ANNUAL REPORT

I. THE PHARMACEUTICALS AND MEDICAL DEVICES AGENCY

1. HISTORY AND PURPOSE OF THE AGENCY

- The critical lessons we, Japanese, learned from the two disastrous incidents caused by adverse drug reaction, thalidomide and SMON (sub-acute myelo-optical-neuropathy), resulted in the establishment of the Fund for Adverse Drug Reactions Suffering Relief in October, 1979 in accordance with the stipulations of the Adverse Drug Reaction Suffering Relief Fund Law (1979, Law No. 55), in order to promptly relief patients suffering from adverse drug reactions. In 1987, the Fund started a research promotion operation with the name of the Fund for Adverse Drug Reaction Relief and R&D Promotion. In 1993, the fund was reorganized into the Organization for Pharmaceutical Safety and Research (OPSR/Kiko), in order to perform equivalency review for generic drugs. Later, in 1996, the services concerning clinical trials and conformity audit of application materials were added.

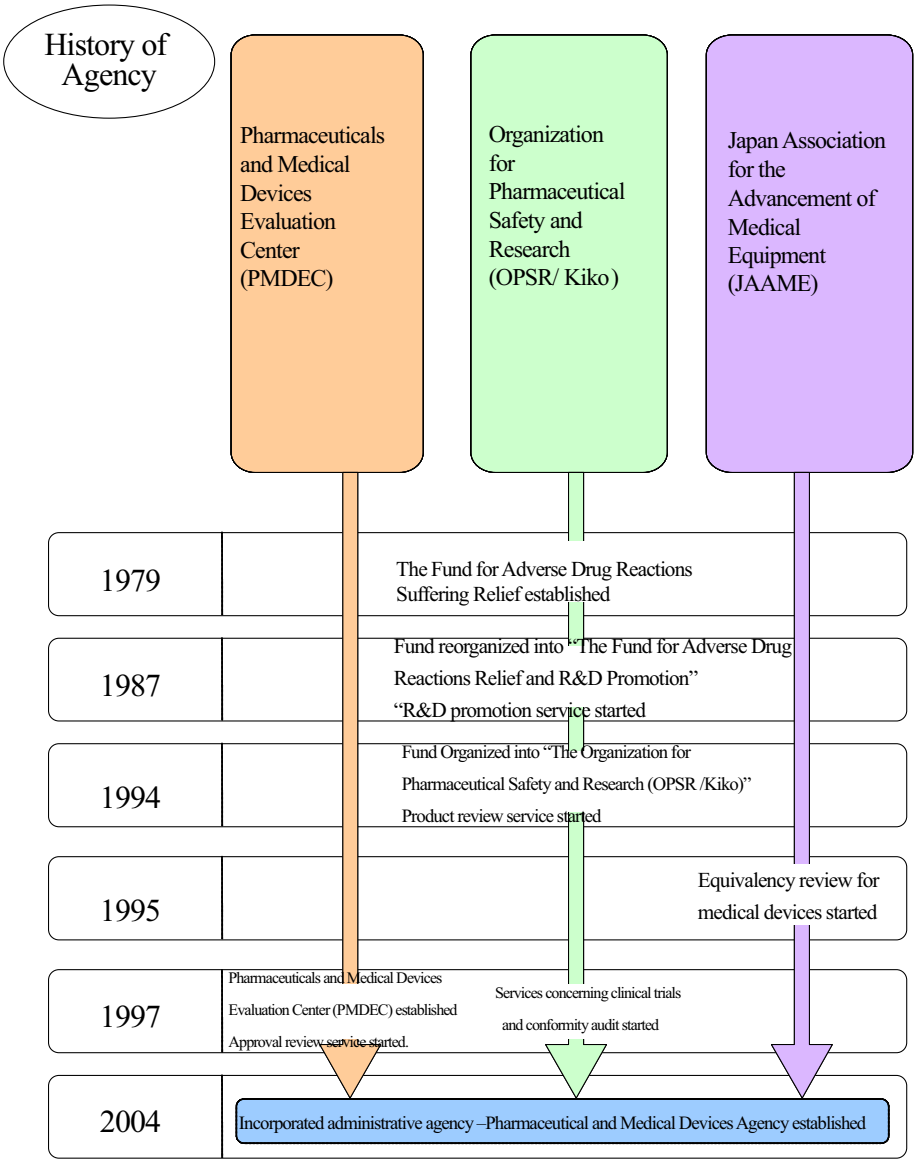
- In 1997, the Pharmaceuticals and Medical Devices Evaluation Center (PMDEC), was established at the National Institute of Health Sciences in order to develop a systematic approval review and to improve the level of review contents. At the Center, teams with experts respectively specialized in pharmaceutical science, medical science, biometrics etc. performed reviews. In addition, since 1995 the Japan Association for the Advancement of Medical Equipment (JAAME) had conducted equivalency reviews for medical devices as a designated investigatory agency under the Pharmaceutical Affairs Law (PAL).

- From 1997 to 1999, a systematic and large-scale increase in the number of employees, who were engaged in the review and safety operations, was executed at the former Ministry of Health and Welfare (MHW) and the three agencies above (121 persons in 1996 → 241 persons in 1999). However, the reform to further increase its personnel and to strengthen its organizational structure faced a limit as a governmental organization.

  In the midst of this reform, based on the Cabinet decision on “Special Service Agency Restructuring Plan” in December 2001, the Organization for Pharmaceutical Safety and Research (OPSR) was abolished, and the new Pharmaceutical and Medical Devices Agency (PMDA) was founded consolidating the operations distributed to the Pharmaceuticals and Medical Devices Evaluation Center (PMDEC) and the Japan Association for the Advancement of Medical Equipment (JAAME) in order to further enhance the review and safety measures. In 2002, the draft of the Law for the Incorporated Administrative Agency - Pharmaceuticals and Medical Devices Agency was discussed and passed at the 155th special session of the Diet, and resulted in the establishment of the Agency (PMDA) on April 1, 2004 in accordance with the Law for the Incorporated Administrative Agency - Pharmaceuticals and Medical Devices Agency (2002 Law No. 192).

- The purpose of the Agency is to contribute to the improvement of the public health by providing prompt relief services for the sufferers of biological product-derived infectious diseases as well as adverse drug reactions (ADRs) (Adverse Health Effect Relief Services), by performing consistent operations/services in quality, efficacy and safety of drugs and medical devices through clinical trial consultation for approval review (Review Operations), as well as by collecting, analyzing and providing information on post-marketing safety (Post-marketing Safety Operations).

  Previously, the Agency included the service (R&D Promotion Services) to promote the basic research and development of pharmaceuticals and medical devices that contribute to maintaining and advancing public health. However, the regulatory and the promotion operations/services were separated, and the R&D Promotion Services were transferred to the National Institute of Biomedical Innovation (NiBio) in April 2005 in order to allow the Agency to focus completely on review, safety and relief operations.


History of Agency
Pharmaceuticals and Medical Devices Evaluation Center (PMDEC)
Organization for Pharmaceutical Safety and Research (OPSR/ Kiko)
Japan Association for the Advancement of Medical Equipment (JAAME)
1979
The Fund for Adverse Drug Reactions Suffering Relief established
1987
Fund reorganized into "The Fund for Adverse Drug Reactions Relief and R&D Promotion"
"R&D promotion service started
1994
Fund Organized into "The Organization for Pharmaceutical Safety and Research (OPSR /Kiko)"
Product review service started
1995
Equivalency review for medical devices started
1997
Pharmaceuticals and Medical Devices Evaluation Center (PMDEC) established
Approval review service started.
Services concerning clinical trials and conformity audit started
2004
Incorporated administrative agency –Pharmaceutical and Medical Devices Agency established

2. SUMMARY OF OPERATIONS

(1) Adverse Health Effect Relief Services

- The Agency takes over services from OPSR and makes payments for medical fees, disability pensions and bereaved family pensions to the sufferers from diseases or disabilities caused by adverse drug reaction. (Adverse Drug Reaction Relief Services)

- In April 2004, the Agency started another type of benefit payment to the sufferers whose health was damaged due to infections from drug and medical devices containing the ingredients and materials derived from biological entities. (Biological Product-derived Infectious Disease Relief Services)

- The Agency is commissioned by the government and pharmaceutical companies to provide healthcare allowance and nursing expenses to the SMON patients (Relief Service). In addition, the Agency works under the commission of the Yu-ai Welfare Foundation to make payments of healthcare allowance to the HIV-positive and AIDS patients. (Relief Service)

(2) Reviews and Related Operations

- In accordance with the Pharmaceutical Affairs Law, the Agency evaluates the efficacy, safety, and quality of pharmaceuticals and medical devices applied for review based on the current scientific and technological standards. In addition, the Agency conducts re-examination and re-evaluation of drug and medical devices and review of confirmation application on genetically-modified organisms that is based on the stipulations in the Law on the preservation of biodiversity through the control of the use of genetically modified organisms (2003, Law No. 97). (Approval Review Services)

- In response to the requests from applicants who conduct clinical trials and others, face-to-face consultation and advice are given on clinical studies for new drugs and medical devices as well as clinical trials for re-evaluation and re-examination. (Face-to-face Advice/Consultation Service)

- The Office of Conformity Audit conducts on-site/field review and document review on the products, whose applications were submitted for approval review, and re-evaluation or re-examination to ensure the materials submitted complies with GLP (Good Laboratory Practices) and GCP (Good Clinical Practices) and other standards. (Conformity Audit Service)

- In addition, the Office of Compliance and Standards conducts on-site reviews and document reviews of new drug and new medical devices manufacturers in order to confirm that their manufacturing facilities and the management methods comply with GMP (Good Manufacturing Practices), and that they can produce products of appropriate quality (GMP Review Service).

(3) Post-marketing Safety Operations

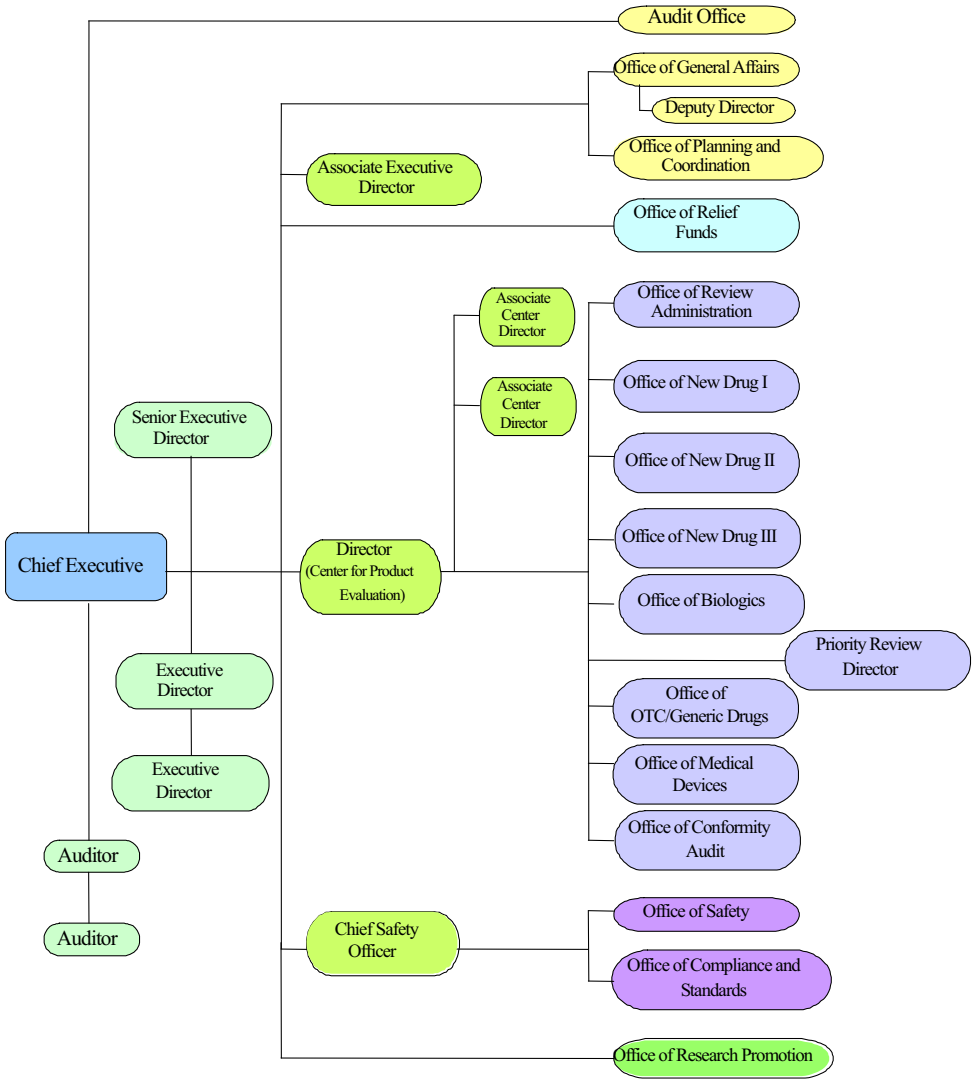
- The Agency's safety department intends to improve the safety of pharmaceuticals and medical devices in the market and ensure patients and healthcare professionals to access them safely and properly. For this purpose, the department functions in cooperation with the Ministry of Health, Labour and Welfare (MHLW) as follows;
    1. To organize collected information on safety of pharmaceuticals and medical devices from a broad range of sources, such as company reports, reports from medical institutions and information from foreign regulatory agencies and academic societies on adverse drug reactions (ADRs) and infectious diseases. (Information Collection and Compilation Service)
    2. To conduct reviews and investigations with regard to post-marketing safety measures based on the collected information in 1 above. (Review and Investigation Service)
    3. To provide consultation and advice in response to the inquiries from manufacturers or consumers. (Consultation Service)
    4. To disseminate information on the safety of pharmaceuticals and medical devices widely to healthcare professionals, patients and companies in a timely manner. (Information Provision Service)
    5. To conduct research on the standards, such as the Japanese Pharmacopoeia stipulated in the Pharmaceutical Affairs Law. (Standard Development and Investigation Service)

(4) Research & Development Promotion (transferred to the National Institute of Biomedical Innovation in April 2005)

- The Agency took over the following three tasks from OPSR as a part of its operations, R&D promotion service; however, the task was shifted to the National Institute of Biomedical Innovation (NiBio) in April 2005.

    1. Conducting basic research for the development of pharmaceuticals and medical devices useful for the treatment of key diseases in healthcare such as AIDS, cancer and diabetes by research contract with national research institutes and universities, and disseminating the results of the research (Basic Research)
    2. Outsourcing research on the development of new pharmaceuticals and medical devices to private companies (Research Promotion)
    3. Providing consultation, advice, and a subsidy in order to promote research and development of the pharmaceuticals and medical devices necessary to treat serious illnesses with 50,000 patients or less found domestically in Japan (Development and Promotion of Orphan Drugs etc.)

[PMDA's Organizational Structure, FY 2004]



Note: The chart above shows the organizational structure as of fiscal 2004. The Office of Research Promotion was transferred to the National Institute of Biomedical Innovation (NiBio) in April 2005.

II OPERATION RESULTS/ACHIVEMENTS OF FY 2004

PART 1. IMPROVEMENT IN OVERALL OPERATIONS AND QUALITY IN SERVICE OF AGENCY

(1) Efficient and Flexible Operation Management

1. Operation through target management

- The Agency is to clarify the targets and operational responsibilities of each department and to strive for identifying the problems and improving them through regular management of operation progress on a daily basis.

- For this purpose, the Agency conducted target management with a development of task planning charts based on the fiscal year plan of the Agency and the responsibilities of each office and division.

- Specifically, the Agency conducted training for the management level (June and July 2004) and for general staff (August, 2004) on the significance and necessity of target management. Following the training, each office created a task planning chart, and its contents were confirmed by the Board of Directors composed of office directors and the higher level of personnel from August to October 2004. In addition, in January 2005, each office reported to the Board of Directors on the progress of their task plan of the first to third quarter of fiscal 2004, and the annual plan for fiscal 2005 for the Agency was developed based on these reports.

(* Target Management… A management system based on setting several targets for a single fiscal year and using the achievement rate of the targets as an indicator to show the level of success and difficulty)

2. Enhancement of operations management and top management

- The Agency shall strengthen its function to develop strategies for overall operations as well as its system to manage operations such as risk management and an internal-check function, with an aim to build an organization in which management judgment by the Chief Executive can be speedily reflected to its operations.

- Therefore, the Agency arranged opportunities for the Chief Executive to maintain a direct understanding regarding its operation progress and provide necessary instructions. The Agency also established the offices to develop plans for the overall operations and grasp the achievement level of the target management and developed a risk management system.

- In detail, a Board of Directors, composed of the Chief Executive, office directors and the higher level of personnel, was established, and held a regular meeting weekly.

- Moreover, in order to deal with the critical issues that the Agency faces such as strengthening review system and preparing for the smooth implementation of the revised Pharmaceutical Affairs Law in FY 2005, the Agency established the "Headquarters for Implementation of the Revised Pharmaceutical Affairs Law" in July 2004 headed by the Chief Executive of the Agency. Thereby, the headquarters discussed the policies for staff recruitment, improved measures of the review system and the adverse health effect relief service and appropriate policies for GMP reviews.

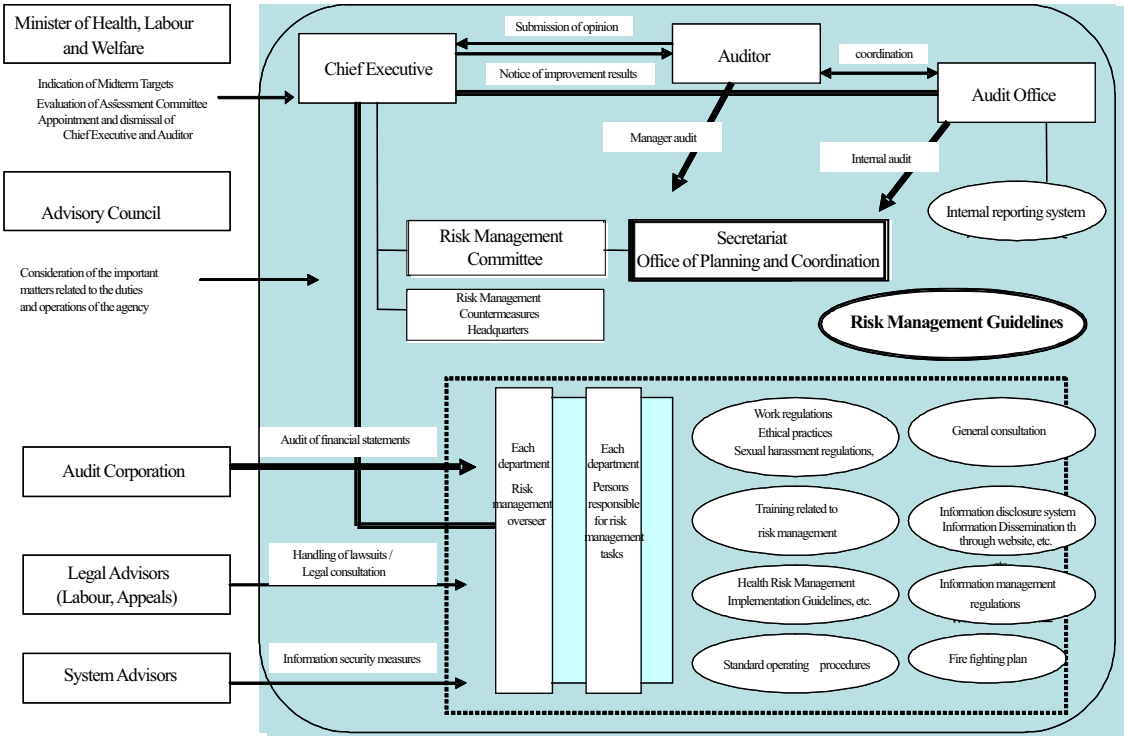
- Furthermore, in order to facilitate reviews of pharmaceuticals and medical devices of special concern and to ensure smooth review operations regarding face-to-face consultation on clinical trial, the "Progress Management Committee of Review Operations" chaired by the Chief Executive was formed in January 2005. The committee meets at the end of each month aiming to precisely track the review progress and improve the process management.

