II. OPERATION RESULTS / ACHIEVEMENT OF FY 2005

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

(1) Development and Implementation of 2005 Fiscal Year Plan

The Agency is required to develop the Midterm Plan in accordance with the Midterm Targets designated by the Minister of Health, Labour, and Welfare, and the plan needs to receive an approval by the Minister (The first period for the Midterm Targets is between April 2004 and March 2009.). In order to achieve the plan, the Agency is required to develop each fiscal year plan, notify the Minister of the plan and also to make it open to the public.
The Agency has basically performed its operations according to the 2005 fiscal year plan that was finalized by the end of FY 2004 and notified to the Minister.

The Agency needed to notify the Minister of change in its fiscal budget expenditure on March 22, 2006 because the number of new recipients of adverse drug reaction relief benefits exceeded the expected number in the fiscal year.
In addition, the Agency modified the Midterm Plan in response to the Minister's directive on the change of the Midterm Targets regarding " Optimization Plan for Operational Performance and Information System of Incorporated Administrative Agency," the "Major Policies of Administrative Reform," and the " The change in the Midterm Plan and Targets led to no modification in the fiscal year plan 2005.

Besides the interaction with the Ministry of Health, Labour, and Welfare (MHLW), the Agency has developed a better organization and a robust management system in order to demonstrate the performance level that meet the public's expectations.

On April 27, 2005, the Agency announced the following three points as Priority issues for PMDA in FY 2005:
i) Enhancement of Review Operation
ii) Consolidation of Post-marketing Safety Operation
iii) Improvement of Adverse Health Effect Relief Service

In addition, the Agency announced, on October 7, 2005, "the priority issues to be achieved by the end of 2005" in order to steadily perform and achieve the issues specified in the Midterm Plan, the fiscal year plan 2005, and the Priority Issues for PMDA in FY 2005.

It is stipulated that the each ministry in charge should have an "Evaluation Committee on Incorporated Administrative Agency" that takes administrative processing for the agencies under its control. (Article 12 of the General Law on Incorporated Administrative Agency)

The Agency received an evaluation on its performance of FY 2004 on August 30, 2005, by the "Evaluation Committee on Incorporated Administrative Agency" of MHLW with 20 As, 2 Bs, and 2 Cs out of 24 total evaluation items, based on the following scale. (Two Cs are assigned to the evaluation items, "Prompt Relief Services" and "Clinical Trial Consultations") The Agency posted the evaluation on its website and reported it to the Advisory Council which was held in October 2005.

(Note) Five-level scale of S, A, B, C and D with S being the highest

S: Significantly exceeding the level required in the Midterm Targets

A: Exceeding the level recognized in the Midterm Targets

B: Somewhat exceeding the level required in the Midterm Targets

C: Slightly below the level required in the Midterm Targets

D: Apparently below the level required in the Midterm Targets; therefore, needed drastic improvement

On November 14, 2005, the "Committee on Evaluation of Policy and Incorporated Administrative Agency" of the Ministry of Internal Affairs and Communications expressed the following opinion on the evaluation on the Agency by the "Evaluation Committee on Incorporated Administrative Agency" of MHLW;

"The Agency is an organization that aims for higher operational efficiency by consolidating the services of the Pharmaceuticals and Medical Devices Evaluation Center of the National Institute of Health Sciences (PMDEC) and the Organization for Pharmaceutical Safety and Research (OPSR/Kiko), as well as part of the services of the Japan Association for the Advancement of Medical Equipment (JAAME) The Agency should be properly evaluated on streamlining and efficiency of its operations and management based on the original purpose of its establishment."

(2) Efficient and Flexible Operations

1. Operation through target management

Agency has to clarify targets and operational responsibilities of each department, and strive to identify and remedy the problems through managing its operational progress on a daily basis.

The Agency managed its operations according to operating plans that are developed by each responsible office or division based on PMDA's fiscal year plan. (Target Management)

Specifically, each office clarified what to be implemented and concreted actions to be taken in its operating plans to achieve its fiscal year plan (based on the fiscal year plan 2005 of the Agency). Then, the Board of Directors, consisting of the office directors and the other higher level of management and executives, got briefed about the operating plans by the directors, and the plans

were confirmed in April2005.

Moreover, each office presented an interim report on progress of its task operating plan to the Board of Directors from October to November 2005, and also reported from January to February 2006, on the progress of the plan achieved in the period of the first to third quarters of the 2005 fiscal year to the Board. Then, the Agency developed the 2006 fiscal year plan based on these reports.

2. Enhancement of operational and top management

The Agency considers it necessary to strengthen its function to develop strategies for overall operations, as well as the system to manage operations such as risk management and an internal-check; thereby, it has built an organization in which management judgment by the Chief Executive can be speedily reflected in its operations.

Therefore, the Agency ensured communication opportunities for the Chief Executive to clearly see its operation progress and to provide timely management instructions. Concretely, the Agency has regularly held a weekly meeting of the Board of Directors, consisting of office directors, the other higher level of management and the Chief Executive since FY 2004.

The Agency conducted several other reforms. Among them was reorganization of the "Headquarters for Implementation of the Revised Pharmaceutical Affairs Law (PAL)" initiated in July 2004 that led to the "Headquarters for PMDA Reform" as a forum for a discussion to improve the relief services, review system, and the clinical trial environment. The Agency also participated in the discussion in the "Panel on Improving Clinical Trials" led by MHLW and initiated its internal "Committee on Clinical Trial Issues" on August 2, 2005, under the headquarters to identify the issues related to clinical trials from the viewpoint of the authority that directly reviews clinical data in applications.

Moreover, in order to deal with some critical issues to the Agency, such as smooth reviews and timely clinical trial consultations on drugs and medical devices, and to see the progress and improvement in the operations, the Agency established the "Progress Management Committee on Review Operations" headed by the Chief Executive in January 2005. The committee has also hold regular meetings to grasp the review progress of each application and take necessary and timely actions for this fiscal year.

