenses for reviews	3,111,565,431		
Operating expenses for safety measures	1,870,777,001		
Specified relief benefits	1,416,000,000		
Benefits for healthcare allowances, etc.	799,692,059		
Benefits for special allowances, etc.	223,062,000		
Expenses for investigative research	280,062,400		
Provision of liability reserve	475,975,331		
Other operating expenses	11,517,611,980		
General administrative expenses	3,098,533,756		
Financial expenses	3,034,688		
Miscellaneous losses	59,109,700		
Extraordinary losses	1,103	25,340,859,711	
(2) (Exemption) Self-generated income, etc.			
Income from user fees	-11,960,259,931		
Income from contributions	-9,525,458,000		
Income from usage fees	-105,307,500		
Income from commissioned operations for government	-47,160,887		
Income from commissioned operations for others	-1,443,158,251		
Reversal of assets funded by donnations, as per contra	-3,234,997		
Financial revenue	-291,119,088		
Miscellaneous gains	-8,571,126	-23,384,269,780	
Total of operating expenses			1,956,589,931
II. Amount equivalent to depreciation that are not recorded as expenses			8,288,094
III. Estimated amount of non-allowance bonuses			24,243,081
IV. Estimated increased amount of non-allowance retirement benefits			104,703,293
V. Opportunity costs			
Opportunity costs of investments by the national government or local governments, etc.			0
VII. Government service implementation costs			2,093,824,399

I. Important Accounting Policies

Accounting Standards for Incorporated Administrative Agencies, Annotations of Accounting Standards for Incorporated Administrative Agencies (amended on January 27, 2015), and Q & A on Accounting Standards for Incorporated Administrative Agencies and Annotations of Accounting Standards for Incorporated Administrative Agencies (amended in February 2016) (hereafter referred to as “Amendments”) were employed to generate financial statements.

However, regarding the Accounting Standards for Incorporated Administrative Agencies No.43 (annotation #39), an interim measure is applied as specified in a supplemental provision No.8 in Amendments of Act on General Rules for Incorporated Administrative Agencies, and segment information is published under the current segments until the term of the interim measure has expired.

1. Criteria for allocation of revenue from administrative subsidies

The percentage-of-completion method is employed. The percentage-of-period method is employed to deal with all administrative activities, except those where progress is clearly correlated with administrative subsidies.

2. Evaluation criteria and evaluation methods for securities

Held-to-maturity bonds

They are handed by the amortized cost method (straight-line method).

3. Evaluation criteria and evaluation methods for expenses for work-in-process reviews, etc.

They are handled by the lower-of-cost-or-market method based on specific identification method.

4. Methods of accounting for depreciation

(1) Tangible fixed assets

[1] Tangible fixed assets other than lease assets

The straight-line method has been employed.

Durable years of main assets are as follows.

Tools, equipment and fixtures	2 - 22 years
Building and accompanying facilities	3 - 22 years

An amount equivalent to depreciation of particular depreciable assets (Accounting Standards for Incorporated Administrative Agencies No. 87) is shown to be deducted from the capital surplus as cumulative total of depreciation that are not recorded as expenses.

[2] Lease assets

Lease assets related to non-ownership-transfer finance lease transactions

The straight-line method, in which the lease period is durable years and the residual value is zero, has been employed.

(2) Intangible fixed assets

The straight-line method has been employed.

Software is used within the corporate body based on an available period (5 years) within the corporate body.

5. Criteria for allocation of allowances and estimated amounts related to bonuses

Amounts occurring for the current term are allocated from among the expected amounts of payment of bonuses for the next term to executives, regular employees, etc.

However, allowances are not allocated for amounts which are funded from the administrative subsidies and governmental subsidies from among the said expected amounts of payment.

6. Criteria for allocation of allowances and estimated amounts related to retirement benefits

To prepare for retirement benefits for executives and regular employees, the allowances and estimated amounts are allocated based on the expected amounts of retirement benefit obligations at the end of the current fiscal year. Actuarial differences are to be collectively amortized in the next fiscal year after the occurrence. However, allowances related to retirement benefits are not allocated for amounts which are funded from the administrative subsidies.