- For strengthening the strategic planning and coordinating function of the Agency, the Office of Planning & Coordination was established at the foundation of the Agency in April 2004. The office takes responsibility for the proposed projects and coordinates the operations of the Agency.

- In order to improve the operational management, such as risk management and an internal-check function, the guidelines on risk management were created in December 2004 specifying the basic items on the establishment of a risk management committee, its role, and the expected actions to be taken by the committee in a crisis. In addition, the Agency established a code of conduct for the Agency's management and personnel and the clause on internal audit and voluntary reporting as the internal-check function.
  Moreover, the practice manual on risk management was created so that the Agency's staff can implement risk management in its daily operation and take an immediate action depending on the type of risks.

- The PMDA's guidelines on health risk management were established, and the necessary items were specified in them to implement the Agency's duties in accordance with the "Health Risk Management Implementation Guidelines for Pharmaceuticals and Others" issued by MHLW such as handling of health risk information.

(Risk Management System)



***Risks Agency faces:**

(a) Risks to the Agency itself

- Possibility of an event that damages or threatens the reputation of the Agency in society
- Possibility of an event that significantly hinders or threatens the execution of the Agency's operations
- Possibility of an event that damages or threatens the agency financially

(b) Risks to the Agency's operation

- The risks relevant to the Agency's operations and the risks likely to cause and expand adverse health effects by using pharmaceuticals and medical devices (pharmaceuticals, medical devices, quasi-drugs, cosmetics as well as drugs and devices that are subjects of clinical trials).

3. Establishment of advisory councils

- The "Advisory Councils" are deliberative bodies that allow the Agency to exchange opinions with a wide range of academic and experienced professionals and to seek for the improvement proposals regarding the operations and management system of the Agency. The addressed plans and proposals have been adopted for the Agency's effective and efficient operations. The

Agency appointed academic and experienced persons, healthcare professional, representatives from pharmaceutical and relevant industries and representatives of consumers and sufferers from adverse health effects of drugs to the councils. The council also discusses the overall operations of the Agency in pursuit of fairness and transparency of its operations from a broad perspective. Under the Council, the "Review Operation Committee" and the "Safety Operation Committee" were set in order to discuss specifically each operation of the Agency.

- The "Advisory Council on the relief, review, safety services" (chaired by Masaaki Hirobe, Tokyo University Professor Emeritus) was held on July 14, 2004 and March 11, 2005, and the "Advisory Council on research promotion services" (chaired by Fumimaro Takaku, President of Jichi Medical School) was held on July 30, 2004 and March 15, 2005. At these councils' meetings, the report on the achievement of FY 2003, the plan for FY 2004 and the draft plan for FY 2005 were discussed.

- In addition, the members of the "Committee on review and safety services" (chaired by Masaaki Hirobe, Tokyo University Professor Emeritus) met on November 11, 2004 while the members of the "Committee on relief services" (chaired by Hideaki Mizoguchi, Chief of the Saitama Prefecture Red Cross Blood Center) met on November 25, 2004 to discuss the operation results of the first half of the fiscal year, as well as future issues and actions of the Agency. In selection of two members of the latter committee, the Agency adopted an open recruitment to obtain a wide range of views.

- In order to ensure transparency of the Agency, these deliberations above were, in principle, disclosed to the public. The reports and materials of the meetings have been posted on the website to be available.
  *Please refer to http://pmda.go.jp/hyougikai/hyougikaikankei.html

4. Development of effective operations management system

- The agency is to establish an effective system of operation management through a flexible personnel allocation tailored to situations and an effective use of external experts.

- For this purpose, the review department adopted a tem review system, in which flexible operations are particularly required. Office directors have a number of review directors, and they supervise each review team under this system.

- The Agency invited to appointed experts to work as expert members to provide their opinions on

scientifically important matters in the expert discussion on review, and their registration procedure was completed by the end of July 2004. The names of the expert members were posted on the Agency's website in September. (The number of appointed expert members was 789 as of March 31, 2005.)

- The Agency appointed lawyers and patent attorneys as an advisor in the fields requiring specific knowledge, such as law, management, systems, intellectual property. In addition, we make the best use of private companies to support us in introducing system operation management, risk management, and target management. This utilization allows the Agency to keep the number of its permanent staff minimum.

- In order to ensure the integration and coordination of the various systems for the Agency's overall function, the Agency appointed an information system advisor who has knowledge of pharmaceutical affairs and advanced expertise of the overall system.

5. Standardization of operating procedure

- The standardization of the various operating procedures allowed the Agency to use part-time employees and minimize the necessary number of its permanent staff members. In details, the Agency created standard operating procedure (SOP) for its major tasks, and the content of the SOP documents has been verified and checked. The maximum effort was made to employ part-time employees, particularly, for the simple and routine works.

6. Promotion of information through database

- The Agency is to make a maximum effort to organize documented information into electronic format incorporating into database, which allows the Agency, wherever possible, to systematically store, retrieve, use and analyze the information and documents.

- From the perspective to organize, store, and analyze various documented information electronically, it is necessary for the Agency to implement a comprehensive coordination for the consistent planning, implementation, development and improvement of the system in order to ensure the coordination and compatibility of the various information systems used throughout the Agency.

- In order to discuss about this comprehensive coordination, the "Management Committee on information systems" was founded in July 2004. The committee proceeded an understanding of the information systems owned by the Agency, identified the information to be shared, created an

electronic information sharing system based on the use of a common LAN system and promoted coordination of the system among the departments.

- On the website, we posted the notifications from the Ministry of Health, Labour, and Welfare, and the Agency, which were relevant to the Agency's operations or necessary for the public.
  *http://pmda.go.jp/notice2004.html

(2) Cost Reduction by Increased Efficiency of Operations

1. Reduction of general management expenses

- The agency is to steadfastly improve its operations and endeavor to increase its efficiency. With reduction of its personnel expenses by reviewing wage levels and procurement costs, the budget for the Midterm Plan regarding the general administrative expenses (excluding retirement allowance) shall have taken into account the following savings at the end of the effective period for the Midterm Targets:
  1) Approximately 15% of savings in comparison with FY 2003 level
  2) The general administrative expenses due to accrue from FY 2004 in connection with the revisions to laws and systems and other matters shall be saved by approximately 12% in comparison with the FY 2004 level.
  3) The general administrative expenses due to accrue from FY 2005 in connection with the enforcement of the revised Pharmaceutical Affairs Law in FY 2005 shall be saved by approximately 9% in comparison with the FY 2005 level.

  This Midterm Budget on administrative expenses was based on the Midterm Targets on cost reduction specified by MHLW. The Midterm Targets are expected to be achieved by executing in accordance with the Midterm Budget.

- In fiscal 2004, in order to effectively execute the Midterm Budget and achieve the reduction of general administrative expenses, the periodic salary increases for permanent staff members were halted based on the annual plan in April 2004. In addition, efforts were made to reduce procurement costs by introducing open competitive bidding/competing bids.

2. Reduction of program expenses

- By increasing efficiency in operations such as the promotion of computerization, the budget for the Midterm Plan with regard to program expenses (excluding benefit-related expenses, and single-year expenses due to accrue in connection with creation of programs) shall have taken into account the following savings at the completion of the effective period for the Midterm Targets:

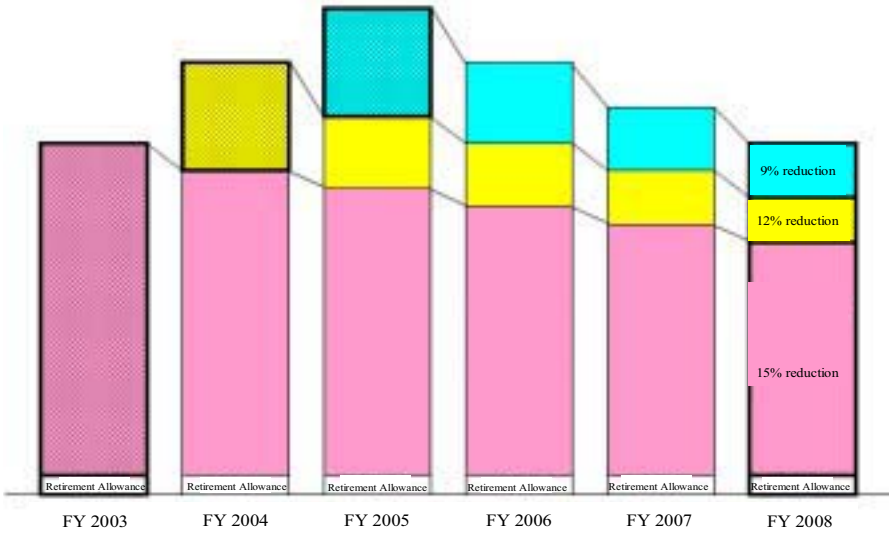
1) Approximately 5% of savings in comparison with the FY 2003 level
2) The program expenses due to accrue from FY 2004 in connection with the revisions to laws and systems and other matters shall be saved by approximately 4% in comparison with the FY 2004 level.
3) The program expenses due to accrue from FY 2005 in connection with the enforcement of the revised Pharmaceutical Affairs Law in FY 2005 shall be saved by approximately 3% in comparison with the FY 2005 level.

The Midterm Budget for program expenses was based on the Midterm Targets for cost reductions specified by MHLW. The Midterm Targets are expected to be achieved by executing the budget in accordance with the Midterm Budget.

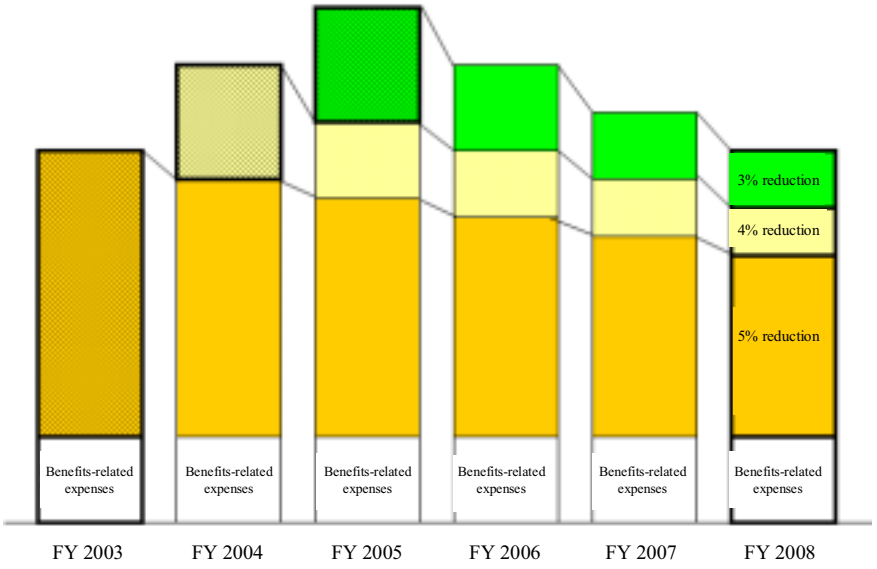
- While pursuing efficiency, the Agency considered the possibility of future demand/requests from the perspective of pharmaceutical research and development. We also conduct steadfast examination on the progress of existing operations. Therefore, the Agency operated R&D promotion service in collaboration with MHLW in order to keep up with the latest trends of research promotion in Japan.

[Reduction of General Administrative Expense and Program Expenses (Simplified Image)

General Administrative Expenses



Program Expenses



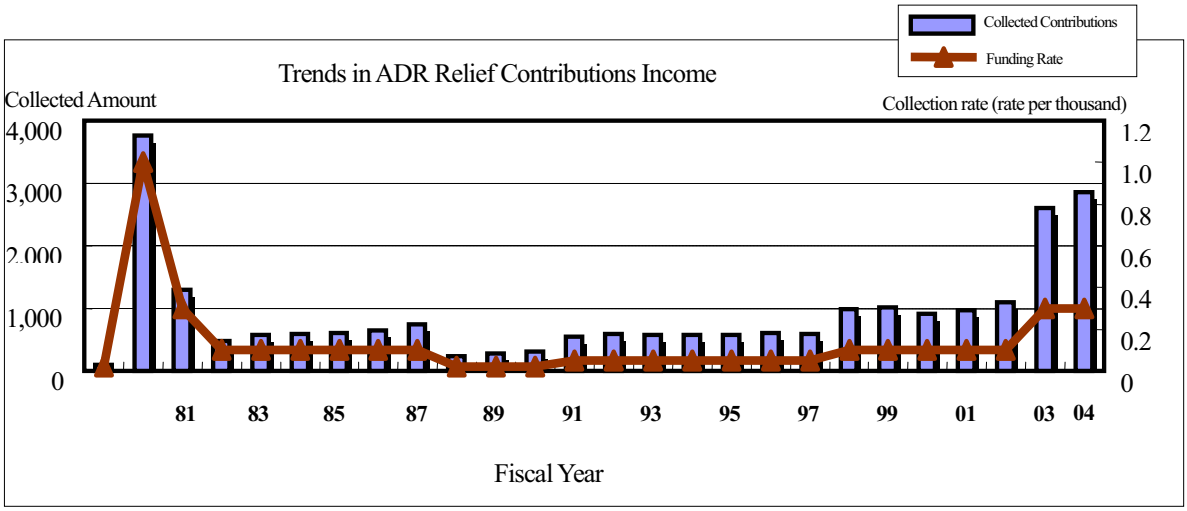
3. Collection and management of contributions

- The pharmaceutical and medical device manufactures/importers are to financially contribute to the Agency with paying adverse drug reaction contributions (for only drugs), infectious disease contributions and safety measure contributions. Thereby, the Agency ensures its financial resources for the operations of adverse health effect relief services and other operations to improve efficacy and safety of pharmaceuticals and medical devices.

- Therefore, the Agency promoted efficiency in its operations by managing contributions for infectious disease and safety measures, which were newly founded in FY 2004, with the data on the products marketed by each contributing company to adverse drug reaction (ADR) relief.

- Specifically, the Agency developed the upgraded contribution management system by adding the database on the infectious disease contributions as well as safety measures contributions to the current collecting system for adverse drug reaction (ADR) contributions. The Agency utilized such computerized information to prevent omitting the declared products and manufacturers/importers and to manage those who had not paid contributions. As a result, the Agency can easily and promptly check the amount of each type of contributions and effectively utilize the compiled data for the discussions to revise funding rates. In addition, in order to ensure the convenience for those who are required to make contributions and the rapid transfer of the contributions, the Agency arranged the entrusted banks for collection, made a new contract with the post office and developed a money collection system.

  (Reference)
  Data required for the newly added infectious disease contributions and safety measures contributions with the basis of collection management system of the current adverse drug reaction relief contributions collection as follows:
  Pharmaceutical manufactures/importers: medical device manufactures/importers: medical devices by manufactures/importers (classification number and general name of medical devices): declaration documents for each manufacture/importer, a list of manufactures/importers in arrears and manufactures/importers of pharmacy compounding drugs, etc.



- In the Midterm Plan, the contribution collection rate for ADR and Infectious disease shall be no less than 99%. This figure is also expected to be in effect for fiscal 2004. (The average collection rate of ADR contributions over the past five years is approximately 99%.)

- With regard to the safety measures contributions, the Agency shall aim to raise the collection rate to the levels similar to those of ADR and infectious disease contributions by the end of the effective period of the Midterm Targets. To the end of this period, the Agency is to work for the promotion of wide recognition of the system.

- Based on the Midterm Targets above, the Agency took the following measures to improve the effective collection of each contribution;

  1) We concluded a contract on commission with the Japan Pharmaceutical Association regarding the contribution collection from manufactures/importers of pharmacy compounding drugs.

  2) The safety measure contribution is a new system started in FY 2004. The Agency called for cooperation of industry groups by requests, explanations and lectures as well as public advertising on its websites and in the industrial papers. The Agency also developed and distributed a handbook for the declaration and payment procedure of contribution in order to inform all the parties obligated to contribute to the funds. Moreover, in order to increase the collection rates, a written request for payment was sent to the manufactures/importers in arrears (excluding those of pharmacy compounding drugs), and the requests were also posted on the industry groups' websites.

  Furthermore, the Agency posted an advertisement requesting the payment of the required contributions in the relevant industrial papers.

[FY 2004 Contributions Collection Results]

Category		Subjects	Number of payers	Collection rate	Contribution amount
Adverse drug reaction contributions	Manufactures /importers	833	833	100%	(million yen) 2844
	Pharmacy	10,662	10,550	98.9%	11
	Total	11,495	11,833	99.0%	2,855
Infectious disease contributions	Manufactures /importers	108	108	100%	554
Safety measures contributions	Manufactures /importers	3,925	3,076	78.4%	1,091
	Pharmacy	10,662	10,541	98.9%	10
	Total	14,587	13,617	93.4%	1,101

(3) Improvement of Services to Public

1. General consultation service

- The Agency is to strengthen the system to address consultations and complaints from the general public with the purpose of improving its services to the public.

- To achieve this goal, the “general consultation guidelines” have been specified to show the way to handle inquiries to the Agency and to review comments and opinions helpful for the operation improvement, and the general consultation service started to function on February 1, 2005. For the service, the Agency set questionnaires at its reception counter and began collecting visitors’ comments and opinions about the overall operation of the Agency.