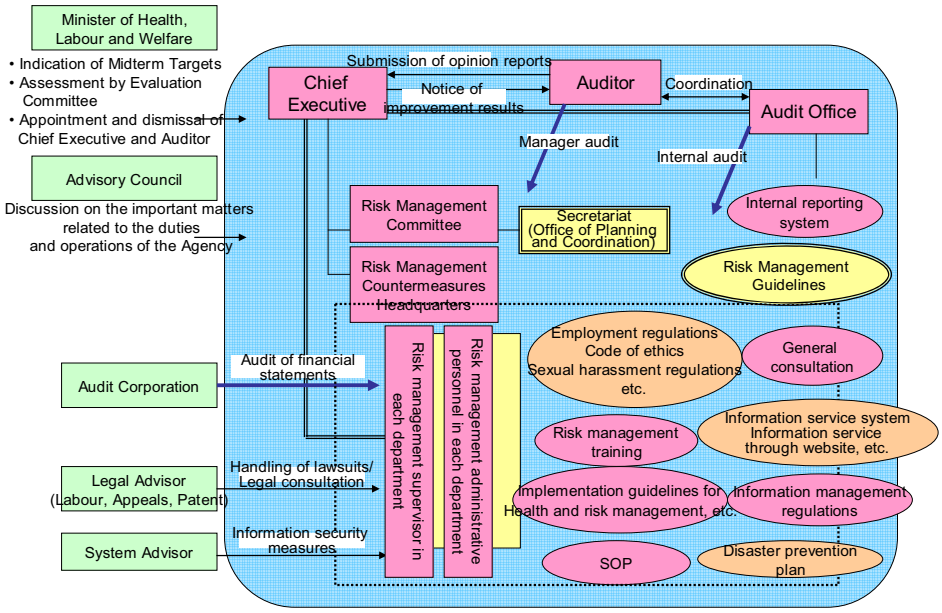
In April 2005, the Agency newly created the Coordination Division, under the Office of Planning and Coordination, which works for operational planning, technical support for performance evaluation and operational coordination, system control center, public relations, and general

consultations on the Agency's operations.

As for the operation management on such as risk management and internal check, the Agency established the "Risk Management Committee" and created guidelines for risk management in January 2006 based on the "Risk Management Policies" developed in FY 2004. In addition, the Agency has established the "Code of Conduct for the staff and Executives", internal auditing and whistle-blowing as a step for strengthening its internal check function. From FY 2005, the Agency assigned a full-time chief auditor, under Chief Executive for the purpose.

Furthermore, the Agency sought to inform its entire staff of disaster prevention plan for the event of fire and earthquake threats.

PMDA Risk Management System



***Risks the Agency faces:**

a. Risks to the Agency

・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 Agency's operations

・Possibility of an event that financially damages or threatens the Agency

b. Risks that the Agency needs to address in its operations

・Risks relevant to the Agency's operations and likely to cause and expand adverse health effects by using drugs, medical devices, quasi-drugs, cosmetics as well as those are subject to clinical trials.

3. Meeting of advisory councils

The “Advisory Council” is a deliberative body (chaired by Masaaki Hirobe, Professor Emeritus of University of Tokyo), consisting of academic and experienced professionals, healthcare professionals, representatives from pharmaceutical and its industries, and representatives of consumers and sufferers from adverse drug reactions. The council allows the Agency to exchange views with a wide range of academic and experienced professionals and to seek their proposals to improve its operations and management system. The Agency made use of these plans and proposals in the council for effectiveness and efficiency as well as fairness and transparency of its operations. The council is expected to discuss form a broad perspectives about its overall operations. Under the council, the “Committee on Relief Services” (chaired by Hideaki Mizoguchi, Director of the Saitama Prefecture Red Cross Blood Center) and the “Committee on Review and Safety Operations” (chaired by Masaaki Hirobe, Professor Emeritus University of Tokyo) were set, and their specific agendas and dates of the meetings during FY 2005 are as listed below;

[Advisory Council] FY 2005

Agenda for 1st Meeting (June 22, 2005)

(1) PMDA Annual Report FY 2004
(2) Priority Issues for PMDA in FY 2005
(3) Financial Report for FY 2004
(4) Others

Agenda for 2nd Meeting (October 17, 2005)

(1) Performance Evaluation for FY 2004
(2) Report on Progress of Major Operations in 1st Half of FY 2005
(3) Priority Issues for PMDA to Be Completed by End of 2005
(4) Others

Agenda for 3rd Meeting (March 6, 2006)

(1) Fiscal Year 2006 Plan (Draft)
(2) Financial Plan for FY 2006 (Draft)
(3) Modification of Midterm Plan
(4) Others

[Committee on Relief Services] FY 2005

Agenda for 1st Meeting (June 2, 2005)

(1) Annual Report FY 2004

(2) Fiscal Year 2005 Plan
(3) Others

Agenda for 2nd Meeting (December 1, 2005)
(1) First Semiannual Report for Fiscal 2005 and Future Perspective
(2) Improvement Plans on ADR Relief Services

Agenda for 3rd Meeting (March 16, 2006)
(1) Fact Finding Report on Health Hazards Caused by ADRs
(2) Summary of Operations in FY 2005 (regarding April to December 2005)
(3) Fiscal Year 2006 Plan (Draft)
(4) Budget Plan for FY 2006 (Draft)
(5) Modification of Budget Plan for FY 2005 (Draft)

[Committee on Review and Safety Operations] FY 2005
Agenda for 1st Meeting (May 31, 2005)
(1) Annual Report FY 2004
(2) Fiscal Year 2005 Plan
(3) Others

Agenda for 2nd Meeting (December 8, 2005)
(1) First Semiannual Report for FY 2005 and Future Perspective
(2) Others

In order to ensure transparency of the listed meetings, these meetings are open to public in principle and the agendas and the materials to the council have been successively posted for the public on the website at http://pmda.go.jp/hyougikai/hyougikaikankei.html

4. More efficient operation system
The agency has aimed to establish a more efficient operation system through both a flexible personnel allocation tailored to situations, and an effective use of external experts.

The Agency successively adopted a team system in the review department that particularly requires flexible responses to situations. The each office director of the department has review directors who supervise some review teams in this system. In addition, the Agency newly assigned a vice review director under a review director to efficiently respond to an increasing number of review teams this fiscal year.