7. Criteria for allocation of liability reserves

To prepare for the payment of relief benefits in the future, amounts specified in the statement of operation procedures are allocated pursuant to the provisions of Article 30 of the Act on Pharmaceuticals and Medical Devices Agency (Act No.192 of 2002).

8. Method of allocating opportunity costs in government service implementation cost statements

Rate for opportunity costs from government and local government

The opportunity cost was calculated at a rate of 0%, based on an administrative notice dated April 1, 2016, “Handling of Calculation of Opportunity Costs in Government Service Implementation Cost Statements, etc. in Financial Statements for Fiscal Year 2015 Subjected to Introduction of ‘Quantitative/Qualitative Monetary Easing with Negative Interest Rates’ (Points to Consider)” (jointly issued by the Administrative Management Bureau, Ministry of Internal Affairs and Communications and the Public Accounting Office, Legal Division, Budget Bureau, Ministry of Finance). This administrative notice is specified to be referred to by another administrative notice dated April 5, 2019, “Handling of Calculation of Opportunity Costs in Government Service Implementation Cost Statements (Points to Consider)” (jointly issued by the Administrative Management Bureau, Ministry of Internal Affairs and Communications and the Public Accounting Office, Legal Division, Budget Bureau, Ministry of Finance).

9. Methods of accounting for lease transactions

Finance release transactions for which the total of lease fees is 3 million yen or more are handled by accounting method according to the method for usual sales transactions.

Finance release transactions for which the total of lease fees is less than 3 million yen are handled by accounting method according to the method for usual lease transactions.

10. Methods of accounting for consumption tax, etc.

These are handled by the tax-included method.

II. Items to note

1. Notes for balance sheets

(1) Notes regarding matters including current prices of financial products

[1] Items related to the status of financial products

Deposits are to be deposits for settlement.

Also, investments in financial products for purposes of funds management are limited to long-lived deposits, public and corporate bonds, and similar categories of securities. As investment securities, the PMDA holds only public bonds, FILP agency bonds, and class A or higher corporate bonds and does not hold stocks, etc. based on rules such as the provisions of Article 47 of the Act on General Rules for Incorporated Administrative Agencies.

[2] Items related to matters including current prices of financial products

Balance sheet amounts, current prices, and amounts of difference between them on closing date are as follows.

(Unit: yen)

Classification	Balance sheet amount	Current price on closing date	Amount of difference
A. Cash and deposits	25,222,110,880	25,222,110,880	0
B. Securities and investment securities	41,676,220,831	42,567,150,000	890,929,169
C. Accounts payable	(2,202,951,125)	(2,202,951,125)	0

The figures in parenthesis are recorded as liabilities.

Notes: Method of calculating current prices of financial products and items related to securities, etc.

A. Cash and deposits

Current prices approximate book values, and therefore are based on these book values.

B. Securities and investment securities

Current prices are based on prices at the stock exchange or prices offered by correspondent financial institutions.

Items to note for securities are as follows.

1) Held-to-maturity bonds with current price

(Unit: yen)

Classification	Balance sheet amount	Current price on closing date	Amount of difference
Bonds with current prices exceeding balance sheet amount	41,676,220,831	42,567,150,000	890,929,169
Bonds with current prices not exceeding balance sheet amount	0	0	0
Total	41,676,220,831	42,567,150,000	890,929,169

2) Scheduled amounts of redemption after closing date for held-to-maturity bonds

(Unit: yen)

Classification	≤1 year	>1 and ≤5 years	>5 and ≤10 years	>10 years
Government bonds	2,100,000,000	6,300,000,000	900,000,000	0
Government-guaranteed bonds	1,500,000,000	8,900,000,000	3,400,000,000	0
Local government bonds	0	0	700,000,000	0
Corporate bonds	0	0	11,900,000,000	0
FILP agency bonds	0	0	5,600,000,000	0
Total	3,600,000,000	15,200,000,000	22,500,000,000	0

C. Accounts payable

The accounts are settled in short period and current prices, approximate book values, are therefore based on these book values.