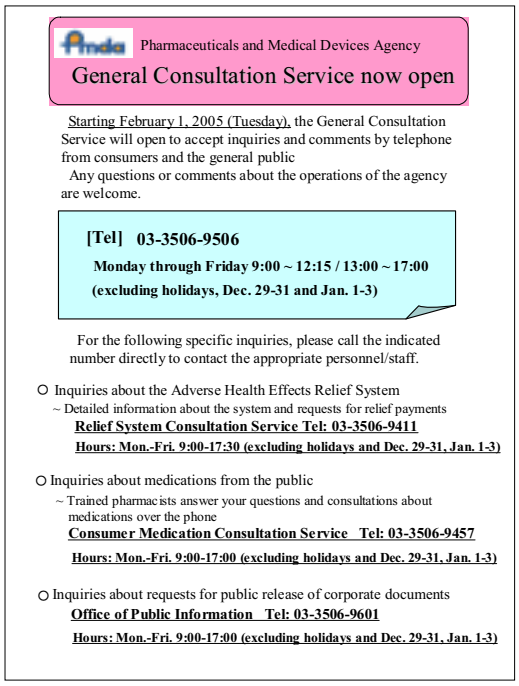
- The Agency developed a reception record book and response/service card to organize and track the conducted consultations. The Agency also prepared a monthly report on the progress of the consultation and response/service.

- As of the end of March 2005, the total of 219 consultations were requested to the general consultation service, and more than half of the cases (151) were the inquiries regarding consultations and applications for pharmaceuticals and medical devices approval.

	Inquiry / Consultation	Complaint	Opinion / Request	Others	Total
Consultation cases	209 (144)	7 (6)	2 (1)	1 (0)	219 (151)

Note 1: The numbers in parentheses indicate the cases related to consultation and applications for pharmaceuticals and medical devices approval, and the numbers are also included in the total.

Note 2: The Office of Review Administration accepts inquiries on consultation and applications for pharmaceuticals and medical devices approval separate from the general consultation service.



Pharmaceuticals and Medical Devices Agency

General Consultation Service now open

Starting February 1, 2005 (Tuesday), the General Consultation Service will open to accept inquiries and comments by telephone from consumers and the general public

Any questions or comments about the operations of the agency are welcome.

[Tel] 03-3506-9506

Monday through Friday 9:00 ~ 12:15 / 13:00 ~ 17:00

(excluding holidays, Dec. 29-31 and Jan. 1-3)

For the following specific inquiries, please call the indicated number directly to contact the appropriate personnel/staff.

○ Inquiries about the Adverse Health Effects Relief System

~ Detailed information about the system and requests for relief payments

Relief System Consultation Service Tel: 03-3506-9411

Hours: Mon.-Fri. 9:00-17:30 (excluding holidays and Dec. 29-31, Jan. 1-3)

○ Inquiries about medications from the public

~ Trained pharmacists answer your questions and consultations about medications over the phone

Consumer Medication Consultation Service Tel: 03-3506-9457

Hours: Mon.-Fri. 9:00-17:00 (excluding holidays and Dec. 29-31, Jan. 1-3)

○ Inquiries about requests for public release of corporate documents

Office of Public Information Tel: 03-3506-9601

Hours: Mon.-Fri. 9:00-17:00 (excluding holidays and Dec. 29-31, Jan. 1-3)

2. Responses to complaints from companies regarding reviews and post-marketing safety operations

- In addition to developing a fully functioning system to respond to the appeals of consultations and the complaints from general consumers, the Agency shall work to enhance the system to respond to the inquiries regarding its review and safety operations from the relevant companies.

- As part of this effort, the Agency set a responsible office director to hold a face-to-face meeting in September 2004 when there was an inquiry from an applicant regarding review progress of a new pharmaceutical, new medical device, or improved medical device. Appropriate explanations were provided about the expected time necessary to reach the next review stage.

- As another effort of the Agency, starting in March 2005, when appeals from applicants about the review and post-marketing safety operations, the responsible office director (in the case of a second complaint, the director of the Center for Product Evaluation or the Chief Safety Officer) directly conducted an investigation and provided a response within 15 working days.

- In addition, in March 2005, the "response manual in consultation" was created to facilitate to respond to the appeals from companies. The Agency is to consider and discuss some of the complaints helpful to improve our operations.

3. Website posting

- The achievement of the Agency's operations from April to September 2004 were compiled into the "First Semiannual Report of Fiscal 2004" and disclosed on its website. Appropriate reports were made at the Advisory Council and the operating committees, and the materials for these meetings were also posted on its website.

- There was also an article placed in the monthly publication "Kousei Roudou" issued in July (issued by MHLW) with the purpose to introduce the Agency.

4. Report on financial standing

- To ensure transparency of the expenditures of the Agency, it discloses its financial standing including the use of user fees and contributions.

- Therefore, in April 2004, the Agency adopted the accounting regulations stipulating a division of accounting for each accounting. Under these regulations, the appropriate closing account is to be developed for the initial fiscal year, 2004, and this is to be published in the national gazette and on the Agency's website in August 2005.

5. Auditing and related matters

- The Agency is to adopt external auditing in accordance with the incorporated administrative agency system and also systematically conducts internal auditing on its operations and budget according to the Plan. Reporting the results of the conducted audits ensures the transparency of its operations and its contents.

- In details, the Agency established the regulations on the auditing by the auditors specifying that the auditors can attend important meetings and address their opinions, that the regulations clarifies the range of documents sent to auditors and the method of audits. Based on these

regulations, the auditors constantly monitor the Agency's operations and conduct unscheduled audits. We also organized internal auditing guidelines in consideration of the relation with the auditors.

(4) Personnel Issues

1. Discussion of a personnel evaluation system

- The Midterm Targets for the Agency aims to implement, in an appropriate manner, a personnel evaluation system that takes into consideration the work performance of staff members. The Midterm Plan aims to introduce a personnel evaluation system that will lead to an increase in staff motivation. Evaluation and target achievement status of staff members shall be reflected appropriately in remuneration, salary increases and promotions.

- In FY 2004, the Agency proceeded discussions on the work performance evaluation required for the personnel evaluation system and the target management system, the base for personnel evaluation system, was tested. To introduce the target management system staff training was conducted and each office created a work planning chart and it was presented to the executives and then reported periodically to the executives on the progress of the planned works as a trial.

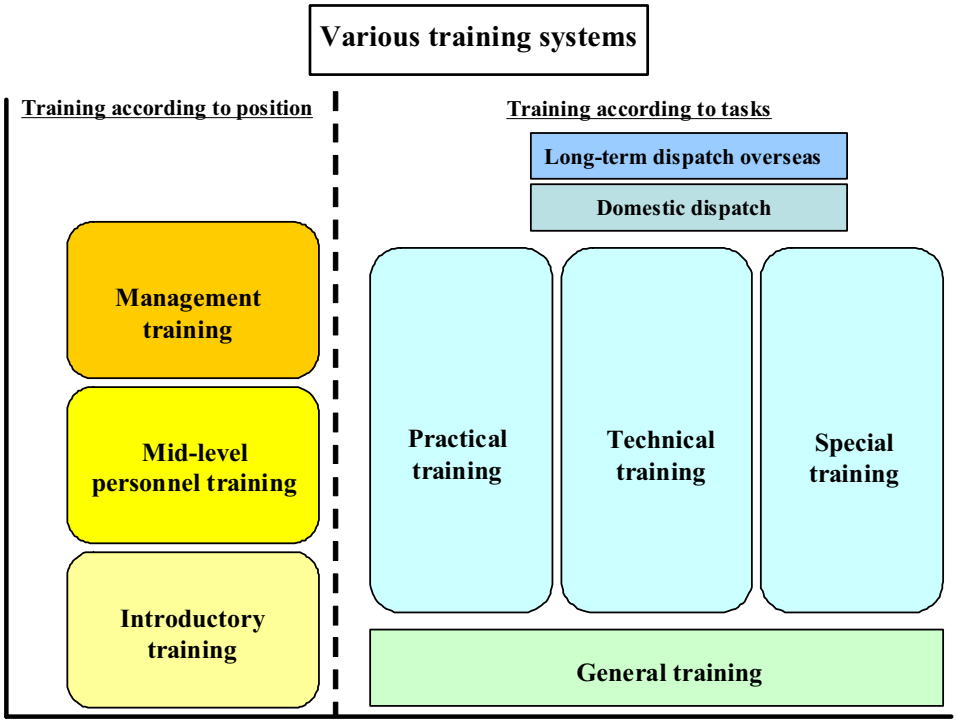
2. Systematic implementation of training

- The review, post-marketing safety and relief operations of the Agency require high level of expertise, and we see the rapid and on-going scientific and technological advancement in the field of pharmaceuticals and medical devices. In such circumstances, it is necessary to implement appropriate ability to develop to enhance the expertise of staff members. In FY 2004, a systematic training program was implemented in accordance with the operations and services goals and appropriate training was provided corresponding to the qualification and capability of an individual staff member. The Agency had its staff actively participate in both domestic and overseas academic conferences and seminars in order to absorb new knowledge and improve their skills.

- Specifically, the training committee was formed in April 2004, and the basic objectives for training were established. The committee devised some plans for introductory training, internal training and external training based on the needs of each office. In addition, the committee developed the rules on long-term overseas assignments or studies and external training in Japan or foreign universities and others. The committee also discussed an active participation in academic conferences and seminars and established the training programs for fiscal 2005.

- In 2004 fiscal year, the Agency conducted the introductory training, internal training and external training as well as programs dispatching the staff to universities in and out of Japan or to foreign pharmaceutical regulatory authorities. Under this program, 39 staff members were sent to 21 sites and a staff member to the FDA for long-term training. Moreover, we held 7 lectures on various technical issues (special training) during 2004 inviting experts who belong to foreign pharmaceutical companies as a lecturer, and conducted other training programs on special issues such as tours in medical device development and production facilities.

- In addition, in July 2004, the rules regarding participation in domestic academic conferences were established, and tracking of the participation of each office to the conferences was conducted every fiscal quarter. (676 cases as of the end of March)



3. Appropriate personnel placements

- To ensure the expertise of staff members and the continuity of operations, the Agency is to conduct appropriate personnel placements.

- To achieve this end, the knowledge and work experience the staff members possess are considered when making personnel placements. Basically, the Agency avoided short-term assignments except for the cases of health problems or special reasons from the Agency's work.

4. Securing human resources through open recruitment

- In order to ensure smooth enforcement of the revised Pharmaceutical Affairs Law in FY 2005 and rapid and proper implementation of the review and the post-marketing safety operations, it is an important issue to employ competent personnels with high levels of expertise, with due consideration to the impartiality of the Agency.

- The Midterm Plan of the Agency specifies the number of permanent staff members at the beginning of the midterm period (on April 1, 2004) was 317 (including executives, hereinafter the same). The number of permanent staff members at the end of the midterm period (on March 31, 2009) is 346. However, the actual number of the permanent staff members as of April 1, 2004 ended up 256, significantly lower than the number set in the Midterm Plan.

- Therefore, a project team for staff recruiting, personnel and organizational issues was established under the "Headquarters for Implementation of the Revised Pharmaceutical Affairs Law", and the project team developed the hiring plan by expertise and reviewed employment benefit/treatment, working conditions of assigned experts and others. The Agency decided to employ competent personnel necessary for the understaffed areas focusing on open recruitment through its websites and publicity in the industrial magazines. The Agency publicly announced the recruitment of permanent staff members eight times, and three times for assigned experts including the recruitment made prior to the beginning of the Agency's operation. The results of the Agency's open recruitment and its unofficial hiring notifications are shown in the chart below.

[Employment through Open Recruitment]

1) Technical staff (Open recruitment, 5 times)	
Number of applicants	About 650
Number of the employed	21
Number of the employed as of April 1, 2005	32
Number of the persons scheduled to be employed	15
2) Administrative staff (Open recruitment, 3 times)	
Number of applicants	About 300
Number of the employed	11
Number of the employed as of April 1, 2005	4
3) Assigned experts (Open recruitment, 3 times)	
Number of applicants	About 50
Number of the employed	3
Number of the employed as of April 1, 2005	5
Number of the persons scheduled to be employed	8

- The Agency is to make an effort to secure competent human resources by re-examining employment conditions for the positions particularly difficult to keep capable personnel. Also the Agency is to take provisional measures on restrictions, under the Agency's work regulations related to those who engaged in GMP and biometrical operations in order to employ staff members from a private sector with due consideration to the neutrality and impartiality of the Agency.

- In order to hire necessary personnel to meet the Midterm Plan for the review and the safety departments, the Agency will further proceed open recruitment in FY 2005.

[Numbers of the Agency's Permanent Staff Members]

	April 1, 2004	April 1, 2005	Numbers Expected (in the Midterm Pan) Beginning of FY 2004	Numbers Expected (in the Midterm Plan) End of FY 2008
Total # in Agency	256	291	317	346
Review Department	154	178	–	–
Safety Department	29	43	–	–

Note 1: The total # in Agency includes executive positions. 11 staff members of the R&D Promotion department are included in the total numbers as of April 1, 2004, and in the numbers expected at the beginning of FY 2004. On the other hand, the numbers as of April 1, 2005, and the numbers expected at the end of FY 2008 do not contain 11 staff members of the R&D Promotion department. The number expected (in the Midterm Plan) at the end of FY 2008 was 357 before the R&D Promotion services were transferred to the National Institute of Biomedical Innovation (NiBio).

Note 2: The Review department consists of Director of the Center for Product Evaluation, Associate Center Directors, Office of Review Administration, Office of New Drug I・II・III, Office of Biologics, Priority Review Director, Office of OTC/Generic Drugs, Office of Medical Devices and Office of Conformity Audit.

Note 3: The Safety department consists of Chief Safety Officer, Office of Safety and Office of Compliance and Standards.

5. Appropriate human resources management based on work regulations

- The Agency is to conduct personnel management in an appropriate manner with certain restraints on the recruitment and placement of its executive and staff members as well as on employment of those who leave the Agency in order to avoid any suspicions of inappropriate ties with the pharmaceutical and medical device companies.

- To achieve this, the Agency required the newly-employed staff members to submit a written pledge, and added some restrictions stipulated under the work regulations on employment, personnel placement and re-employment after retirement. The Agency conducted appropriate personnel management by having its staff members thoroughly informed about the new regulations.

- Specifically, (1) The Agency established its work regulations and its explanations on requiring its staff members to submit a written pledge to observe the work regulations and to keep the confidentiality of its operations, the restrictions in engaging in its operations to those who have a

work history in a pharmaceutical company and the restrictions on working for a pharmaceutical company after leaving the Agency (2) An ethical standard and its explanations, such as a code of conduct and prohibited interactions between the Agency's staff and the stakeholders including pharmaceutical companies was established. The Agency also developed summaries and Q&A lists concerning these specified regulations and made its staff members informed through the internal website and in the occasions of training for the newly-joined staff members.

- In addition, from the perspective of further informing the Agency's staff about the work regulations and others, a draft of a handbook for distribution that combines the work regulations to be observed by the staff members and a list of Q&As were made. (As the code of conduct applicable to government civil servants was revised in April 2005, the Agency will add the newly revised contents to the handbook.)

(5) Ensuring Security

1. Office entrance/Exit controls

- The Agency was to establish its internal security control system by installing entrance/exit control equipments at the entrance of each office in order to maintain security and confidentiality day and night.

- Therefore, the access to the each office area is limited only to the Agency's staff members with its ID card under the security control system, and the history of individual staff members' entering/leaving was recorded whenever they pass the office's entrance doors.

- Additionally, the Agency set the rules on its access control system and thoroughly informed its staff members about the rules in order to strictly implement the access controls.

2. Security of information system

- The Agency is to ensure the security of information in its information systems.

- Based on the fiscal year plan, the Agency made an effort to ensure the security of information in its information system as follows.

- The regulation on security of information and the rule on management and use of the information system were stipulated. The former regulation specifies the basic requirements to prevent the loss or leaking of the Agency's information property (documents, information system etc.). The latter rule specifies the issues necessary to ensure the security of information system such as

management of information system, security measures and computer virus countermeasures.

PART 2. IMPROVEMENT IN OPERATION OF EACH DEPARTMENT OF THE AGENCY, AND IN ITS QUALITY SERVICE

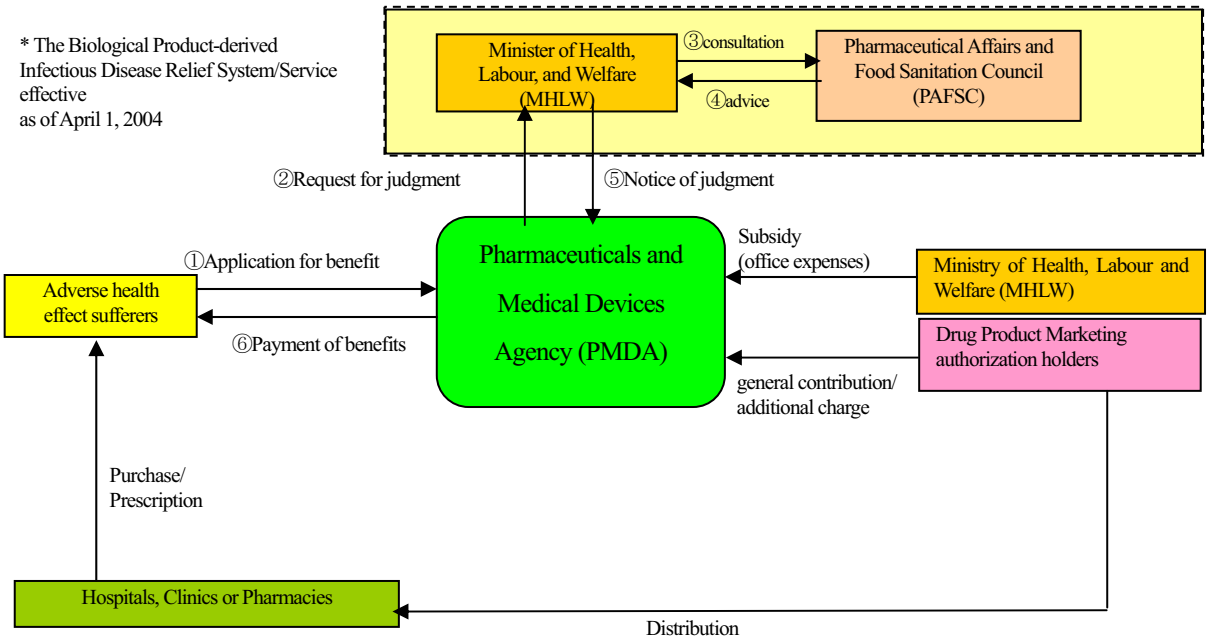
1. ADVERSE HEALTH EFFECT RELIEF SERVICES

The Agency is taking the following measures in order to publicize the adverse drug reaction relief and biological product-derived infectious disease relief system (hereinafter referred to as "the relief system") to as many people as possible, to manage the relief system appropriately and to provide appropriate and prompt relief services to those who suffered from adverse drug reactions (ADRs) and adverse health effects from biological product-derived infections:

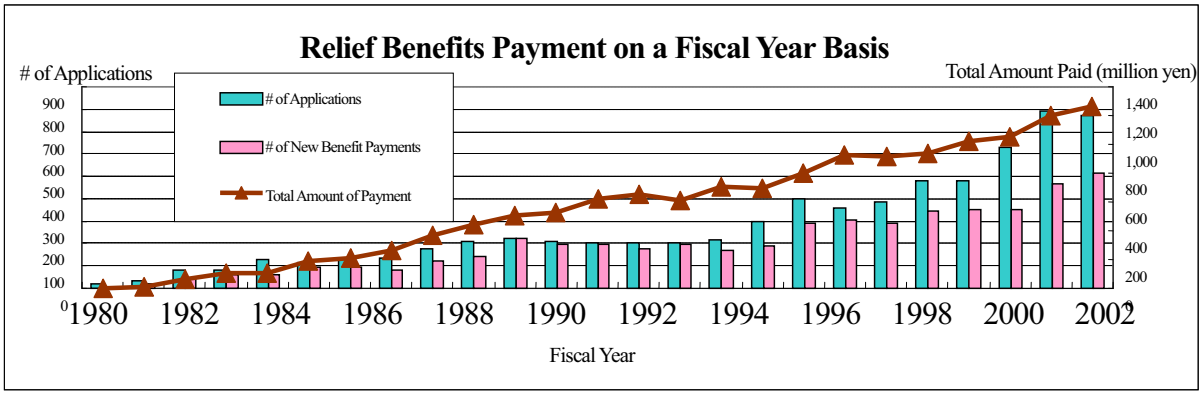
(1) Expeditious Processing of Relief Applications

- In order to speedily proceed administrative process of relief benefit applications, the Agency is to investigate and arrange the fact when requesting the Minister of Health, Labour and Welfare (MHLW) for medical and pharmaceutical judgment after reviewing applications for relief payment. For this purpose, the Agency newly assigned staff to conduct the following tasks: 1. Conducting fact-finding studies on applied cases: 2. Developing the summary chart of the case over time: 3. Creating the investigation reports.