The Agency has invited commissioned external experts since FY2004 to ask for their professional opinions and advices on scientifically significant matters at expert consultations on review and safety measures.
（The number of the commissioned external experts on review and safety measures was 847 as of March 31, 2006.）
Similarly, the Agency also began to invite commissioned external experts to ask for their opinions on adverse health effect from drugs or bio-derived product -caused infections in FY 2005.
(The number of commissioned external experts on adverse health effect was 44 as of March 31, 2006.)

Names of the commissioned external experts are listed on the website, and the list is occasionally updated, when necessary.

Agency also commissioned lawyers and accountants as advisors and employed part-time system engineers in order to provide appropriate operations in the fields that require specific knowledge of law, tax issues and information system, etc. In addition, the effective use of private companies that send staff in the area of operations management of information system, system development of risk control, and introduction of personnel evaluation system resulted in minimizing the number of permanent staff of the Agency.

Since the fiscal year 2004, the Agency has invited commissioned information system advisors who have expertise in the entire information system with the knowledge of pharmaceutical affairs in order to ensure integration and coordination of the Agency's various functions related to its existing information system.

5. Standardization of operating procedures

It is considered the standardization of the various operating procedures enables the Agency to effectively utilize part-time staff and work to limit the number of permanent staff. Therefore, the Agency developed the Standard Operating Procedure (SOP) for its major tasks, and the SOP has been occasionally reviewed and modified. The maximum effort to use part-time employees was made especially for simple and routine works.

6. Development of Information System

The Agency founded the "Management Committee on Information Systems" in fiscal 2005 as a forum to comprehensively discuss development of its entire information system and primary policies on its upgrade. During the fiscal year, the committee discussed operational status of each information system, upgrade of the shared LAN system as its information infrastructure, and improvement of security of the secure e-mail system of the Agency. Also, the Agency promoted

establishment of databases. Among them are the Agency's Regulations Database s that facilitates electronically to provide collected information and to manage and search its contents including revisions. Another example is a database that compiles the inquiries from the general public regarding the Agency's operations. Those improvements enabled the Agency to transfer the written information into electronic format, which allows the Agency to store, retrieve, use and analyze the compiled information and documents systematically and easily. In addition, the Agency started to upgrade a database regarding approved drugs, adverse drug reactions, and failures in order to apply such information widely to its operations.

It is announced that the Optimization Plan of operation and system for incorporated administrative agencies need to be set by the end of fiscal 2007 following the policies addressed by the government. Therefore, the Agency has modified the Midterm Plan based on the directive of MHLW about some change in the targets to be achieved by the Agency. Specifically, the Agency aimed to ensure transparency in reducing the system cost and supplying the system, by reviewing its system components and procurement. In order to steadily achieve this specific target, the Agency has just started to consider necessary steps for development of its optimization plan by assigning a Chief Information Officer (CIO) and commissioning an external expert to assist the development of the plan including assisting the CIO.

In addition, the Agency has promoted posting of some notifications from the Agency and MHLW that are relevant to the Agency's operations or significant to the public on the website at http://pmda.go.jp/notice2005.html

(3) Cost Reduction by Increased Efficiency of Operations

1. Reduction of general management expenses

The agency is expected to steadfastly improve its operations and endeavor to increase its efficiency. (The followings are the required conditions stipulated in the Midterm Plan.)
With restraint of its personnel expenses by reviewing wage levels and reduction of procurement costs, the Midterm Budget Plan regarding the general administrative expenses (excluding retirement allowance) need to take into account the following savings at the end of the effective period of 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 Plan is based on the Midterm Targets on cost reduction specified by the minister. The Agency is expected to develop the fiscal budget plan based on the Midterm Plan and achieve the Midterm Targets by appropriately operating within the planned budget.

In fiscal 2005, in order to effectively perform the budget plan, the periodic salary increase for the Agency's permanent staff has been halted since fiscal 2004 according to the fiscal year plan. In addition, efforts to reduce procurement costs by increasing the number of open competitive biddings helped the Agency achieve the reduction of its general administrative expenses.

[Number of general competitive biddings]
FY 2005: 18 cases (7 of them were regarding general administrative expenses.)
FY 2004: 9 cases (6 of them were regarding general administrative expenses.)

While establishing the better structure to expedite drug approval reviews in accordance with the "Basic Policy for Economic and Fiscal Management and Structural Reform" (Cabinet Decision on June 21, 2005), the Midterm Targets were modified on March 31, 2006, to get along with the policy that specifies "The Agency needs to reduce its personnel expenses by 5% within the next five years according to the Midterm Targets. Additionally, it should review the salary for the executives and staff based on the system reform on salary of national government officials." presented in the "Key Principles for Administrative Reform" (Cabinet Decision on Dec. 24, 2005). Based on the modification, the Agency also modified the Midterm Plan, stipulating that it will reduce its personnel expenses by 5% in the next five years from FY2006 and at least by 3% by the end of 2008, the effective period of the first Midterm Targets.