(2) Estimated amount of non-allowance bonuses

Estimated amount of bonuses to be covered by the administrative subsidies and governmental subsidies: 141,179,096 yen

(3) Estimated amount of non-allowance retirement benefits

Estimated amount of retirement benefits to be covered by the administrative subsidies: 376,616,373 yen

2. Notes for profit and loss statements

(1) Expenses for health and welfare services are expenses required for investigative research conducted to improve the QOL (Quality of Life) of people such as those covered by the system who suffered a serious and rare adverse drug reaction for which supports are not necessarily sufficient when taking general measures intended for disabled people. These expenses consist of rewards for cooperation for investigation, etc.

(2) Expenses for reviews and related services are expenses required for the operation of reviews and related services for drugs, medical devices, etc. These expenses consist of rewards, travel expenses, expenses at government offices in charge of clerical tasks, etc. Also, expenses for safety measures, etc. are expenses required for the operation of post-marketing safety measures for drugs, medical devices, etc. These expenses also consist of rewards, travel expenses, expenses at government offices in charge of clerical tasks, etc.

(3) Expenses for investigative research are expenses required for investigative research of persons infected with HIV through blood products for the purpose of contributing to the prevention of the onset and spread of AIDS. All of these expenses are classified as healthcare expenses for HIV-infected persons.

(4) Income from user fees is income paid by applicants for drug or medical device product approval, and is utilized as a financial resource for conducting review services for drugs and other regulated products.

(5) Income from contributions is income paid by drug and medical device marketing and manufacturing authorization holders as a financial resource for conducting relief services for victims of regulated product-related adverse health effects and post-marketing safety operations.

3. Notes for cash flow statements

Relationship between the end-of-term balance of funds and money amounts of accounting items shown in the balance sheet

Cash and deposits: 25,222,110,880 yen

End-of-term balance of funds: 25,222,110,880 yen

4. Notes for government service implementation cost statements

The estimated increased amount of non-allowance retirement benefits includes 57,904,700 yen for executives and regular employees temporally transferred from the government.

5. Notes for asset retirement obligations

The PMDA has obligations for restoration to original state at the time of leaving business office based on the real estate leasehold contract, but the actual period of use of lease assets related to these obligations are not clear.

As such, it is difficult to predict when these obligations will be implemented, and it is not possible to reasonably estimate asset retirement obligations. For this reason, asset retirement obligations that match these obligations have not been allocated.

6. Notes for allowances for retirement benefits

(1) Outline of the retirement benefits system employed

The PMDA has established a retirement lump sum grants system as a defined-benefit system.

(2) Reconciliation between beginning-of-term and end-of-term retirement benefit obligations of FY 2018.

(Unit: yen)

Classification	April 1, 2018 - March 31, 2019
[1] Beginning-of-term retirement benefit obligations	2,781,652,218
[2] Service expenses	311,978,306
[3] Interest expenses	9,529,242
[4] Actuarial difference of the current term	-42,087,602
[5] Retirement benefits paid	-41,758,900
[6] End-of-term retirement benefit obligations ([1] + [2] + [3] + [4] + [5])	3,019,313,264

(3) Reconciliation of retirement obligation and allowances for retirement benefits reported on the balance sheet

(Unit: yen)

Classification	As of March 31, 2019
[1] Retirement benefit obligations	3,019,313,264
[2] Unrecognized actuarial difference	42,087,602
[3] Allowance for retirement benefits ([1] + [2])	3,061,400,866

(4) Profit and Loss of retirement benefit

Classification	April 1, 2018 - March 31, 2019
[1] Service expenses	313,929,389
[2] Interest expenses	9,630,209
[3] Amortization expenses for actuarial difference	-166,447,718
[4] Retirement benefit funded from the administrative subsidies	1,296,500
[5] Retirement benefits expenses ([1] + [2] + [3] + [4])	158,408,380

Note: Retirement benefit expenses for workers temporally transferred from other institutions are included: [1] 1,951,083 yen for service expenses; and [2] 100,967 yen for interest expenses.

(5) Items related to basic calculation of actuarial

Classification	As of March 31, 2019
Discount rate	0.39%
Method of periodic allocation of estimated amounts of retirement benefits	Straight-line attribution
Amortized period of actuarial difference	1 year Actuarial differences are to be collectively amortized in the next fiscal year after the occurrence.

III. Important Acts of Bearing Obligation

There are no corresponding events.

IV. Important Subsequent Events

There are no corresponding events.

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