【Adverse Drug Reaction Relief System】



※ In FY 2004, there were 769 applications total to the ADR relief service, and the number of cases judged as payable or not payable were 633 (513 of them were judged as payable); there were 5 applications to the infectious disease relief service, (2 of them were judged as payable).



- In addition, the Agency aims at eight months of the standard administrative processing time --- from application to judgment of either eligible or ineligible for the payment including the period of the MHLW's judgment from medical and pharmaceutical point of view. In collaboration with the MHLW, the Agency is to process the applications for benefits smoothly and complete 60% or more of requests made within FY 2008, which is also the end of the Agency's Midterm Targets period, on its eligibility for the payment within the targeted standard administrative process time.

- For this target, the Agency, consulted with the MHLW, made a clear allocation of the administrative processing time for medical and pharmaceutical judgment between the MHLW and the Agency, 4 months to the MHLW and the other 4 months to the Agency. (excluding the pending period when additional or supplementary materials are required to applicants and/or medical institutions) The Agency also periodically renew the list of cases being processed and requested the MHLW to deliver a speedy judgment.

- However, as the number of the applications in the process increased dramatically because of the significant increase of new applications for the benefits during FY 2002 to 2003, the accomplishment rate has continuously dropped.

- Therefore, the Agency considered the increase of staff numbers and the restructuring of the Office of Relief Funds to provide the adverse health relief services speedily. The Agency also studied the introduction of consultations with the external experts from various fields appointed by the Chief Executive of the Agency in order to support the MHLW's judging operations, with the shift to the Dual Judgment Committee of the MHLW (The introduction is planned in FY 2005.).

*The Increase of Staff Members of the Office of Relief Funds and Establishment of Relief Application Review Division

	April 1, 2004	April 1, 2005
○Number of Staff Members:	18	27
○Number of Divisions:	4	5

【Number of Applications and Judgments for ADR Relief】

Fiscal Year	FY 2002	FY 2003	FY 2004
Number of applications	629	793	769
Number of cases judged	431	566	633
Number of cases withdrawn	0	2	1
Number of cases being processed*	593	820	956
Accomplishment rate **	46.6%	17.6%	14.5%
Processing time (the median)	8.3 months	10.6 months	12.4 months

【Number of Applications for Infectious Disease Relief】

The number of applications was 5 and the number of cases judged was 2.

(Accomplishment rate** was 100%)

* "The number of cases being processed" indicates the number at the end of each fiscal year.

** "The accomplishment rate" is the percentage of cases judged within 8 months out of the number of total cases judged during the fiscal year.

(2) Unified Management of Information through the Database

- In order to improve efficiency in the relief services, the Agency upgraded the existing database on ADR relief service and enhanced its time-clock management, statistical analysis and search functions. The Agency also established a new infectious disease relief service in FY 2004 making use of its existing information system on adverse health effect relief service.

(3) Promotion of Appropriate Communication of Information through Cross-functional Collaboration

- The Agency has sought cross-functional collaboration among its departments and the information on the judgment of benefit payment of ADR relief in FY 2004 was reported to the post-marketing safety department without personal information, particularly, in order to properly provide the information on the eligible cases for the ADR relief benefits payment. The Agency also reported 5 applications of infectious disease relief and 2 eligible cases for benefit payments to the post-marketing safety department.

(4) Surveys on Actual Situations of Adverse Health Effects from Pharmaceuticals

- Health and welfare services were legislated because it was considered necessary to implement other operations than the relief benefit payments to the sufferers from adverse health effects for taking speedy measures against ADR cases. (Article 15, Pargraph 1, Item 1: the Law on Incorporated Administrative Agency, Pharmaceuticals and Medical Devices Agency (PMDA))

- In order to execute a fact-finding survey in FY 2005 about the actual situations of harms of the relief benefits recipients as the health and welfare services, the Agency set up the "Study Group for the Fact-finding Survey on Adverse Health Effects", chaired by Hisao Sato, Professor of the Japan College of Social Work, in October 2004 and conducted three meetings on Oct. 8, Dec. 15 in 2004 and Feb. 16 in 2005 to consider the subject and items of the survey questionnaires.

(5) Expansion of the Consultation Service

- The former OPSR (Organization for Pharmaceutical Safety and Research) had its consultation service to respond to questions on its system and the application procedure for the relief benefits. The Agency expanded the former service and developed a new consultation service to widely respond to various questions about its relief service and how to apply for it. For this purpose, the Agency assigned its staff to consultation service and the consultation office is open from 9:00 to 17:30 (without lunch break).

Phone: 03-3506-9411
E-mail address of the relief consultation service: kyufu@pmda.go.jp

【Newspaper Advertisement】

【Yakutai (Paper bag containing prescribed drugs)】

In order to directly inform patients taking prescribed medicines of the post-marketing relief services, the Agency made use of advertising opportunities given at the back of a Yakutai (a small paper bag containing prescribed drugs that is given in hospital or pharmacy). The Agency distributed, across Japan, approximately 1.5 million Yakutais with its advertisement to 141 pharmacies in health insurance system, entrusting an advertising agency on commission with a design of the ad, print and selection of the areas pharmacies to be distributed.

Fiscal Year	FY 2002	FY 2003	FY 2004	Annual Growth rate of FY 2004 to FY 2003
# of consultations	1,737	5,338	3,873	down 27%
# of web accesses	--	35,726	41,947	up 17%

- The Agency is to increase the number of consultations and its web accesses by implementing proactive public relations activities for its relief services. In the plan for FY 2004, the Agency targeted about 5% increase of the number of consultations and web access compared with the FY 2003 level.

- The decline in the number of consultations in FY 2004 is considered to be due to posting the Agency's advertisements in newspapers including the URL of PMDA. The availability of the information on the relief services via internet to the public caused the decrease of consultations via phone with the increase of website access.

(6) Expansion and Review of Information Dissemination Regarding the Relief Services

1. Disclosure of cases of benefit payment on website

- The Agency plans to disclose the achievements of its operations and other information of FY 2004 on its website in order to enhance the content of disseminated information on the relief service and to further pursue the transparency of its operation and service. In addition, the Agency has just posted the information on judgments of relief benefit payments from April to June 2004 on its website with due consideration to protecting personal information. The Agency will continue to provide the information above after July 2004 on its website in succession.

  Information is available on eligible and ineligible cases for relief benefits payment at

  http://pmda.go.jp/help/information.html

2. Improvement of pamphlets and other communication tools

- The Agency is to improve the quality of its pamphlets and application manuals to be understood and used easily by doctors and patients, and to reduce the numbers of flawed applications that disturbed its administrative process. The actions taken by the Agency to enhanced its operational efficiency was specifically as follows;
  1) The content of the application guide for the ADR relief services has been reviewed and revised.
  2) The outline of the relief service has been added to the "Q&A on the biological product-derived infectious disease relief service".
  3) Applications and other forms, which were previously available for applicants on request by

mail, can now be obtained via website.

Applications can be downloaded at http://search.pmda.go.jp/fukusayo_dl/

(7) Proactive Public Relations Activities

- The Agency purposed to publicize and inform the relief service widely to the public and conducted the effective and proactive public relations activities as follows:

  1. Advertisements have been displayed in the newspapers and on Yakutais, and tie-up articles were placed in magazines.

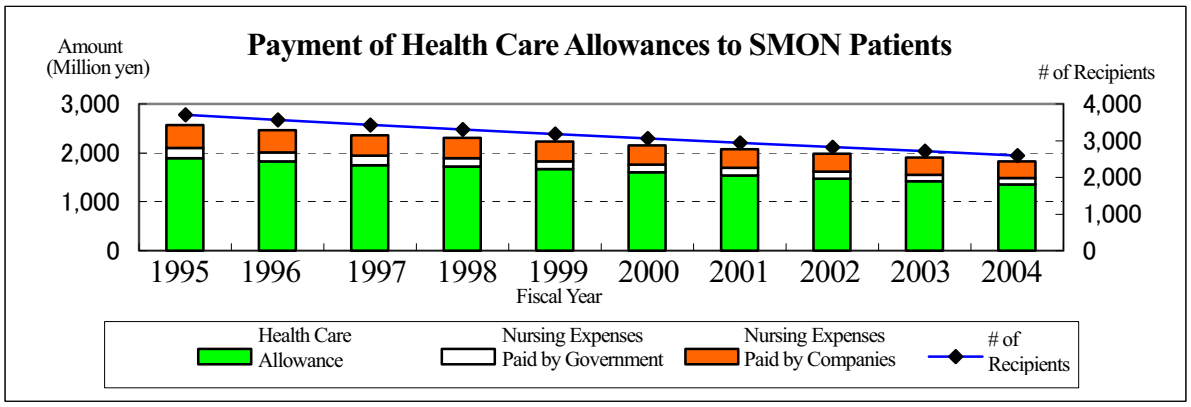
  2. Advertisements on the infectious disease relief service and advertisements on the relief services for the HIV-positives and others were placed in five medical/pharmaceutical magazines respectively.

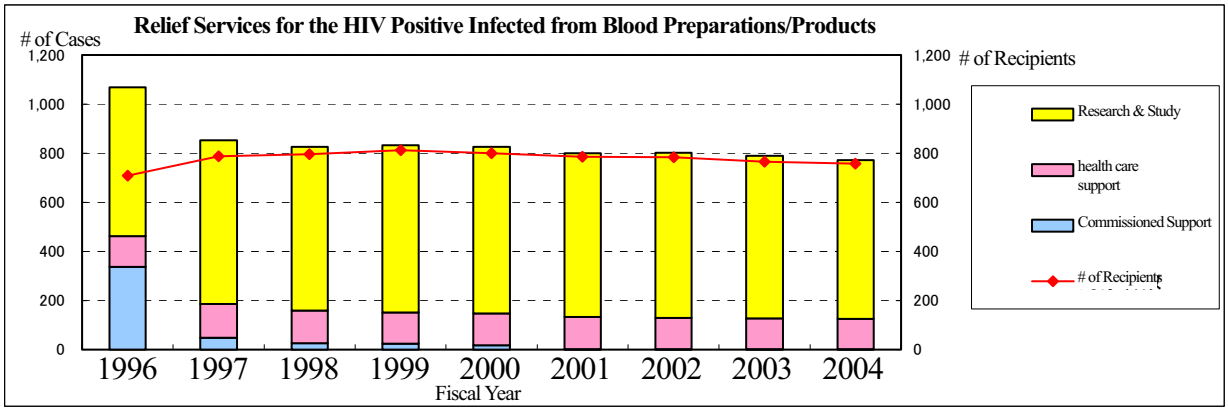
  3. The staff from the Agency have visited 15 medical institutions to explain the relief services.

  4. The Agency displayed the posters and distributed the leaflets explaining the overview of the relief service at the 18th annual meeting of the "Japanese Society for AIDS Research".

(8) Appropriate Conduct of Relief Services for SMON (subacute myelo-optico-neuropathy) Patients and the HIV-positive and AIDS Patients Infected by Blood Preparations/Products

- In order to appropriately provide health care allowances to SMON patients and the HIV-positive and AIDS patients infected by tainted blood preparations/products, the Agency conducted the relief services under the commission with due consideration to handling confidential personal information.




Relief Services for the HIV Positive Infected from Blood Preparations/Products
# of Cases
1,200
1,000
800
600
400
200
0
# of Recipients
1,200
1,000
800
600
400
200
0
1996
1997
1998
1999
2000
2001
2002
2003
2004
Fiscal Year
Research & Study
health care support
Commissioned Support
# of Recipients

2. REVIEWS AND RELATED OPERATIONS/ POST-MARKETING SAFETY OPERATIONS

In order that the public can feel assured in the use of international level of pharmaceuticals and medical devices, the Agency shall ensure that better pharmaceuticals and medical devices are provided to medical practice settings faster and with greater safety; pharmaceuticals and medical devices are used properly; health hazards are prevented or responded to properly and promptly in the event of such occurrences; and that such pharmaceuticals and medical devices can play their part in enhancing the public health for long terms. For these purposes, the Agency has taken the following measures in order to strengthen its systems for consultation/review and post-marketing safety measures, make both operations organically collaborate and achieve its Midterm Targets and the targets set forth in the FY 2004 plan.

(1) Faster Access to Innovative Pharmaceuticals and Medical Devices

1. Ensuring the benefits of pharmaceuticals and medical devices for the public and healthcare Professionals

- The Agency shall ensure that the public and healthcare professionals swiftly enjoy the maximum benefits of innovative, yet safe, pharmaceuticals and medical devices that answer their needs. Additionally, the Agency is requested to ensure benefits for the pharmaceutical and medical device industry that are brought forth by such swiftness.

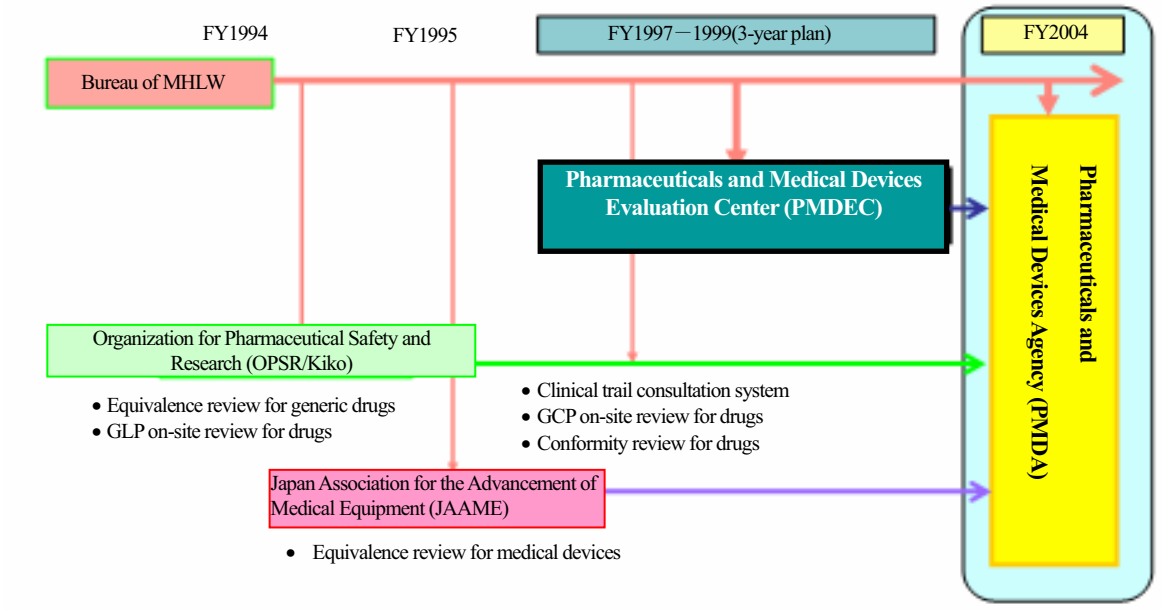
a. Clinical trial consultations and reviews

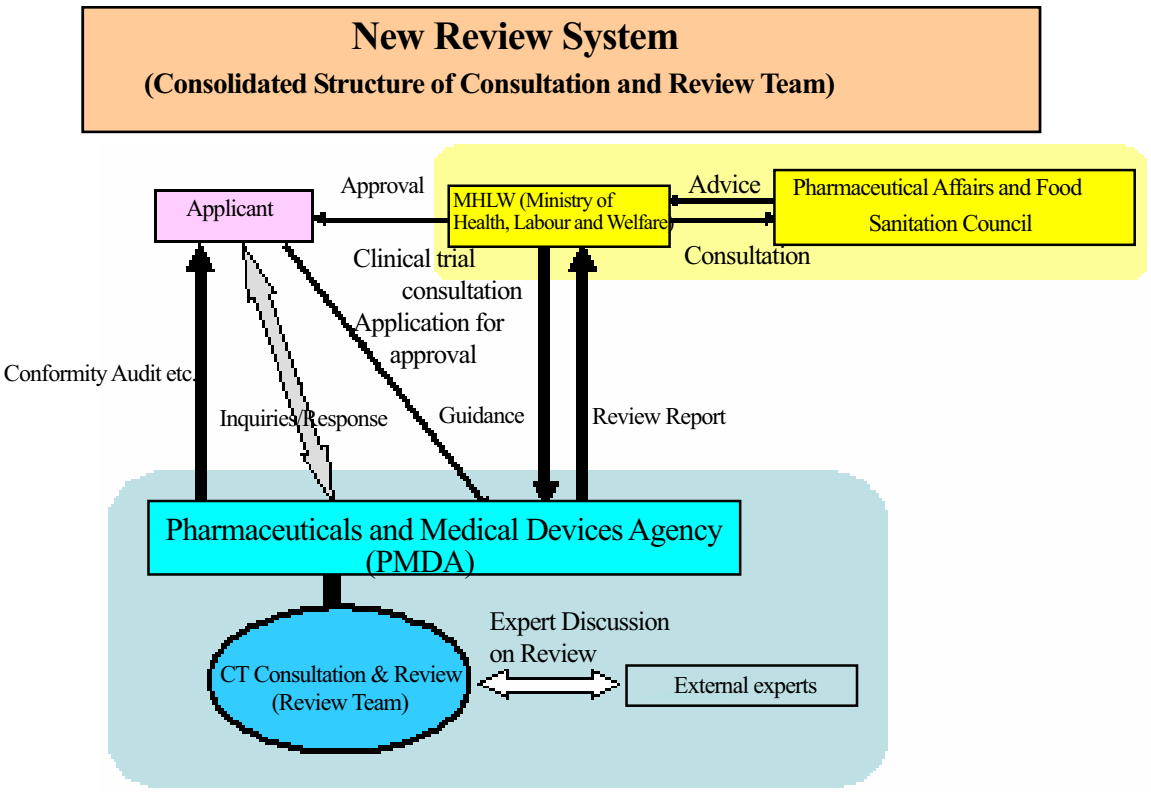
- The review system for pharmaceuticals and medical devices has been improved significantly since 1997. With the inauguration of the Pharmaceuticals and Medical Devices Agency (PMDA) in 2004, the review system was further upgraded by integrating separate review activities, while leaving the authority of approval for and final judgment on pharmaceuticals and medical devices at MHLW.