2. Reduction of project expenses

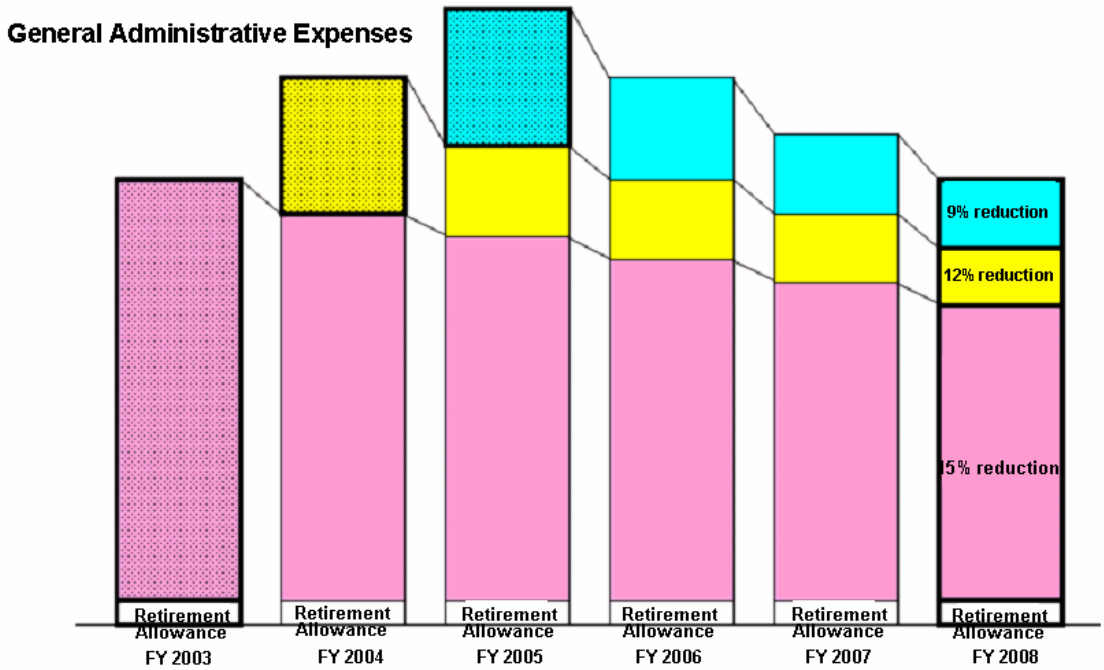
The agency is expected to increase efficiency in operations such as the promotion of computerization.
The Midterm Budget Plan with regard to project expenses (excluding benefit-related expenses, and single-year expenses due to accrue in connection with project launch) needs to take into account the following 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 project expenses due to accrue from FY 2005 in connection with the enforcement of the revised PAL in FY 2005 shall be saved by approximately 3% in comparison with the FY 2005 level.

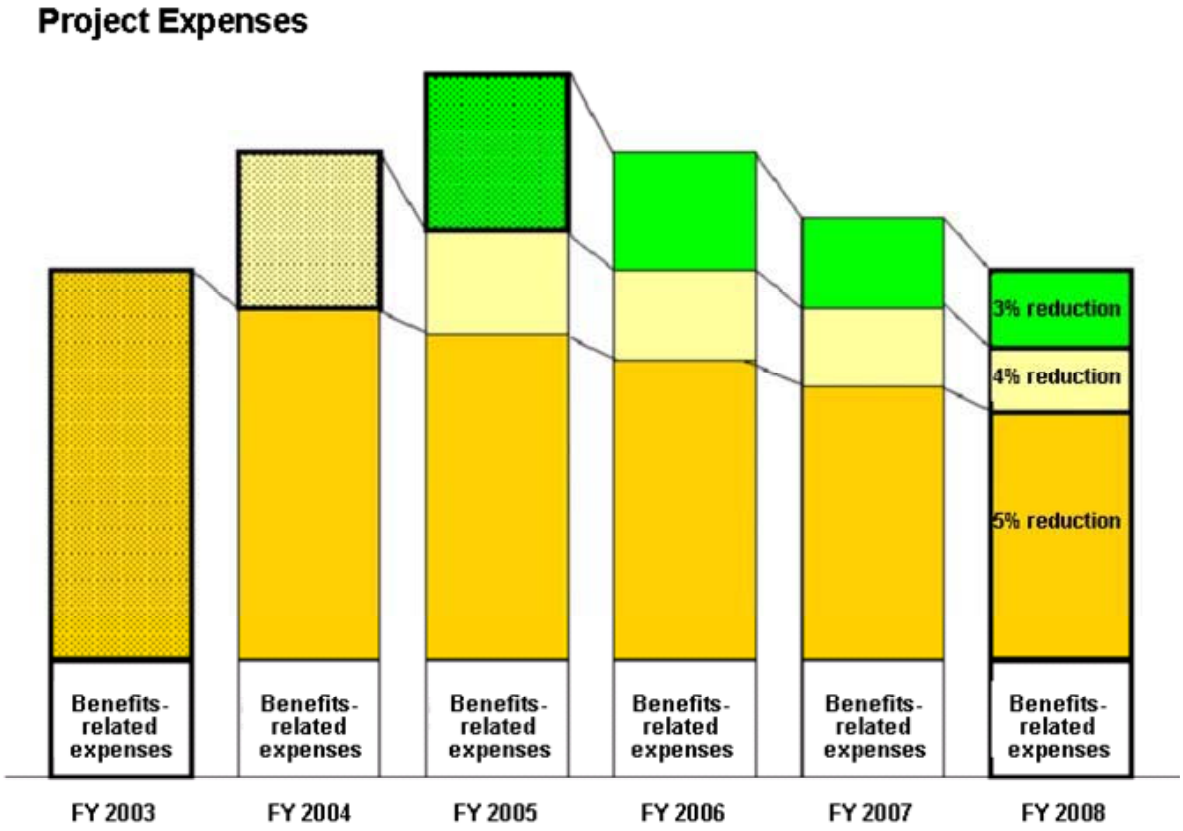
The Midterm Budget Plan for project expenses was also based on the Midterm Targets for cost reductions specified by the Minister. The Agency is to develop the fiscal year plan based on the Midterm Plan and is expected to achieve the Midterm Targets by appropriately operating within the planned budget.

In fiscal 2005, the Agency made an effort while considering the impacts to its operations, to reduce the project expenses by increasing the number of general competitive biddings as well as by reviewing the cost reflecting on the settlement of accounts of FY 2004.