- Specifically, the review system was to be strengthened by implementing the following measures:
  - i) In order to provide consistency across activities and improve efficiency, a new incorporated administrative agency, the Pharmaceuticals and Medical Devices Agency (PMDA) was established integrating three organizations in charge of review operations.
  - ii) The Agency was to greatly increase its staff including reviewers by about 100 during the Midterm Targets period.
  - iii) The Agency conducts an entire operation process from clinical trial consultation to review under the same team with consistency and coordination. (Because pre-review consultation and review were done by different organizations and staff so far, there were discrepancies between their opinions and policies.)

iv) The Agency aimed to strengthen its review function of biological and biotechnology-derived products and medical devices to respond to future needs.

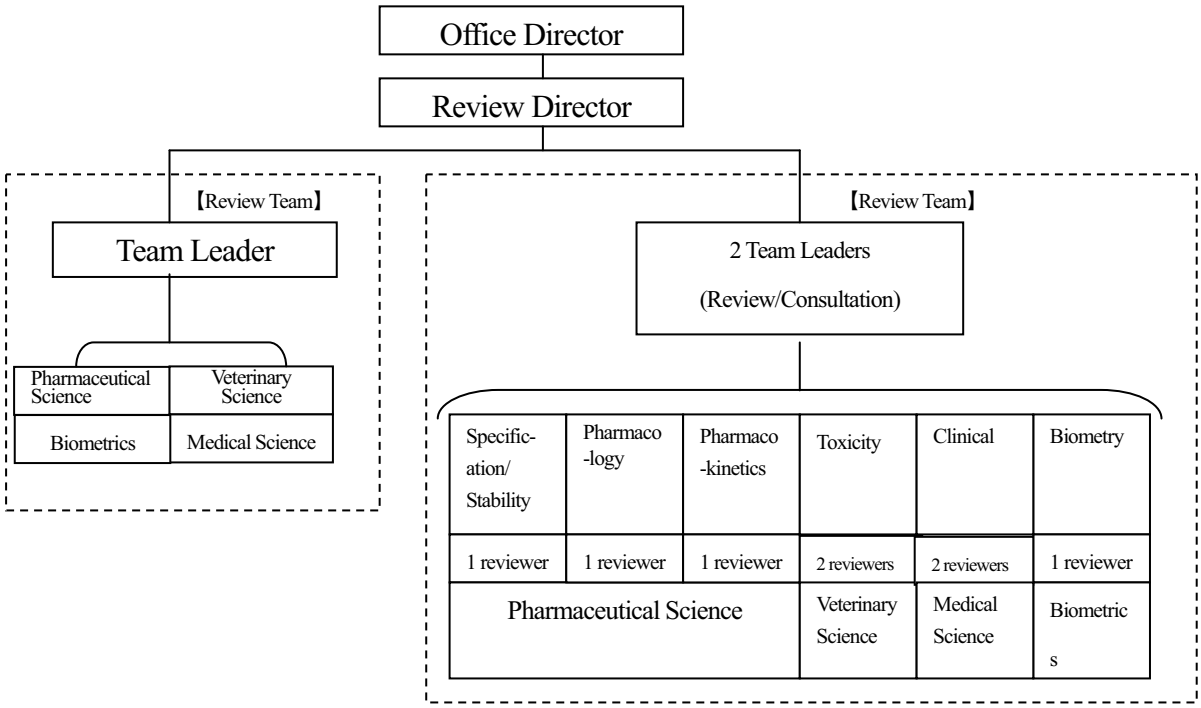
Transition of Approval Review System on Drugs and Medical Devices





During the approval review for new drugs, experts with degrees in pharmaceutical science, medical science, veterinary science, biometry and other specialties form teams to conduct reviews of drugs' "quality", "toxicity", "pharmacological implication", "pharmacokinetics", "clinical implication", and "biometrical implication". Each review team shall basically consist of an Office Director, a Review Director, Team Leader(s), Deputy Team Leader(s) and Reviewers of each expertise.

【Structure of a review team】 ※In case of NDA



- For clinical trial consultation, the Review Director, a Reviewer in charge and a deputy Reviewer who were appointed from the review team discussed its policies based on drafted instructions and advices to applicants, conducted the face-to-face advice or clinical trial consultation and made consultation record.

【Number of consultations and reviews on new drugs in FY 2004】

Clinical trial consultations:

① Preliminary consultations conducted: 287

② Clinical trial consultations conducted: 193

Reviews:

① Expert discussions conducted: 192

(Document reviews: 127, Face-to-face reviews: 65)

② Discussions in Committees of PFSC

(Pharmaceutical Affairs and Food Sanitation Council): 39

Reports made to PAFSC Committees: 14

・ For new pharmaceuticals, the Agency has assigned dedicated offices and teams (12 teams in total during FY 2004), each of which undertakes reviews of pharmaceuticals belonging to one therapeutic category.

【Work of the offices of new drug】

Department Name	Therapeutic Category	
Office of New Drug I	Anti-infective drugs (Category 4)	Antibacterial agents, vermifuge, antifungal agents, antiviral agents except anti-HIV agents
	Oncology drugs	Anti-cancer drug
	Anti-AIDS drugs	Anti-HIV agents
Office of New Drug II	Category 2	Cardiovascular drugs, anti-Parkinson's disease drugs, antithrombotics, anti-Alzheimer's disease drugs
	Category 5	Reproductive system drugs, drugs for urogenital system, combination drugs
	Radiopharmaceuticals	Radiopharmaceuticals
	In vivo diagnostics	Contrast medium
Office of New Drug III	Category 1	Gastrointestinal drugs, hormone drugs, dermatologic medicines
	Category 3	Central/peripheral nervous system drugs, sensory organ drugs except drugs included in Category 6, narcotics
	Category 6	Respiratory tract drugs, anti-allergy drugs, sensory organ drugs for inflammatory diseases
Office of Biologics	Biological products	Vaccines, antitoxic serum
	Blood products	Serum globulin, blood coagulation factors
	Cellular and Tissue-derived products	Products for cell therapy

* As Category 3 was split into two in April 2005, the new category, Category 6, was added to the classification.

b. Grasping the needs of public and healthcare professionals

・ Through dialogue with healthcare professionals at academic conferences, the Agency shall grasp their needs. While attending domestic and international academic conferences, the Agency has actively exchanged ideas with healthcare professionals.

* In total, more than 400 people have attended over 200 domestic and international academic conferences and seminars.

・ For extending indication of anticancer drugs, the investigation panel for combination therapy of anticancer drugs (chaired by Dr. Kiyoshi Kurokawa, Visiting Professor, Research Center for Advanced Science and Technology, the University of Tokyo) was set up within MHLW to respond to the needs from healthcare professionals in various fields. At the panel, prompt approval of unapproved indication in the anticancer drugs was sought. Based on the panel's report, pre-assessments were conducted by the PFSC in May and August 2004. All the ten cases applied by the related companies were approved through review which targeted to process within 4 months.

・ In order to periodically grasp the needs of academic societies and patients on drugs that had been approved in the US and/or the EU but not yet in Japan, an investigation panel for issues on use of unapproved drugs (chaired by Dr. Kiyoshi Kurokawa, Visiting Professor, Research Center for Advanced Science and Technology, the University of Tokyo) was established within MHLW. The Agency shall respond properly to the issues considering the future trend.

・ As to the needs survey planned in FY 2005, the Agency considered the targets, method and items and then, decided to carry out questionnaire, interviewing and online surveys targeting the public and healthcare professionals.

2. Measures for efficient and prompt reviews

・ PMDA shall establish targets (the target time under normal times excluding such exceptional cases as times under significant changes in the review system or in social conditions) to reduce the review process time (referred to as “the process time that MHLW and PMDA consumed for products approved in the fiscal year”) for applications submitted on and after April 1, 2004. By so doing, the Agency shall improve its operations and establish an efficient review structure.

・ In order to achieve the target time for applications for each category submitted on and after April 1, 2004, the Agency has decided to improve its operations such as overall acceleration of reviews.

a. Approval reviews for new pharmaceuticals

・ In new pharmaceuticals, the Agency aims to process 70% of the total NDA reviews within 12 months of review process time during the Midterm Targets period (aiming to the 80% accomplishment in FY 2008). In order to attain the target, the Agency made efforts to improve operational efficiency and took concrete measures to accelerate and properly manage review process by (i) establishing and observing the procedures for review and examination; (ii) conducting self review of the actual review process time; (iii) informing review staff of the achievement results of the compliance with the procedures and targeted process time; and (iv) developing SOPs, etc.

・ With regard to new pharmaceuticals for which approval applications are filed (the active ingredients, quantities, administration and dosage, indications, and effects are distinctly different from those of existing drugs), the review teams with expertise in pharmaceutical science, medical science, veterinary science, biometrics etc. conducted approval reviews.

・ As to NDA reviews, in order to ensure consistency between the review teams and carry out review work promptly and appropriately, the Agency developed the implementation manual of NDA reviews and related procedures and the standard operating procedures for each operation. The Agency conducted the operations by following these manuals, and collected monthly data on the achievement level of targeted process time and informed the results to the review staff.
・ In order to attain its performance target throughout the Midterm Targets period and conduct review related work appropriately, the Agency established the committee on progress management of review related operations in January 2005 so that the Chief Executive and other executives of the Agency could grasp operational progress surely and improve the progress management. The committee held meetings to monitor operational progress at the end of every month. In the review department, office directors grasp the operational progress on daily basis, and based on the

information reported by the office directors at the liaison meeting of the review related offices, the Director of the Center for Product Evaluation and Associate Center Directors provide necessary instructions.

(Results of overall NDA reviews)

- In FY 2004, for the NDAs submitted on and after April 1, 2004, the Agency attained its performance target by processing 100% of the total 17 applications within 12 months. Sixteen out of the 17 approved applications, however, were for priority review drugs, and the achievement rate was 65% in the total NDAs including those submitted before April 1, 2004 (32 out of the total 49 applications).

- Although the number of the approvals in FY 2004 was almost at the same level as in the previous year, the median of the review process time shortened significantly because the Agency assigned high priority to review 10 applications of extension of indication which were taken up by the investigation panel on combination therapy of anticancer drugs.

【Number of approved NDAs】

	2002*	FY 2003	FY 2004
No. of approvals & review process time (median)	52 (10.8 months)	51 (11.3 months)	49 (8.6 months) [65%]**

*) The data in 2002 is based on the calendar year.

**) The percentage in bracket [ ] indicates the ratio of the number of applications processed within 12 months of review process time and includes those filed before April 2004, which is excluded from the Midterm Targets.

- As for 140 and 89 applications submitted before and after the establishment of PMDA in April 2004 respectively, the Agency processed these reviews keeping the order that the applications were submitted and considering fully the targeted review period. But, the Agency has called for pharmaceutical companies to withdraw their applications that we found difficult to approve because they had not replied to our inquiries.

- As to the applications submitted before the establishment of the Agency, 53 of them were approved or withdrawn during FY 2004. However, in order to achieve the target on review process time, it is necessary for the Agency to conduct reviews vigorously so that we can concentrate on the applications submitted on and after April 1, 2004 as soon as possible.

【Results of new drug review in FY 2004】

	Cases*	Withdrawal	Approved	In Progress
Applied before April, 2004	140	12	41**	87
Applied after April 1, 2004	89	4	17	68
Total	229	16	58	155

*) The number is based on review reports discussed at and reported to the Drug Committees of PFSC.

**) The number includes the 9 approved applications which were discussed and reported by the executive committee of PFSC.

(Results of priority NDA review)

- As to priority review applications specified by the Minister of Health, Labour and Welfare, the Agency aimed to process the 50% of total priority NDA reviews within 6 months of review process time by the end of the effective Midterm Target period.

- Applications for orphan drugs and other drugs that are regarded as highly medically needed disease (drugs for serious indications and with distinctly superior efficacy and safety to existing drugs or treatment) were reviewed on a priority basis.

【Annual changes on the number of approval of priority reviewed application】

	FY 2001	FY 2002	FY 2003	FY 2004
No. of applications	21	4	10	22

- The Agency approved 100% of total 16 applications for the priority NDAs filed in and after April 2004 within 6 months, which was targeted for the Midterm plan and the plans for FY 2004. However, the achievement rate including applications submitted before March 31, 2004, decreased to 86%. (19 out of the total 22 applications).

b. Review of new medical devices

- The Agency aimed to process 70% of new medical device application reviews within 12 months in FY 2004; 80% in FY 2005 and 2006; and 90% in FY 2007 and 2008. In order to attain these goals, just as measures taken for NDA reviews, the Agency took concrete measures by establishing operating procedures for review and examination to improve operations and to accelerate review.

- As to new medical device application reviews, in order to carry out review work promptly and appropriately, the Agency established the procedure of new medical device application review and the standard operating procedures for review and other related work. The Agency collected monthly

data on achievement level of targeted process time and informed the results to the review staff. The progress management committee of review operations had monthly meetings to monitor operational progress. In the review department, the director of Office of Medical Devices grasped operational progress on a daily basis, and at the liaison conference between the review related offices, Director of the Center for Product Evaluation and Associate Center Directors provided necessary instructions.

(Results of new medical device application review)

・ For the applications for new medical devices submitted on and after April 1, 2004, the Agency approved 100% of the application (1/1case) within 12 months, which was targeted in the Midterm plan and plans for FY2004. However, the achievement ratio of the total new medical device approvals including their applications submitted before March 31, 2004 decreased to 50%. (4/8 applications), and the median of the actual process time was 386 days (12.7 months).

【Number of approved new medical devices】

	2002*	FY 2003	FY 2004
No. of approvals & review process time (median)	3 (2.9 months)	13 (8.9 months)	8 (12.7 months) [50%]**

*) The data in 2002 is based on the calendar year.

**) The percentage in bracket [ ] indicates the ratio of the number of applications processed within 12 months of review process time, and includes those filed before April 2004, which is excluded from the Midterm Targets.

・ For the 132 and 54 applications submitted before and after the establishment of PMDA in April 2004 respectively, the Agency processed these reviews keeping the order that the applications were submitted and taking the targeted review period. The Agency called for medical device companies to withdraw their applications that we found difficult to approve because they had not replied to our inquiries.

・ As to the applications submitted before the establishment of the Agency, 46 of them were processed during FY 2004. In order to achieve the review period, it is necessary for the Agency to conduct reviews vigorously so that we can concentrate all our resources on the applications submitted on and after April 1, 2004 as soon as possible.

【Results of new medical device reviews in FY 2004】

	No. of Cases*	Withdrawals	Approvals	In Progress
Applications submitted before April 1, 2004	132	38	8**	86
Applications submitted on and after April 1, 2004	56	2	1	53
Total	188	40	9	139

*) The number indicates the number of applications for new medical devices.

**) The number includes the one approved as an improved medical device.

(Results of priority review for new medical devices)

- As to priority review applications specified by the Minister of Health, Labour and Welfare, the Agency aims to attain its performance target of completing 70% of priority NDA reviews within 9 months of review process time by the end of the effective period of the Midterm Targets.

- Applications for orphan medical devices and other devices that are regarded as highly medically needed disease (drugs for serious indications and with distinctly superior efficacy and safety to existing drugs or treatment) were reviewed on a priority basis.

【Annual changes on the number of priority reviews for medical devices】

	FY 2001	FY 2002	FY 2003	FY 2004
No. of applications	5	4	4	2

c. Compliance review of application materials

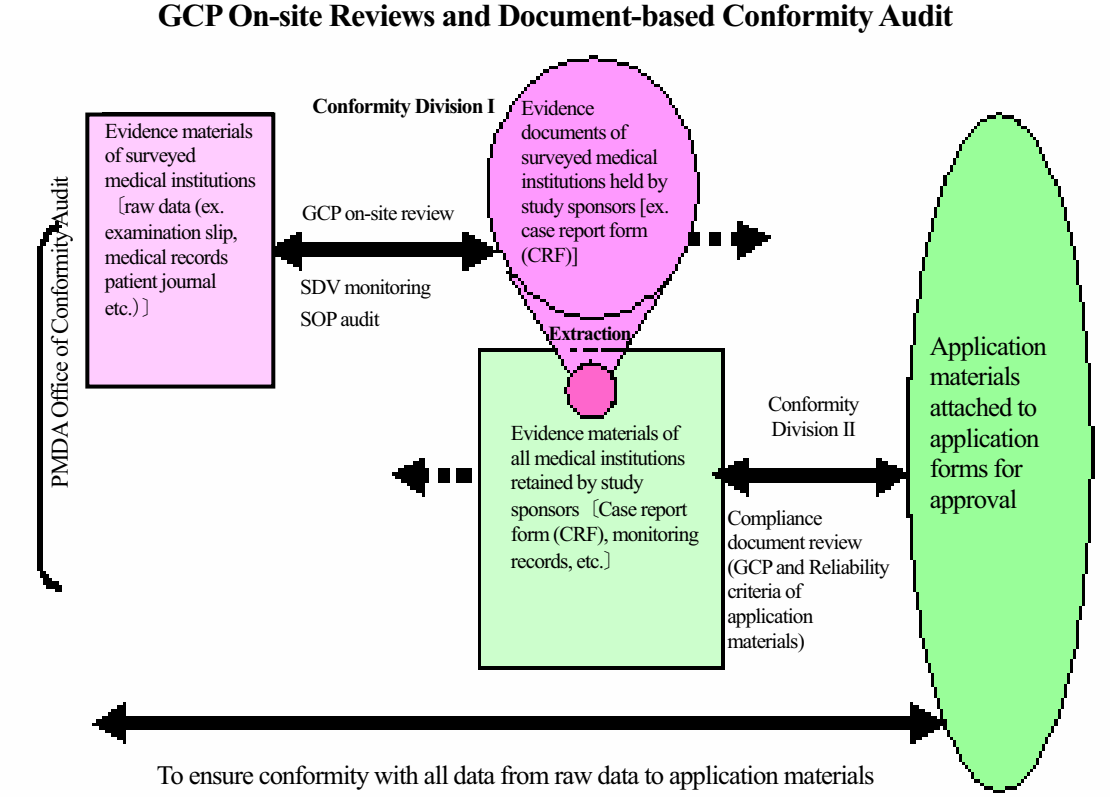
- The Agency efficiently reviewed the materials included in new drug and medical device applications for approval to ensure that such materials comply with GLP (Good Laboratory Practice), GCP (Good Clinical Practice), GPMSP (Good Post-marketing Surveillance Practice) and the reliability criteria.