[Reduction in General Administrative Expense and Project Expenses

(Conceptual Figure)





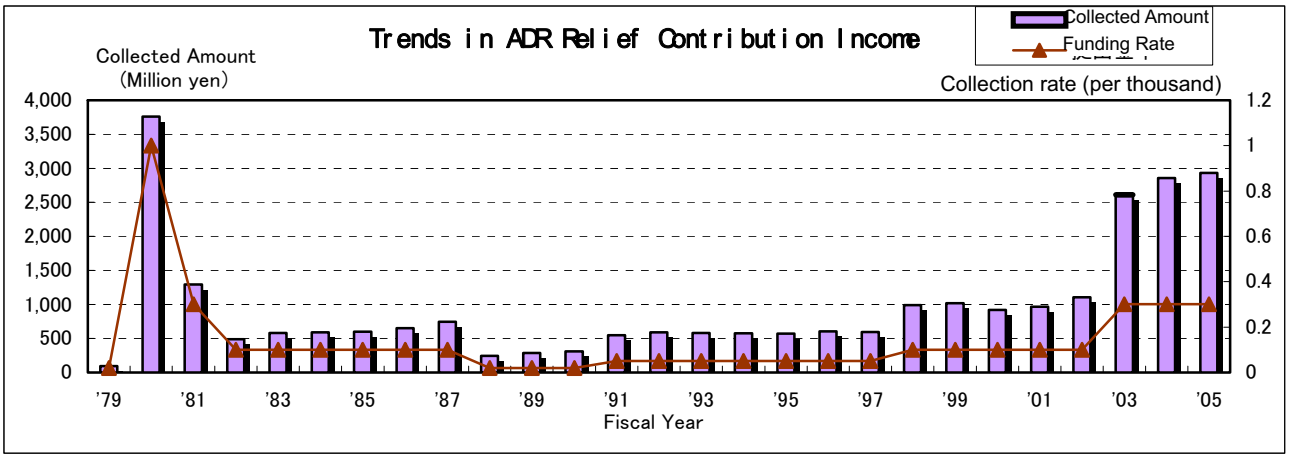
3. Collection and management of contributions

The contributions from marketing approval holders (MAHs) of the industry enables the Agency to ensure its financial resources for adverse health effect relief services for sufferers from ADRs and bio-derived product-caused infections and other operations to improve efficacy and safety of drugs and medical devices. Specifically, the contributions from MAHs of approved drugs are used for the adverse drug reactions relief service, ones from MAHs of approved bio-derived products are used for the infectious diseases relief service, and ones from MAHs of drugs and medical devices are used for the safety measures.

The Agency simplified its operations and promoted its efficiency as well as improved the integrated system to manage collecting contributions for adverse drug reactions, infectious diseases, and safety measures in order to comply with the revision of the PAL.

Specifically, the Agency upgraded its computerized contribution management system on relevant MAHs and product lists to respond to the revision of the PAL. Thereby, that aimed to prevent the Agency from omitting relevant MAHs and declared products, and managed contributions collected and MAHs in arrears. For the purpose of the simple and efficient contribution operation, the Agency also improved the function of the database to take in the basic information on FD, such as

cost account and collected contribution. In addition, the Agency made a contract with the major banks and the post offices for contribution collection in order to promptly transfer the collections and to ensure convenience for the contributors.



The Agency sets the contribution collection rate for ADR and Infectious disease to be no less than 99% in the Midterm Plan. The resulted contribution collection rate for ADR and Infectious disease were 99.6% and 100% respectively in this fiscal year.

On the other hand, the Agency is to raise the collection rate of safety measure contributions to the levels similar to those of ADR and infectious disease contributions by the end of the effective period of the Midterm Targets, along with informing the collection system widely to the industry. In fiscal 2005, the Agency achieved 98.1% of collection rate of the safety measure contributions. (Ref. The collection rate of the contribution for FY 2004 increased from 93.4% at the end of fiscal 2004 to 97.1% at the end of fiscal 2005.)

In order to efficiently improve the contribution collection rate;
1) The Agency commissioned the Japan Pharmaceutical Association to collect the contributions from licensed MAHs of pharmacy compounding drugs.
2) The safety measure contribution is a new system started in FY 2004. The Agency called for cooperation of the industry association by explanation and lectures as well as advertising on the websites and in the industrial papers. The Agency also developed and distributed a handbook for declaration and payment procedure of the contribution in order to inform all the parties obligated to pay the contribution. Moreover, in order to increase the collection rates, a written request for contribution payment was sent to all the MAHs in arrears (excluding those of pharmacy compounding drugs).

[FY 2005 Contribution Collection Results]

Category		Subjects (Cases)	Number of payers who made contributions (Cases)	Collection rate	Contribution amount
Adverse drug reaction contributions	MAH	787	787	100%	(million yen) 2,923
	Pharmacy	10,037	9,930	99.6%	10
	Total	10,824	10,780	99.6%	2,933
Infectious disease contributions	MAH	105	105	100%	553
Safety measures contributions	MAH	3,178	2,982	93.8%	1,143
	Pharmacy	10,037	9,987	99.5%	10
	Total	13,215	12,969	98.1%	1,153

(4) Improvement of Services to Public

1. General consultation service

Based on the “General Consultation Guidelines” that specifies how to handle inquiries to the Agency and to reflect comments and opinions helpful for improvement in the operations, the Agency operates its general consultation service and makes questionnaires at its reception counter available and collects comments and opinions of visiting customers on its overall operations.

As a new attempt of FY 2005 in the service, the Agency started to provide this service during all the office hour, including lunch break, for convenience of customers.

In fiscal 2005, among the total 2,353 cases of the requested general consultations, 1,613 cases, which accounts for 70 % of the total, were the inquiries and requests regarding consultations and applications for drugs and medical devices approval.

FY 2005	Inquiry / Consultation	Complaint	Opinion / Request	Others	Total
Total # of Consultations	2,344 (1,606)	6 (5)	3 (2)	0 (0)	2,353 (1,613)

Note 1: The numbers in parentheses, that indicate the cases related to consultations and applications for drugs and medical devices approval, are also included in the numbers above as total # of consultations.

Note 2: The Office of Review Administration accepts inquiries on consultations and applications for drugs and medical devices approval, separately from the general consultation service.

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

The Agency has worked to fully develop the system to respond to consultations and the complaints from general consumers as well as complaints regarding its review and safety operations from the relevant companies.

Since September 2004, the Agency has provided face-to-face meetings with applicants, on request, regarding review progress of a new drug, new medical device, or improved medical device. In the meeting, the office director of the Agency in charge of each review case needs to provide the applicant with an appropriate explanation about the estimated time necessary for its product to reach the next review stage.
The Agency received 115 requests of this meeting for new drugs, 3 each for new medical devices and improved medical devices in FY 2005.