- The Agency reviewed the documents and data included in new drug and medical device applications to determine if the studies that are the basis of the materials were implemented ethically and scientifically according to the appropriate guidelines such as GLP, GCP and adequate protocols, and if the application materials were prepared appropriately and accurately in accordance with the reliability criteria.

- Japan, the United States and the EU have a common understanding that the purpose of compliance review on reliability criteria is to ensure that the data in the application materials accord with the raw data such as medical records, X-ray films, clinical examination slips, monitoring records and so on, and that all clinical studies to prove the efficacy and safety of applications are subject to the review.

・ In Japan, the conformity between medical records as raw data and case report forms (CRFs) as basis materials is assessed through GCP on-site reviews performed at specified medical institutions. Under the current system, however, the reliability between CRFs as basis materials and application materials is confirmed by document-based conformity audit for the time being which is conducted on all the medical institutions where the clinical trials were performed. Therefore, such application materials are considered to be consisted with international standard.

GCP On-site Reviews and Document-based Conformity Audit



【Annual changes on the number of compliance reviews】

	FY 2001	FY 2002	FY 2003	FY 2004
Compliance document review	151	189	173	161
GLP review	24	40	24	20
GCP review	120	118	143	73
GPMSP review	116	102	66	27

* The number of GCP and GPMSP reviews in FY 2004 is the number of notifications after evaluation.

・ In order to efficiently carry out document-based or on-site conformity review for application materials, the Agency took the following measures:

1) In the Office of Conformity Audit, the four teams consisting of Compliance document review,

GCP, GPMSP, and GLP review teams were set up to conduct reviews, and a responsible person was assigned to each group.

2) Priority applications and applications with the need of swift review were preferentially reviewed prior to ordinary applications.
3) For the accurate and prompt review, the Agency cooperated in developing the document on GPSP* on-site reviews of pharmaceuticals released by MHLW, and developed the standard operating procedure.

   * With the partial revision of the Pharmaceutical Affairs Law enforced from April 2005, GPSP (Good Post-marketing Study Practice) was established as well as GPMSP (Good Post-marketing Surveillance Practice).

・ Although a standard process time of conformity audit has not been placed, the Agency made efforts not to impact review process time for approvals, and thus no delay in approval reviews caused in FY 2004.

d. Approval review for generic drugs, over-the-counter (OTC) drugs and quasi-drugs

・ According to the notification on standard review process time for approval issued by the MHW (Notification No. 960 by the Director of Pharmaceutical Affairs Bureau (PAB) dated October 1, 1985), the Agency set the standard process time to review applications for generic drugs applied in and after April 2004 as follows:

1) Generic drugs:	12 months
2) OTC:	10 months
3) Quasi-drugs:	6 months

・ As to approval reviews of generic drugs and others, in order to carry out review work and other related work promptly and appropriately, the Agency developed the procedure for application review of generic drugs, OTC drugs, insecticide and rodenticide, and quasi-drugs, and also developed the standard operating procedures for review operations. The committee on progress management of review related operations examined monthly collecting data on the achievement level of targeted process time and informed the results to the review staff.

・ The number of approved generic drugs, OTC drugs and quasi-drugs from FY 2001 to FY 2004 was as follows:

【Annual changes on the number of approved generic drugs and others】

	FY 2001	FY 2002	FY 2003	FY 2004
Generic drugs	3,159	1,831	2,243	3,476
OTC	4,865	2,956	1,934	1,781
Quasi-drugs	5,260	3,605	2,992	2,972
Total	13,284	8,392	7,169	8,229

・ During FY 2004, as to achievement ratio of the targeted standard process time for generic drugs applied on and after April 1, 2004, the Agency processed 100% of the total 1,468 applications for generic drugs etc. within 12 months (1,468/1,468 applications), 83% of the total applications for OTC drugs within 10 months (224/270) and 89% of the total applications for quasi-drugs within 6 months (1,277/1,431); the Agency attained the targeted standard process time (median) indicated in the MHW Notification No. 960 issued by the Director of PAB dated October 1, 1985.

【Results of generic and other drugs reviews in FY 2004】

	No. of Applications	Withdrawals**	Approvals	Ongoing
Generic drugs	(2,966)* 5,958	12	3,476	2,470
Over-the-counter drugs	(2,622)* 4,577	6	1,781	2,790
Quasi-drugs	(1,865)* 4,933	23	2,972	1,938

*) The number in the brackets () shows the number of unprocessed applications, taken over from PMDEC, as of March 31, 2004 and breakdown of the lower number.

**) The number of withdrawals is the number of withdrawn applications submitted in FY 2004.

・ For generic drugs, the Agency reviewed to determine that the application materials for approval comply with the Reliability Criteria by collating them with the raw data such as test records, experiment notes and CRFs.

【Annual changes on the number of compliance document review related to Reliability Criteria】

	FY 2001	FY 2002	FY 2003	FY 2004
Number of reviews	1,129	1,228	1,425	1,090

3. Reinforcement of clinical trial consultation system

The Agency shall improve its pre-application consultation process and give priority to conducting clinical trial consultations for pharmaceuticals and medical devices expected to be highly useful in order to

shorten the period of time to their approval.

a. Establishment of priority consultation system

- The Agency established the priority clinical trial consultation system, and conducted to introduce such services and pre-survey of application materials; thereby increasing opportunities to provide guidance and advice at the pre-application stage.

- The Agency introduced the priority consultation system for pharmaceuticals and medical devices considered to be especially important from a medical standpoint. As for clinical trial consultations for drugs, the Agency received priority consultation applications of 9 ingredients during FY 2004 and conducted priority consultations on 7 ingredients of them designated as such subjects. Among these designated ingredients, the Agency provided a face-to-face advice for an application of the two ingredients (for the same combination therapy) in December 2004.
  ※ The Agency received no applications for priority consultations of medical devices and also no applications for face-to-face advices of compliance review on application materials of drugs and medical devices designate as priority consultation items.

b. Acceleration of clinical trial consultations for pharmaceuticals

- The Agency was to work to expedite clinical trial consultation procedures through shortening the duration from application for clinical trial consultation to face-to-face consultation and accelerating the pace of first face-to-face consultation for priority clinical trial. In order to properly manage these operations, the Agency took appropriate measures by developing the operational procedures, making self-check-up on compliance with the manual and informing relevant staff about the observance situations.

- In FY 2004, the Agency aimed to conduct; 1) 45% of the face-to-face advices within 60 business days since requests for consultation were made, 2) 10% of confirmation of records on the face-to-face advices within 30 business days since the advices were made and 3) 50% of the first priority consultation for clinical trial within 30 business days since requests for consultation were confirmed.

- The number of clinical trial consultations for pharmaceuticals conducted in FY 2004 was 193; considering the business days, the Agency processed almost the same application amounts as the previous years. However, the actual results were not reached to the targeted level of FY 2004. The Agency conducted; 1) 29.5% of the face-to-face advices within 60 business days since requests for consultation were made (57/193 applications), 2) 9.8% of confirmation of records on the face-to-face

advices within 30 business days since the advices were made (19/193 applications) and 3) 40% of the first priority consultation for clinical trial within 30 business days since requests for consultation were confirmed (2/5 applications).

・ Major factors in this result was that expectations and demands for clinical trial consultations significantly increased due to the integration of the consultation and approval review, and applications for clinical trial consultations and implementation of the consultations which were suspended during 2 months of transition period in PMDA establishment were added. Therefore, the number of applications for clinical trial consultations in FY 2004 increased by 50% to 334 from the previous year, which exceeded the Agency's capacity for operating consultations, and as a result, the process time from the applications to the face-to-face advices was prolonged. Though the new system to provide both review and consultation operations in one team took time to be efficiently carried out, the Agency conducted about 210 consultations on a 12-month basis during FY 2004 as usual. At the end of FY 2004, however, appointments for consultations were all filled for more than 6 months, and thus the Agency suspended receiving applications in March 2005 and decided to consider improvement measures such as new method of reception. (The Agency has just issued a notification on the improvement of clinical trial consultations for new drugs as a provisional measure on April 26, 2005, and planned to resume receiving applications for consultations to be conducted after October 2005 according to the new method from July.)
◆http://pmda.go.jp/gyoumu.html#sho◆

【Annual changes on the number of clinical trial consultations】

	FY 2002	FY 2003	FY 2004
No. of consultation applications	246	185	334
No. of conducted clinical trial consultations	225	206	193

4. Promotion of international harmonization

・ The Agency shall endeavor to accelerate reviews of new pharmaceuticals taking into account international trends so that by the end of the current Midterm Targets period, it can establish a target time for total review time (process time of the reviewer side plus that of the applicant side for products approved in that year) for the next Midterm Targets period.

a. Approach to international harmonization in ICH and others

・ In the FY 2004 plan, the agency targeted to actively attend ICH Steering Committee Meetings and Expert Working Groups, and to promote the consistency and harmonization of its practices and requirements with such international standards/guidelines as those for the development of review

data which have been agreed among Japan, the US, and the EU in ICH Meetings.

- Based on discussions with MHLW, the Agency considered establishing systems in which the Agency is able to exchange information on consultation, review and post-marketing safety measures with its counterparts in the US and the EU, and also installing facilities for telephone and/or video conferencing.

- The Agency actively cooperated to promote the consistency and harmonization of its practices and requirements with international standards/guidelines by attending the Steering Committee Meetings and Expert Working Groups of ICH, GHTF.
    * ICH: The International Conference on Harmonization (on drugs).
    * GHTF: The Global Harmonization Task Force (on medical devices).

【International conferences on pharmaceuticals】

* The Agency attended the following ICH expert working group on review and post-marketing safety measures of pharmaceuticals:
    - Electronic Standards for the Transfer of Regulatory Information (M2)
    - Data Elements for Transmission of Individual Case Safety Reports (E2B)
    - Pharmacovigilance Planning (E2E)
    - Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process (Q5E)
    - The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs (E14)
    - The Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Internal Prolongation) by Human Pharmaceuticals (S7B)
    - Pharmaceutical Development (Q8)
    - Immunotoxicity Studies For Human Pharmaceuticals (S8)
    - Quality Risk Management (Q9)
    - Regulatory Acceptance of Pharmacopoeial Interchangeability (Q4B)
    - The Pharmacopoeial Discussion Group (PDG)
    - Data Elements and Standards for Drug Dictionaries (M5)

    * MedDRA (Medical Dictionary for Regulatory Activities) Steering Committee Meeting
    * MedDRA SMQ (Standardised MedDRA Queries) Working Group meeting
    * WHO's International Drug Monitoring Center meeting
    * APEC conference in Seoul

【International conferences on medical devices】

The Agency attended the following meetings on review and post-marketing safety measures of medical devices:

- GHTF Meetings (6 times)
- ISO/TC 194 General Assembly in Norway (June 2004)
- ISO/TC 194 meeting in Berlin (February 2005)
- OECD GLP Working Group meeting in the US (February 2005)

- In order to efficiently exchange information, the Agency installed and actively used speakers for telephone conferencing. For video conferencing, the Agency shall decide to purchase the equipment considering the frequency and its necessity.

b. Introduction of total review time

- The Agency shall monitor/manage total review time taking into account international trends to improve its operations,.

- As for management of total review time for NDAs, the Agency confirmed the total elapsed review time with the applicants on the 49 applications approved during FY 2004. As a result of the calculation, the median total review time was 411.0 days (13.7 months).

- The Agency reinforced consultation/pre-application consultation functions to solve as many basic problems as possible at pre-application stage, and interviewed and advised applicants to withdrawal of the unprocessed applications because of failures on the applicants' side.

(2) Improvement in Reliability of Operations

1. Planned recruitment of staff with high levels of expertise and systematic provision of opportunities for training

a. Staff recruitment

- In order to ensure smooth enforcement of the revised Pharmaceutical Affairs Law in 2005, and to conduct reviews and post-marketing safety operations promptly and appropriately, the Agency recruited competent human resources with high levels of expertise, mainly through open recruitment. Recruiting was done with due consideration to the impartiality of the Agency (refer to "PART1, (4), 4 Recruitment of human resources through open recruitment" on page 23).

b. Systematic training

・ The Agency has provided staff members with training opportunities through internal/external training organizations, in a systematic fashion, in accordance with the operations and service goals, and thereby worked to improve the quality and capability of staff members (refer to "PART1, (4), 2. Systematic implementation of training" on page 20).

2. Development of GMP review system

・ The Agency has conducted GMP reviews to assure that drug manufacturers and importers licensed by the Minister comply with standards for the manufacturing control and quality control of pharmaceuticals, quasi-drugs and medical devices [GMP Compliance Reviews under the old Pharmaceutical Affairs Law], which had been undertaken by the Regional Bureau of Health and Welfare until FY 2003. The Agency had 70 GMP on-site reviews in FY 2004.

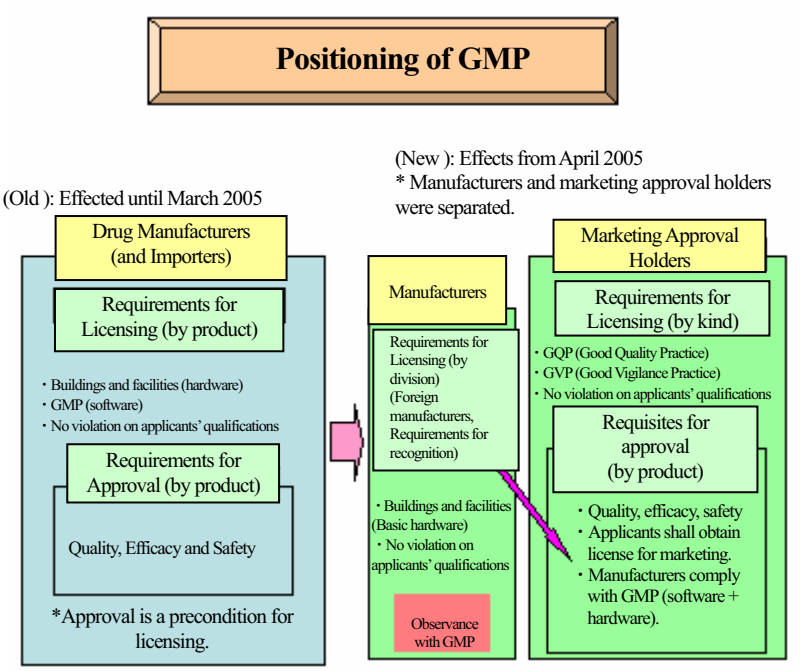
・ The Revision of the Pharmaceutical Affairs Law came into effect April 1, 2005. In the law, manufacturers of drugs and quasi-drugs must comply with requirements of the Ministerial Ordinance on GMP of pharmaceuticals and quasi-drugs and those of medical devices and of the Ordinance on QMS of medical devices and in vitro diagnostics, which were newly established or revised. And the compliance was placed as pre-requisite of marketing authorization. In addition to the current manufacturers licensed by the Minister, the following manufacturers will also become subject to the new GMP/QMS on/off-site reviews to be conducted by the Agency: 1) foreign manufacturers related to all products that require regulatory approval; 2) domestic manufacturers related to new drugs, new medical devices and Class IV medical devices (high-risk medical devices such as pacemakers). Under such circumstances, the number of the related reviews is expected to increase significantly.

* Ministerial Ordinance on GMP of pharmaceuticals and quasi-drugs:
  Standards for the Manufacturing Control and Quality Control of Pharmaceuticals and Quasi-Drugs (MHLW Ordinance No. 179, 2004)
* Ministerial Ordinance on QMS of medical devices and in-vitro diagnostics:
  Standards for the Manufacturing Control and Quality Control of Medical Devices and In-vitro Diagnostics (MHLW Ordinance No. 169, 2004)

・ The number of GMP/QMS compliance reviewers was 6 when the Office of Compliance and Standards was established on April 1, 2004. As the Agency has continued to recruit staff, however, the number of GMP/QMS reviewers increased to 18 as of April 1, 2005. At the same time, in order to reinforce their expertise, the reviewers participated in training programs offered by the National Institute of Public Health and MHLW, conferences held by the Pharmaceutical Quality Forum and the

Japanese Society for Virology, and conducted on-site review training at manufacturers of pharmaceuticals and medical devices in the US, the EU and Asia.

・ While developing the Standard Operating Procedures for conducting GMP/QMS compliance on-site reviews, the Agency studied practical and efficient off-site review methods e.g., conducting, in principle, only document reviews for foreign manufacturers (limited to manufacturers of pharmaceuticals except sterile and bio-derived products) in the countries with which Japan has concluded mutual recognition agreements (MRA), e.g., regarding pharmaceutical GMP with 15 EU countries.



3. Effective use of external experts

・ For review operations, the Agency shall use external experts with appropriate knowledge especially in the highly specialized fields. At the expert discussions for review, the Agency asked for the professional advice on scientifically important matters from the assigned external experts. (The number of the assigned advisors is 789 as of March 31, 2005.)

4. Establishment of information support system

・ To improve the quality of its review operations, the Agency shall integrate information on review and post-marketing safety operations and establish an information support system to facilitate these operations. Therefore, the review and post-marketing safety departments decided to share necessary information through the Information System Management Committee. For this purpose,

the Agency improved the current information system so that staff of the review department can refer to the data on adverse drug reactions which are extracted daily from the database of the post-marketing safety department.

- For smooth enforcement of the revised Pharmaceutical Affairs Law which became effective in April 2005, the Agency developed the following new systems in collaboration with MHLW:
  1) Development of electronic formats (the number of formats: 181) to be used under the revised Pharmaceutical Affairs Law
  2) Development of electronic registers of approved products, etc (register of approval, register of products required no approval, and register of drug master files etc.)
  3) Linkage between the above electronic registers
  4) Linkage between the main system (the new information system of application and approval review) commonly used by MHLW, the Agency, and local governments etc. and the operating system used solely by the Agency (on information on time-clock management etc.)
  5) Development of functions concerning new operations
  6) Improvement of electronic output functions for existing operations
  7) Computerization of paper-based information on approved products
  8) Installation of networks and servers to enhance information security

5. Strengthening of partnership with foreign regulatory authorities

- The Agency aimed to strengthen its relationships not only with the regulatory authorities of the US and Europe, but also with those of Asian countries where clinical trials are conducted, by establishing a new division dedicated to international operations and promoting the exchange of trainees with foreign regulatory authorities.

- In order to strengthen its relationships not only with the counterparts in the US and Europe, but also with those in Asian countries where clinical trials are conducted, the Agency aimed to promote cooperation with the related countries in the development of international guidelines by attending international conferences such as ICH, GHTF and WHO. The Agency also provided lectures on its review and safety operations at the APEC conference in Seoul and other conferences to improve international recognition of the Agency (refer to No. 2, 2, (1), 4.). The Agency also implemented the following measures to strengthen its relationships with foreign regulatory authorities:
  1) The Agency collected information on review system of the US FDA (Food and Drug Administration), EMEA (European Medicines Agency) and MHRA of the UK (Medicines and Healthcare products Regulatory Agency). With the FDA and MHRA, the Agency also exchanged information on the regulations in their countries, their methods of conducting operations and

other matters.

2) The Agency established detailed rules about dispatching the reviewers to foreign regulatory authorities on a long-term basis. Based on the rules, the Agency dispatched a reviewer to foreign regulatory authority after inviting applicants and selection.
3) The Agency accepted one trainee from US FDA and four trainees from the Indonesian regulatory authority.

6. Evaluation of such advanced technologies as biotechnology and genomics / cooperation in developing the national guidelines

- It is required for the Agency to raise the level of guidance and review techniques for such advanced technologies as biotechnology and genomics. The Agency utilized high knowledge of external experts effectively to review such technologies and cooperated in developing the government's review guidelines for new technology-based products.

- For the above, the Agency cooperated in developing the government's guidelines to evaluate new technology-based products such as recombinant live virus vaccines.

- In order to study the effect on the safety and efficacy of drugs caused by genetic factors of individual patients, and to administer medicines to patients in more appropriate conditions, Pharmacogenetics/Pharmagenomics is expected to be applied to drug development. However, there are still many things to be considered, such as how to apply Pharmacogenetics/Pharmagenomics to clinical trials and review operations. While collecting information from scientific point of view, the Agency cooperated in developing the government's notification regarding information provision to administrative agency related to development of its guideline for the use of Pharmacogenetics/Pharmagenomics in clinical trials of pharmaceuticals.

7. Promotion of appropriate clinical trials

- To improve the quality of domestic clinical trials, the Agency decide to conduct enlightening activities to promote appropriate clinical trials by educating healthcare professionals and patients through its website and public relations, taking into consideration the results of on-site reviews on clinical trials at medical institutions, etc.

- For this purpose, the Agency collected data from the leaflet titled "For the development of new drugs: What is a clinical trial?" supervised by MHLW and explanations on systems for clinical trials of drugs under the Pharmaceutical Affairs Law, and posted them on its website.

- In order to help improve clinical trial systems at medical institutions, the Agency provided pharmacists and nurses of medical institutions with a training for Clinical Research Coordinators– the training was composed of lectures in September 2004 and practical training from October 2004 to February 2005.

- Also, to promote effective clinical trial systems, the Agency decided to grant subsidies to core medical institutions which conduct clinical trials efficiently by collecting/compiling information on clinical data and responding to severe adverse reactions from clinical study drugs in cooperation with local core hospitals, clinics and SMOs (Site Management Organizations).

- In FY 2004 as the first year of implementation of its three-year plan, the Agency developed application guidelines for the above mentioned grant and accepted applications through its website etc. Through discussions at the Selection and Review Committee on Regional Network Program for Clinical Trial Promotion, the Agency selected the following two facilities:
  - Chiba University Hospital (Chiba-shi, Chiba)
  - Specified Medical Corporation Shouwakai, Brain Attack Center Ota Memorial Hospital (Fukuyama-shi, Hiroshima)

- The Agency disclosed the information on instructions/suggestions often made during GCP on-site reviews on the website. Also, the Agency delivered lectures at academic conferences so that it would help improve the quality of clinical trials.

8. Timely provision of information including review reports

- In promoting transparency of its operations to the public, the Agency has, with understanding of and in cooperation with related companies, posted review reports of “Drug Information Provision System” to its system, which include results of priority reviews and information on approval of new drugs in order to swiftly provide information about pharmaceuticals after the approvals. Also, to provide the public with information regarding its review and post-marketing safety operations, the Agency has, in cooperation with MHLW, posted information on approval of new drugs etc. on the Review-related Contents section of its Pharmaceuticals and Medical Devices Information website in the following manner:

(Review reports on new drugs)

- Based on the contents of the applications, new drugs are classified into two types: the applications to be discussed by and reported to the Drug Committees of the Pharmaceutical Affairs and Food Sanitation Council (PFSC) (hereinafter referred to as “the Discussed Applications” and “the Reported Applications” respectively).

Among data on newly approved pharmaceuticals, with regard to the Discussed Applications, the Agency shall disclose review reports which describe the process and results of the reviews, plus summaries in which the attached materials submitted by applicants are summarized by them; with regard to the Reported Application Materials, the Agency shall disclose review reports.

- Based on the Notification of the Evaluation and Management Division of MHLW (Shinsa Kanri Kacho) the Agency shall disclose information on new drugs after conferring with related companies on the information to be disclosed for each application.

- In FY 2004, the Agency confirmed the public disclosure versions of 35 review reports and 16 summaries of application materials.

- During FY 2004, in order to help related companies make the draft of summary of application materials to be confirmed for public disclosure (the masked versions) and accelerate the disclosure, the Agency put together the results of discussion established through dialogues with related companies and made points to consider when drafting masked version for public disclosure, which includes a rule that specifies which information must be disclosed.

(Review reports on new medical devices)

- The Agency also planned to sequentially disclose review reports on new medical devices according to the procedures to be specified in the Notification of MHLW.

- In FY 2004, for one application that needed disclosure with priority, the Agency confirmed the public disclosure version of review report based on discussions with related companies.

- For review reports on the medical devices that had been approved in and before FY 2004, the Agency aimed to provide information same as the above and proceeded with the preparatory work (data collection, development of documents to be disclosed etc.) for this purpose.

- In order to help related companies understand the standards of quality of application materials which are required for new medical devices review, the Agency posted the seminar documents as “Information for those who consider applications for approval and pre-application consultation of medical devices” on its website.

  ◆ http://www.pmda.go.jp/shounin/iryoshinseisoudan.html◆

(As of the end of FY 2004)

Report Items	No. in the website(posted on the website)
New Drugs	
Review Reports Discussed at the Drug Committees	137 ingredients (308 applications)
Review Reports Reported to the Drug Committees	80 ingredients
Re-evaluation Results on Quality	427 ingredients or formulations (3,513 applications)
Re-evaluation Results on Drugs	187 ingredients (606 applications)
New Medical Device	
Review reports on Review Item	1 application

◆ http://www.info.pmda.go.jp/info/syounin/index.html◆

(3) Reinforcement of Post-Marketing Safety Operations (Reinforcement of information management and emergency management system)

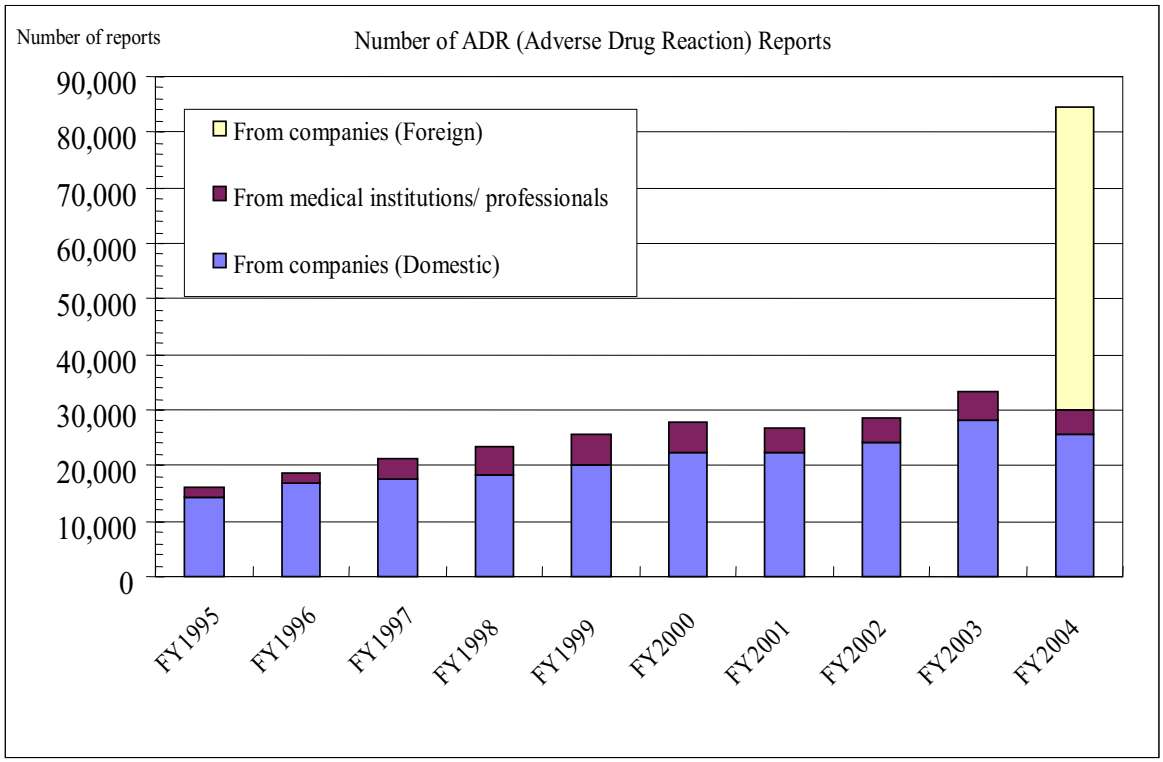
1. Basic direction of safety measures

- The newly established Agency aims to significantly reinforce its post-marketing safety measures so that both its review and post-marketing safety operations can work as an inseparable pair function.

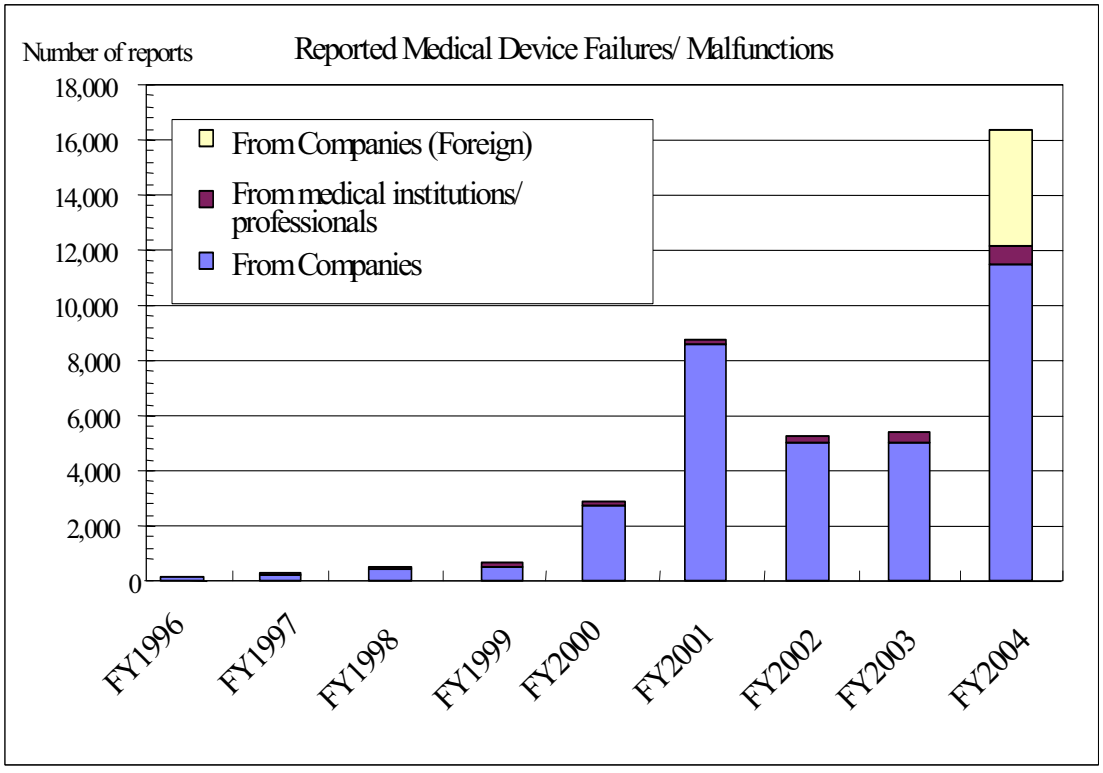
- The number of ADR (Adverse Drug Reaction) reports made during one year reaches as much as 30,000 nationwide and 80,000 worldwide. The Agency could not fully utilized the enormous amount of information because of time and physical constraints.

- The Agency plans to analyze the enormous amount of compiled information more scientifically and objectively by using computer technology and statistical techniques in order to forecast risks and thereby take measures to prevent them at an early stage. The problems in the past have been associated not only with the intrinsic problems/defects of drugs and medical devices but also with the manner in which they were used. The Agency shall provide medical institutions, manufacturers, patients and general consumers with information on proper use of drugs and devices in order to widely disseminate the information.

- As mentioned earlier, the Agency aims to take proactive safety measures by forecasting and preventing risks through scientific evaluation and analysis. In order to enhance its post-marketing safety measures in cooperation with MHLW, the Agency shall establish a department in charge of post-marketing safety operations, assign regular staff who dedicates itself to scientific analysis and evaluation of the data and develop databases.

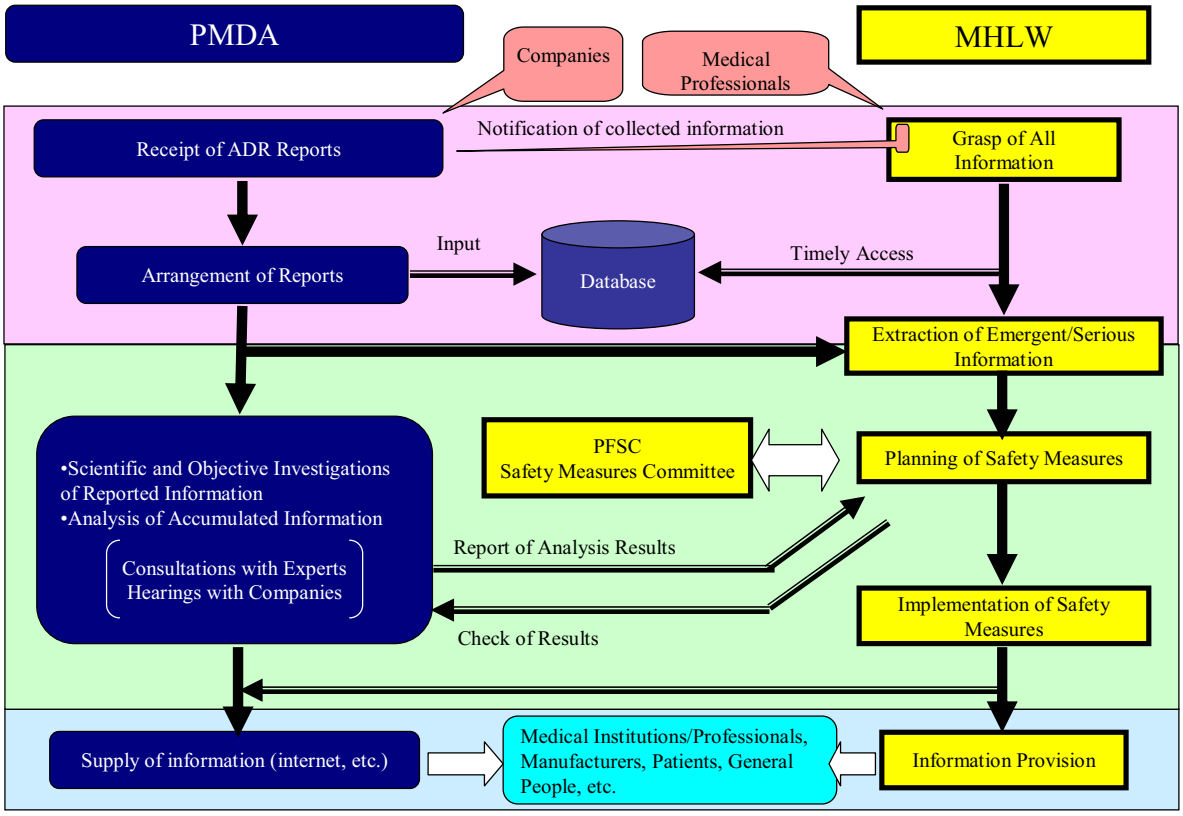


(Note) The company reports (Overseas) were not tallied before FY2004x.



(Note) The Company Reports before FY2004 include overseas reports.

New Safety Measures (Focus on Prediction/Prevention)



2. Introduction of new method (Study to introduce data mining technique)

- By the end of the Midterm Targets period, the Agency shall introduce the data mining technique that extracts the events that frequently concur as highly correlative events from a large amount of data accumulated in a database. The purpose of the introduction is to find new relevancy among multiple adverse reaction information, to study techniques for the detection and analyses of new safety information and to take preventive measures for adverse reactions. The word “data mining” describes the activity of accessing very large volumes of data (=database) just as a mine to retrieve only useful information.

- In FY 2004, the Agency clearly defined the data mining method to be used for Agency operations as “the advanced method to contribute to post-marketing safety measures focusing on basic signal extractions” and posted the result of discussion on its website.

- In particular, the data mining method is to detect combinations (signals)* of drugs and ADRs with likely causality” from the database of ADR reports. The retrieved signals shall be evaluated by clinical and other experts and utilized for taking appropriate measures. This new technique can be

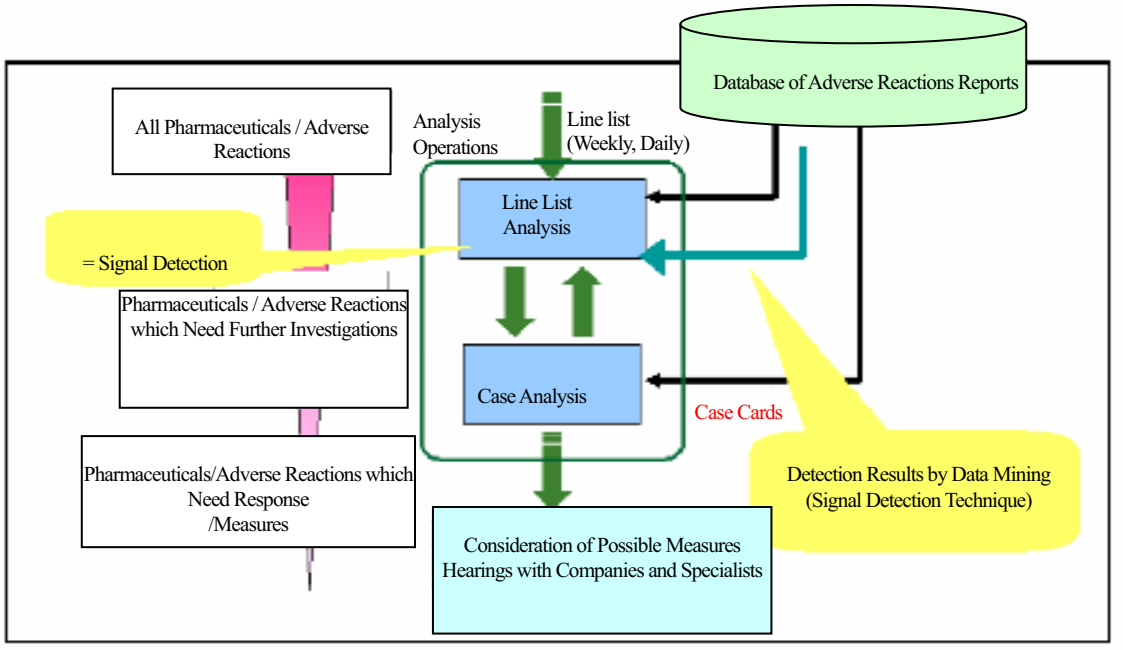
expected to become an operational support tool which enables staff in charge of post-marketing safety measures to find signals at an early stage.