Then, appeals from applicants about the review and the post-marketing safety operations are made, the office director (in the case of a second appeal, the director of the Center for Product Evaluation or the Chief Safety Officer) needs to conduct a further investigation and respond to them by himself/herself within 15 working days. The Agency established this system since FY 2004, but received no appeal regarding the review and the safety operations in FY 2005.

In addition, the Agency developed a consultation manual to facilitate how to deal with the complaints from the relevant companies. The Agency is willing to take the complaints into consideration that would be helpful to improve its operations.

3. More information on website

The Agency compiled the “Annual Report FY 2004” on its achievements of the fiscal year and posted it on the website. The Agency also compiled additional two reports, “First Semiannual Report FY 2005” and the “Summary of PMDA’s Operations in FY 2005 (from April to December 2005),” and posted them on the website. The Advisory Council and the each operations committee of the Agency were briefed about these reports, and the reports and materials presented at these meetings were posted to the public successively on the website.

4. National Forum on Drugs and Medical Devices

The Agency held the “National Forum on Drugs and Medical Devices” at Shinagawa Intercity on November 6, 2005, in order to widely inform the public of the Agency’s operations and services as well as to educate the public on significance and proper use of drugs and medical devices.
The forum, with the theme “Drug Manifesto,” had some presentations and a panel discussion focusing on drugs. Part I of the forum invited two experts as keynote speakers, Dr. Soichiro

Kitagawa, President of the National Cardiovascular Center, and Dr. Gozoh Tsujimoto, Professor of Genomic Drug Discovery Science of Kyoto University, Graduate School, Pharmaceutical Sciences. Part II of the forum had a panel discussion led by a coordinator, Ms. Mieko Kenjyo, Professor of Department of Sociology of Aomori University.

The forum had as many as over 500 participants, including healthcare professionals, students, and the general public.

Part 1---- History and Miracles of Drugs “The Role, Responsibility and Prospect of Drugs”

Lecture 1: “History of Drugs” by Dr. Soichiro Kitagawa, President of the National Cardiovascular Center

Lecture 2: “Genomic-based Drug discovery” by Dr. Gozoh Tsujimoto, Professor of Genomic Drug Discovery Science of Kyoto University, Graduate School, Pharmaceutical Sciences.

Part 2---- Panel Discussion on “Realizing Drug Manifesto”

Coordinator: Ms Mieko Kenjyo, Professor of Department of Sociology of Aomori University

Panelists: Dr. Hatsno Aoki, President of Japan Pharmaceutical manufactures’ Association

Dr. Soichiro Kitagawa, President of the National Cardiovascular Center

Dr. Gozoh Tsujimoto, Professor of Genomic Drug Discovery Science (GDDS) of Kyoto University, Graduate School, Pharmaceutical Sciences

Mr. Jugo Hanai, Chief caretaker, the Japan Confederation of Drug-induced sufferers Organizations

Ms Hiromi Watanabe, Childminder & Cancer patient

Mr. Akira Miyajima, Chief Executive, Pharmaceuticals and Medical Devices Agency

5. Report on financial standing

The Agency disclosed its financial standing, including the use of user fees and the contributions, in government gazette and on the website in order to ensure transparency of its expenditures.

6. Internal Auditing and related matters

The Agency adopted auditing by an external accounting firm in accordance with the incorporated administrative agency system, conducted an audit by its auditor, and systematically conducted

internal auditing by its Audit Office on its operations and accounts for internal control of the organization. The results of the conducted audits were publicly reported to ensure transparency of the Agency's management and operations.

(5) Personnel Issues

1. Discussion of a personnel evaluation system

The Midterm Targets requires the Agency to appropriately implement personnel evaluation based on the work performance of the staff. In the Midterm Plan, the Agency aims to establish such a personnel evaluation system that motivates the staff and appropriately reflect the evaluations and achievements of the staff in their remunerations, salary increases, and promotions.

For the purpose of creating a whole picture of the personnel evaluation system, in FY 2005, the Agency established a Panel on Personnel Evaluation System to develop an outline for introduction of the system and to discuss employee's evaluation, pay grade and remuneration systems.

For the first attempt of the system, the Agency conducted trial personnel evaluation of the upper-level management between the period of October 2005 and January 2006. In addition, the Agency gave training mainly to the other staff members of the Agency in preparation for another trial of personnel evaluation of the entire staff to be scheduled in fiscal 2006.

2. Systematic implementation of staff training

The Agency is required high level of expertise in conducting the review, post-marketing safety and relief operations, and we are facing constantly advancing scientific technologies to develop drugs and medical devices. In such circumstances, it is necessary for the Agency to appropriately enhance the level of expertise of the staff, therefore the Agency has systematically implemented various staff training depending on a type of operations and performance goals and provided appropriate training that is commensurate with the qualification and capability of an individual staff member. In addition, the Agency has had its staff actively participate in both domestic and overseas academic conferences and seminars in order to absorb new knowledge and improve their skills.