* Interaction of multiple drugs is also included.

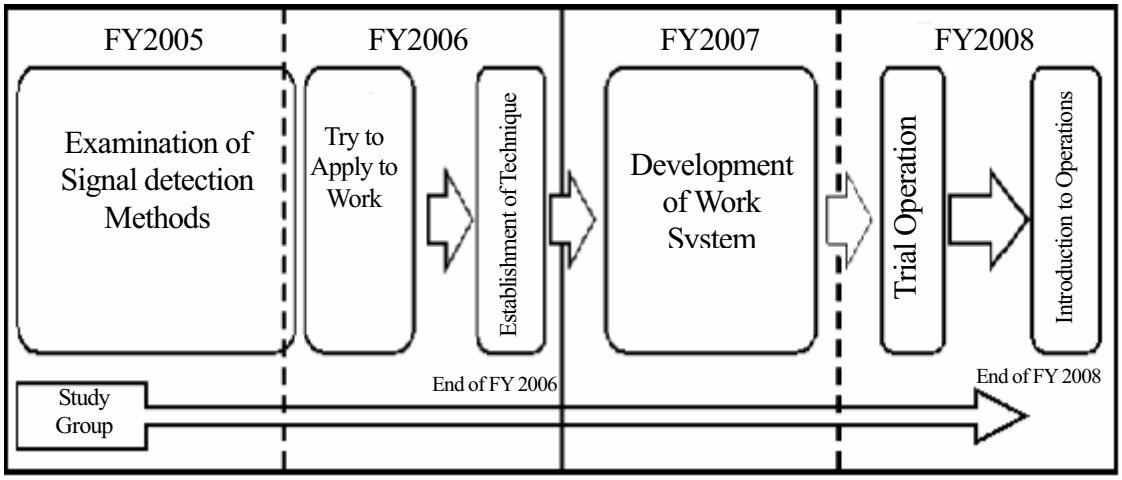
- According to the plan, by the end of FY 2006, the Agency shall establish the advanced method that can detect signals concerning concomitant drugs and demographics of patients (e.g. sex and age), in addition to the basic detection method that is being introduced to foreign countries. By the end of the Midterm Target period (FY 2008), the Agency will introduce the method into post-marketing safety operations.

- The support for this project was contracted to an outside think tank. This plan was also evaluated and reviewed by external experts. Also, staff of the Agency participated in a study group for signal extraction of MHLW to gather related information.

Application of data mining technique to safety measure operations



Schedule of introduction of data mining technique to operations (Plan)

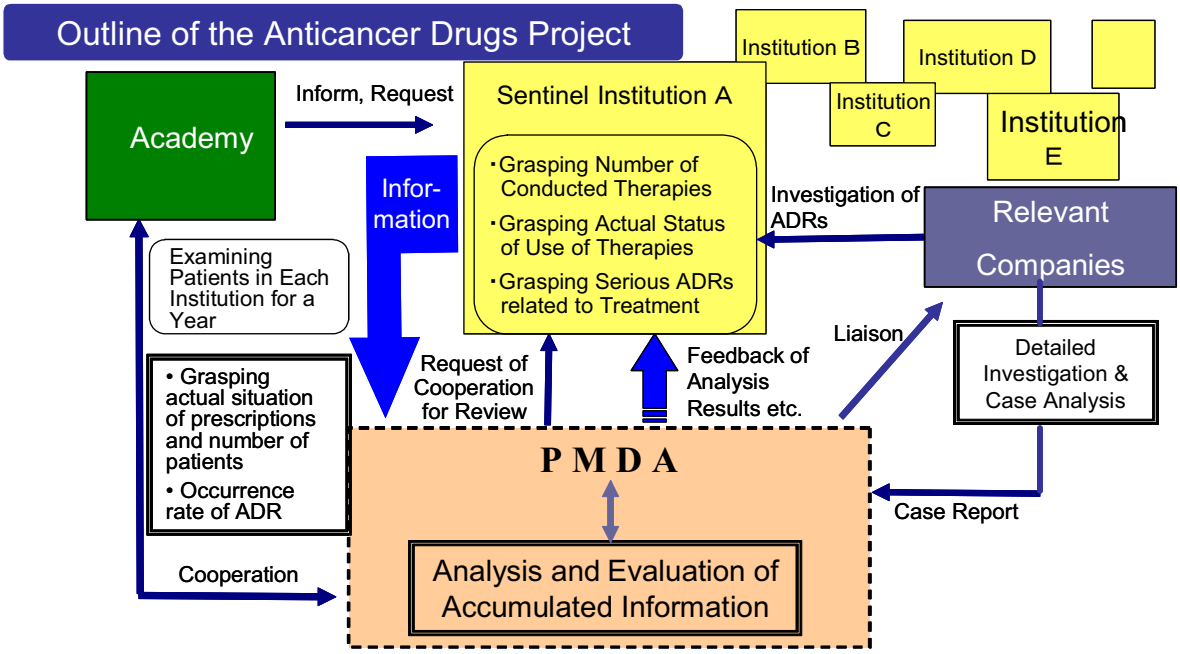


3. Establishment of sentinel medical institution network

・ During the Midterm Plan period, the Agency planned to establish a Sentinel Medical Institution Network as a new system to focus its post-marketing safety measures.

The network aims to collect information intensively within a certain period of time from the medical institutions organized by specific therapeutic category, product and disease in cooperation with the review department to improve the accuracy of analysis of ADR information.

・ In FY 2004, the Agency decided to conduct a fact-finding survey to investigate the actual conditions of use of 22 anti-cancer combination therapies. The investigation committee of MHLW discussed anti-cancer combination therapies. The Agency has proceeded with the preparation in cooperation with MHLW by holding briefings for medical institutions to participate in the survey and negotiating with relevant academic societies and pharmaceutical industries.



[Reference] Reviews about the actual situation of combined therapies of anti-cancer drugs

Symptomatic therapy (22* therapies)

*) Due to the classifications based on the implementation methods of this review, to the method of counting is unique to the Agency.

1	AC therapy (Breast cancer)
2	Pamidronate Disodium (Breast cancer)
3 (1)	Ifosfamide single therapy (Bone and soft tissue tumor)
3 (2)	Doxorubicin single therapy (Bone and soft tissue tumor)
3 (3)	Ifosfamide and doxorubicin combination therapy (Bone and soft tissue tumor)
4 (1)	Ifosfamide (Pediatric solid tumor)
4 (2)	Doxorubicin (Pediatric solid tumor)
4 (3)	Etoposide (Pediatric solid tumor)
5	AP therapy (Uterin corpus cancer)
6	Cisplatin (Malignant bone tumors)
7	VAD therapy (Myeloma)
8	Fluorouracil (Head and neck cancer)
9	Procarbazine/vincristine (Brain tumor)
10	Fluorouracil/leucovorin (Colon cancer)
11 (1)	ESHAP (Malignant lymphoma)
11 (2)	DHAP (Malignant lymphoma)

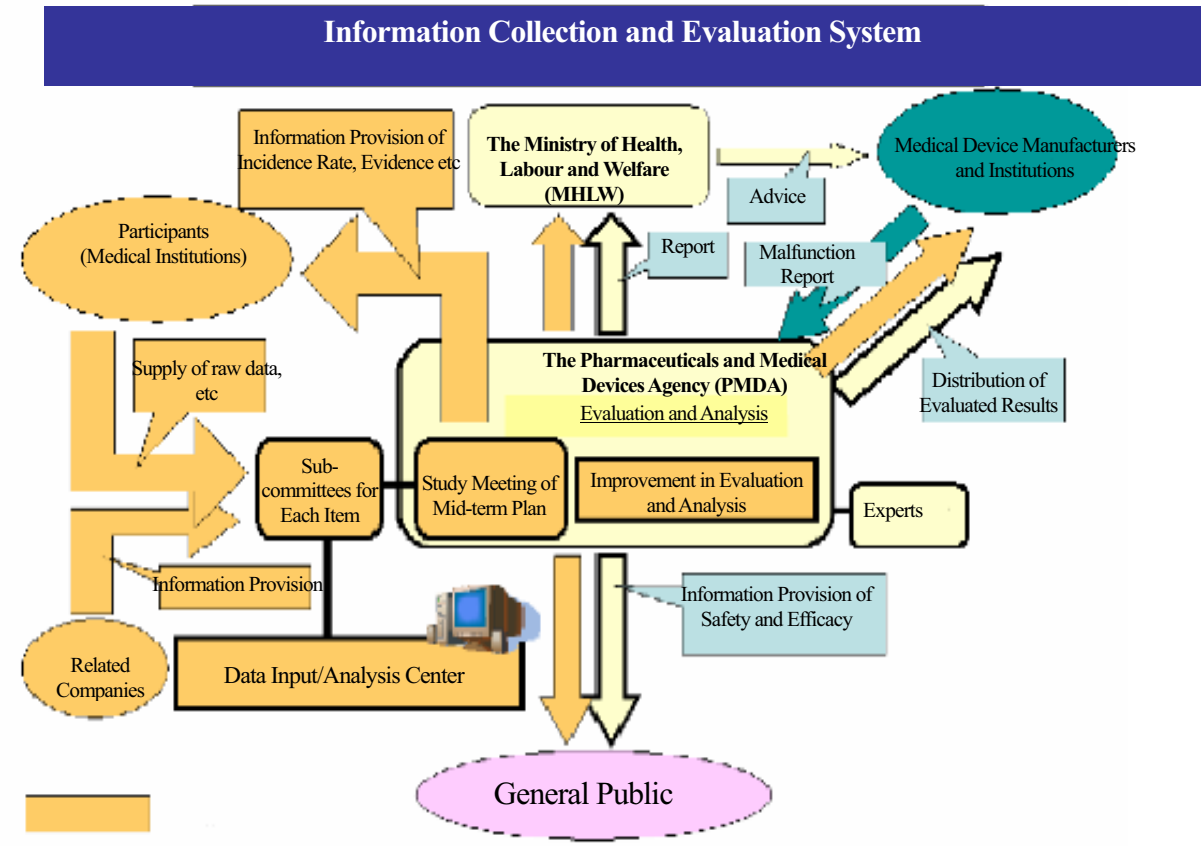
12 (1) Cisplatin (Pediatric solid tumor)
12 (2) Carboplatin (Pediatric solid tumor)
12 (3) Cisplatin (Medulloblastoma)
13 Actinomycin (Ewing's sarcoma family of tumors)
14 (1) EC therapy (Breast cancer)
14 (2) CEF therapy (Breast cancer)

4. Study on system for information collection and review on medical device malfunctions

- The Agency shall be aware of the certain level of occurrence rate of medical device malfunctions that are not attributable to structural defects but due to their characteristics, and establish a system in which scientific evaluation on such malfunctions is conducted. The Agency held a committee composed of health professionals and scholars in which coronary stent and implantable drug infusion instrument were chosen as subjects for the pilot study, and arranged the work schedule for this project.

- For high-risk implantable medical devices that require tracking* such as implantable pacemakers, the Agency shall establish a system to collect and evaluate data regarding the operational status of medical devices such as the malfunction rates over time. The Agency has gathered information on this matter by attending meetings of a research team and working groups under MHLW. Furthermore, the Agency has classified the name of malfunctions of designated devices from the malfunction database and developed a malfunction name list and a classification list of the designated devices malfunction.

* Medical device tracking is intended to ensure that manufacturers of certain devices can locate the users of those devices, in case that corrective action or notification about such devices becomes necessary. The manufacturers store and manage the information on the use of designated devices. Under the Pharmaceutical Affairs Law, such devices are referred to as designated medical devices.



5. Proper examination of reports on ADRs and medical device malfunction

・ The Agency conducted the following measures to appropriately collect, arrange and examine the reports on ADRs and medical device malfunctions submitted by companies and medical institutions:

1) To conduct reception/data-inputting operations efficiently, the Agency:
   a. Raised online reporting rate (69.1% on a full-year basis) by asking those companies that had not yet reported online for their cooperation and reduced the workload associated with data inputting.
   b. Changed the layout of the reception counter.
   c. Introduced and operated an input code checking system.
   d. Introduced an efficient storage system of electronic reports from medical institutions.
   e. Increased the number of staff designated to input data.
   f. Updated the master files of drug and company names.
2) To clarify the method of applying for consultations and the matters to be consulted upon, the Agency posted application forms concerning consultation operations on its website.
3) To improve the quality of staff in charge of collecting/arranging/examining reports, the Agency encouraged such staff to attend academic conferences (29 staff members attended 22 conferences in total) and gathered information on the conferences.

4) While cooperating with MHLW efficiently, the Agency established standard operating procedures for related operations.
5) The Agency held liaison meetings on drugs and on devices every week respectively to exchange information and discuss with MHLW.

6. Computerization of reports on ADRs and medical device malfunctions

a. Improvement of online reporting rate

・ In order to collect information concerning safety measures effectively and efficiently by utilizing IT, the Agency established the system and asked companies for their cooperation to improve the online reporting system of information on ADR/infections which was commenced from October 2003 adopting the forms specified by ICH standards. The target rate of online reporting system in FY 2004 was 60%.

・ For this, while improving environment for electronic transmission of information by introducing and providing an online reporting system on its website, the Agency monitored the electronic reporting rate monthly and asked major companies that had not yet reported online for their cooperation directly, and also promoted the system utilizing lectures at academic conferences. As a result, the reporting rate in FY 2004 exceeded the target of 60% and reached 69.1% on a full-year basis.

b. Development of information system

・ MHLW aimed to develop a system that allows medical institutions, pharmacies and others to report their information on ADRs and infections conveniently via the internet. With the start of this reporting system, the Agency developed a system in which the information processing between the Agency and MHLW can be conducted online.

7. Establishment of post-marketing safety system through information feedback

a. Feedback to companies

i) Companies' access to information concerning ADRs from their own products

・ In order to contribute to improve the risk management systems of companies, the Agency is to establish a system that enables a company to secure access to information that pertains to its own products, such as ADR reports provided by medical institutions or reported by other companies as concomitant drugs. During FY 2004, the Agency started considering the basic principles concerning companies' access to information on ADRs owned by the Agency.

ii) Consultations for companies

・ In order to contribute to improve safety measures of companies, the Agency started to provide

companies with consultations concerning drugs, medical devices and medical safety. The Agency established standard operating procedures and implemented consultations for companies concerning preventive measures of serious ADRs, revision of package inserts of their products, the risk management plan on their marketed products and improvement of their products to prevent medical accidents based on analyses of "hiyari-hatto" (near-incident) information.

- The Agency posted electronic application forms for various consultations on its website to improve convenience for companies.

- In order to implement appropriate consultations, the Agency provided its staff members with lectures on drugs that had just been launched in the market, in cooperation with companies. Also, the Agency reinforced its internal organization – assigned 12 expert members and held two review sessions – for analyses of near-incident information collected from the medical arena.

- The Agency cooperated with MHLW in developing a database concerning drugs with similar names.

b. Feedback to health professionals

- During 2004, the Agency took the following measures to disseminate information on ADR and device malfunction cases to health professionals as well as the public via internet etc:
  1) The Agency has disseminated information on cases which led to the revision of package inserts (PIs) for ethical drugs. To expand the information dissemination on new drugs, the Agency discussed with the review departments.
  2) The Agency aimed to post instructions PI revision of ethical drugs on its website within two days after the issuance of the instructions by MHLW. Based on discussions with related sections of MHLW, the Agency developed and implemented the standard operating procedure. As a result, the Agency achieved this target.
  3) For information on revisions of ethical drug's package inserts, the Agency now makes it possible to post 11,706 PIs on the internet at the end of 2004, and also completed to plan and develop a system in which such information would be available via e-mail to health professionals who seek to receive them.
  4) The Agency prepared for establishing a system in which information on attached documents of medical devices can be accessed via internet. In particular, the Agency cooperated in a pilot study conducted by a research team under MHLW (the study on a system for dissemination of information on attached documents for the proper use of medical devices) and established the system by utilizing the know-how which PMDA developed and operated a system to provide drug information. Regarding the number of information posted on PMDA's website as of

March-end 2005, please refer to III SUPPORTING INFORMATION 7. (3) on page 93.

c. Information provision to general consumers and patients

- In order for general consumers and patients to ensure safety and security in the use of drugs and medical devices, the Agency has conducted a consultation service for them regarding those products. As for consultations on drugs, which have been conducted for 10 years by the Agency and its predecessors, in FY 2004, the Agency recruited two more counselors and launched a consultation service during the lunch break. In order to start a consultation service on medical devices for general consumers and patients, the Agency proceeded with the preparatory work such as by hiring counselors for the service through open recruitment and developing the training plan for them. The Agency also examined and developed specifications for a system in which records on medical device consultations are registered, compiled and analyzed.

- For ethical drugs such as self-injections which patients use at home, or for those drugs that may induce serious ADRs and where detection of a patient's subjective symptoms is essential in detecting ADRs at an early stage, the Agency shall reinforce a service to disseminate information on the designated drugs by e.g., patient-instruction documents. For this purpose, the Agency cooperated with a research team under MHLW in that studies on such instruction documents and worked to grasp the current development of the study.

d. Improvement of the contents and quality of disseminating information

- In order to facilitate cooperation with the Relief Funds and the Post-marketing Safety Departments taking the protection of personal information into consideration, the Agency examined a concrete method of cooperation and aimed to conduct consistent safety reviews from approval to relief according to the method. To achieve this aim:
  1) The Agency established the standard operating procedures for related collaborative operations.
  2) Two staff members of the Drug Safety Division served concurrently as members of the Office of Relief Funds to share information and examined if taking safety measures is necessary based on cases that were eligible or not eligible for relief.

In order to ensure optimal cooperation between the Post-marketing Safety and the Review Departments:

1) The staff members attended the following meetings to gather information from review process: the study meeting on ADR found in clinical trials, expert discussions on review, study meetings on products taken up to the Drug Committees, the New Drug Committees I and II, the Committee on Medical Devices and in vitro Diagnostics, the Committee on Medical Materials and the Executive Committee on Drugs.

2) The staff members attended the study meeting on ADR found in clinical trials so that the Drug Safety Division could provide information on ADRs which were reported in early post-marketing phase vigilance.
3) The Agency established standard operating procedures for related collaborative operations.

- In order to improve the information dissemination service, the Agency shall conduct a related survey during FY 2006. Before the survey, to grasp current situation of the information disseminated to general consumers and health professionals:
  1) The Agency decided to monitor the contents/amount of the information provided via the website every month.
  2) The Agency studied the website design to be easily analyzable audience's interest.