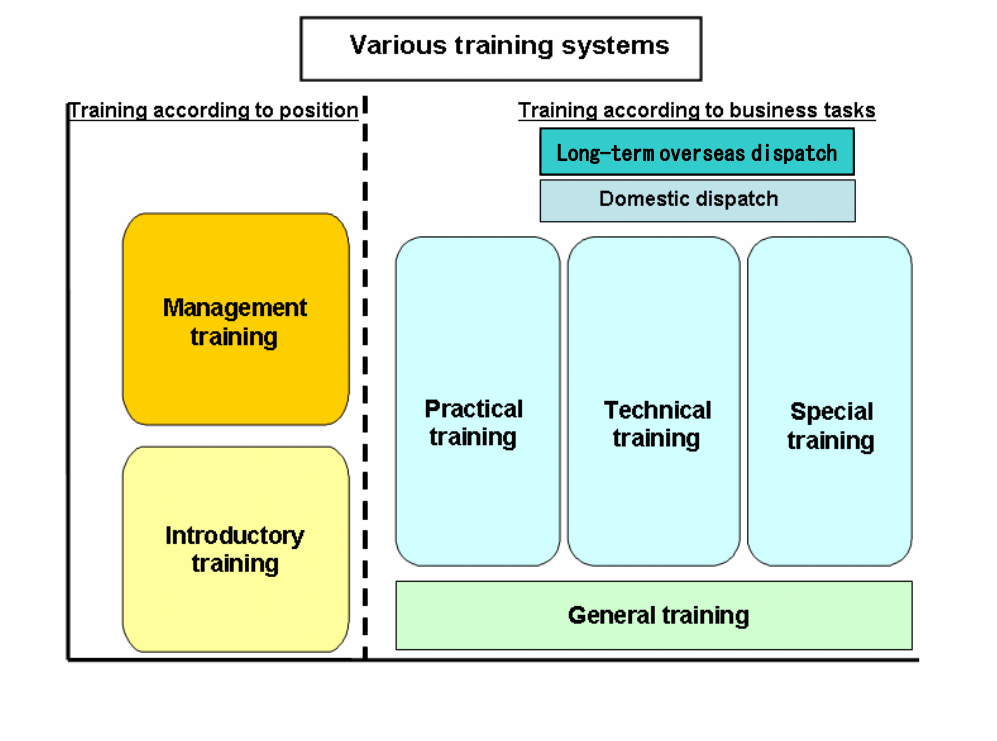
Specifically, the Agency set the objectives for staff training in the training committee and devised some plans for introductory training, internal training and external training based on the needs of each office. Based on the direction set by the committee, the Agency conducted introductory training in April and November 2005, and dispatched the staff to universities in Japan, overseas universities, and pharmaceutical regulatory authorities. Under these training programs, 62 staff members were sent to 66 sites. The Agency also held 26 special lectures specially for technical training during fiscal 2005 inviting experts who belong to domestic or overseas regulatory

authorities, pharmaceutical companies, and universities. In February 2006, the Agency held the first courtesy training, which had been discussed about in the committee, and in March 2006, the first internal “Test of English for International Communication (TOEIC)” was conducted in preparation for training for English conversation.

Moreover, the Agency provided its administrative staff with a course to educate them about basic knowledge of pharmaceutical affairs, and conducted four sessions to hear the requests and opinions of ADR sufferers and patients by inviting lecturers from their organizations and groups.

The Agency provided another type of educational programs for its newly-joined members, two times of facility tours (in 4 drug manufacturing sites, 2 medical device manufacturing sites, 6 medical institutes, and 2 research institutes), and the training committee developed the training plan for fiscal 2006.

In addition, the committee tracked and checked the extent of participation of each office in domestic academic conferences every fiscal quarter. (690 participants in total as of the end of March)



3. Appropriate personnel allocation

The Agency targets to conduct appropriate personnel allocation to maintain expertise of the staff members and the operational continuity.

To achieve this target, the Agency conducted personnel allocation considering the knowledge and work experience of the staff members. Basically, the Agency avoids short-term rotation of personnel except for the cases of health problems of its staff or some undesirable conditions for its operations.

4. Securing human resources through open recruitment

In order to ensure smooth enforcement of the revised Pharmaceutical Affairs Law (PAL) during FY 2005 and to conduct rapid and proper review and post-marketing safety operations, it is significant for the Agency to keep competent human resources with high levels of expertise, while paying due consideration to the impartiality of the Agency.

The Midterm Plan specifies that the Agency is to have 317 permanent staff members including executives at the beginning of the midterm period (on April 1, 2004) and 346 at the end of the midterm period (on March 31, 2009). However, the Agency started with 256 permanent staff members at the beginning of the effective period of the Midterm Plan, which was significantly lower than the number expected in the plan.

Therefore, the Agency has tried to maintain competent human resources for the understaffed

areas through open recruitment on the website and by publicity in the industrial magazines. As a result, the Agency increased 56 new members to 291 by April 1, 2005. The Agency has made a successive effort to inform the public of employment opportunities for the permanent staff six times, and five times for part-time staff during FY 2005. The decisions on recruitment and informal appointment are shown in the list below.

[Employment through Open Recruitment in fiscal 2005 – as of April 1, 2006]

1) Technical staff (Open recruitment, 5 times)	
Number of applicants	About 390
Number of the employed	36
Number of the persons scheduled to be employed	9
2) Administrative staff (Open recruitment, once)	
Number of applicants	About 70
Number of the employed	2
3) Non-regular experts (Open recruitment, 5 times)	
Number of applicants	About 60
Number of the employed	14

The Agency is making an effort to maintain competent human resources for the positions, such GMP inspection and biostatistics, whose recruitment is particularly difficult, and relaxed its employment regulations with due consideration to neutrality and impartiality of the Agency in recruiting individuals who worked for a private company. In this fiscal year, it employed 7 new staff members by taking some measures such as setting exceptional conditions in the regulations.

As a result of open recruitment through FY 2005, the Agency increased 47 new staff members but decreased its staff to 319 as of April 1, 2006, because a large number of the staff was transferred to the affiliated organizations/offices at the end of the fiscal year.
However, the total number of the staff of the Agency has been increasing close to the expected level at the end of the effective midterm period because 20 prospective or transferred staff is waited to join the Agency. The Agency also considers making further effort to keep enough competent human resources for the understaffed fields through open recruitment in the future.

On the other hand, the Agency has continuously made an effort to maintain the critical number of staff in the field of review operations, and increased to 197 staff at the beginning of fiscal 2006 from 178 at the beginning of 2005

[Numbers of the Agency's Permanent Staff Members]

	April 1, 2004	April 1, 2005	April 1, 2006	Numbers Expected (in Midterm Plan) at the End of FY 2008
Total Staff # in Agency	256	291	319	346
- Review Section	154	178	197	–
- Safety Section	29	43	49	–

Note 1:The expected number of the staff including executives at the beginning of effective midterm period, when establishment of the Agency, was 317. (The number includes 11 staff members engaging in the R&D promotion service of the Agency.)

Note 2:The "Total Staff # in Agency" includes 6 executives, but 5 in the data provided as of April 1, 2006.

Note 3:The "Total Staff # in Agency" provided as of April 1, 2004 includes 11 staff members engaged in the R&D promotion service, and the total number expected at the end of the Midterm Plan (completing the midterm period at the end of FY 2008), was 357 before the services were transferred to the National Institute of Biomedical Innovation (NIBIO).

Note 4:The Review Section consists of Director of the Center for Product Evaluation, Associate Center Directors, Office of Review Administration, Office of New Drug I, II, and III, Office of Biologics, Priority Review Director, Office of OTC/Generic Drugs, Office of Medical Devices and Office of Conformity Audit.

Note 5:The Safety Section consists of Chief Safety Officer, Office of Safety and Office of Compliance and Standards.

5. Appropriate personnel management based on work regulations

The Agency is careful to conduct appropriate personnel management in order to avoid any suspicions of inappropriate ties with the pharmaceutical and medical device companies, by imposing certain restraints on recruitment and placement of its executives and staff members as well as on their getting employed after retirement from the Agency.

For the appropriate personnel management, the Agency required newly-employed staff members to submit a written pledge, and it stipulated in its work regulations some employment restrictions on personnel allocation, getting employed after retirement and the staff whose family members belong to pharmaceutical industry. The Agency also tried hard to inform its staff members of these regulations.

More specifically, (1) The Agency established work regulations and their implementation instructions, by requiring its staff members to submit a written pledge to follow the work regulations

and to keep the confidential information on the operations, restricting those who have a work history in a pharmaceutical company or those whose family members belong to the pharmaceutical industry to engage in certain types of the operations, and limiting those who left the Agency to work for a pharmaceutical company. (2) The Agency developed a code of conduct and its implementation instructions specifying ethical standards required to the staff and interactions prohibited between the staff and the stakeholders such as pharmaceutical companies. Therefore, the Agency developed summaries and a Q&As list concerning these specified regulations and standards in order to inform the staff members through the internal website and in introductory training.

In addition, from the perspective of further informing the staff about the work regulations and standards, the Agency created a handbook that explains the regulations, standards, and Q&As list and distributed them to all of the staff.

(6) Ensuring Security

1. Office entrance/exit controls

The Agency has improved its security control system by installing entrance/exit control equipments at the door of each office in order to ensure the security and protect the confidential information in the Agency around the clock.

By the introduction of the security control system, the access to each office is limited only to the staff with ID card and the history of individual staff members' entering/leaving each office was recorded whenever they pass any of the entrance doors. With these measures, outsiders cannot enter the rooms unaccompanied.

In order to ensure the strict access control, the Agency also set rules on the entrance/exit control Including operational management of the system and made a maximum effort to inform its staff members about the rules on the internal website and in introductory training.

2. Security of information system

The Agency has made an effort to ensure security of the information regarding its information system based on the fiscal year plan 2005.

In specific, the Agency has developed a new secure e-mail system to achieve smooth and prompt information exchange between its reviewers and applicants for drugs and medical devices approval. In January 2006, almost 30 companies addressed their participation in a trial of the system, and they made an attempt in preparation for its official introduction in FY 2006.

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

1. ADVERSE HEALTH EFFECT RELIEF SERVICES

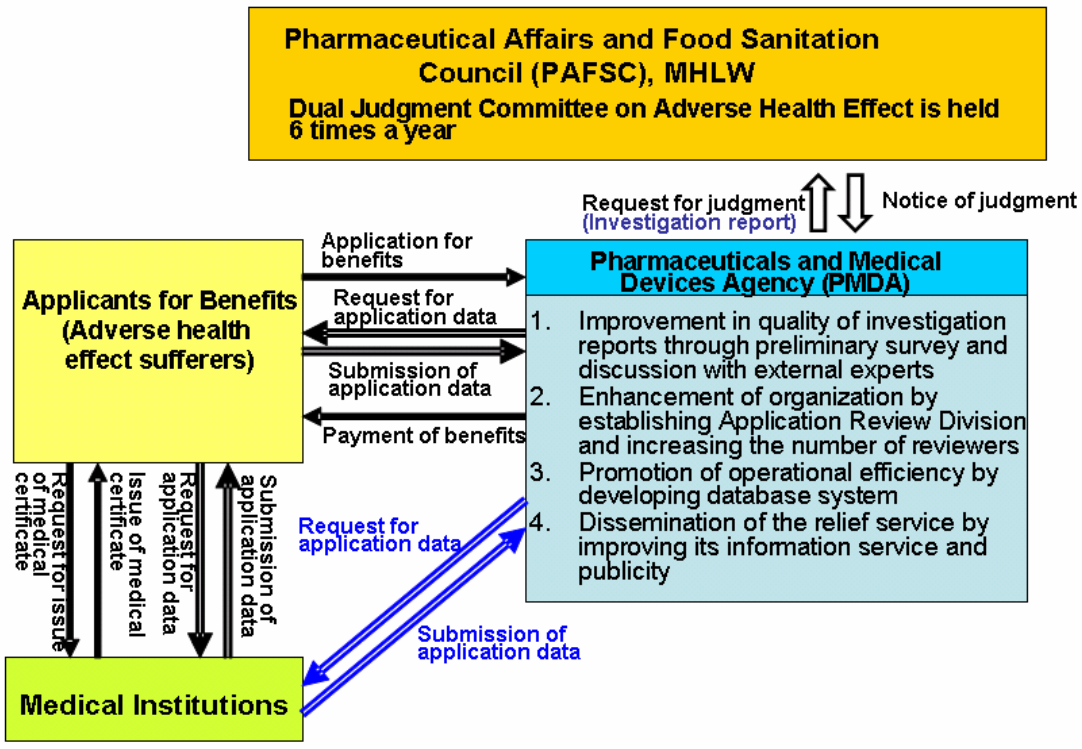
The Agency is taking the following measures in order to widely inform the public of its services on adverse drug reaction relief and bio-derived product caused infection relief (hereinafter referred to as “the relief services”), to operate the relief services appropriately, and to provide adequate and prompt relief services to those who suffered from adverse drug reactions (ADRs) and adverse health effects from bio-derived product-caused infections:

(1) Expeditious Processing of Relief Applications

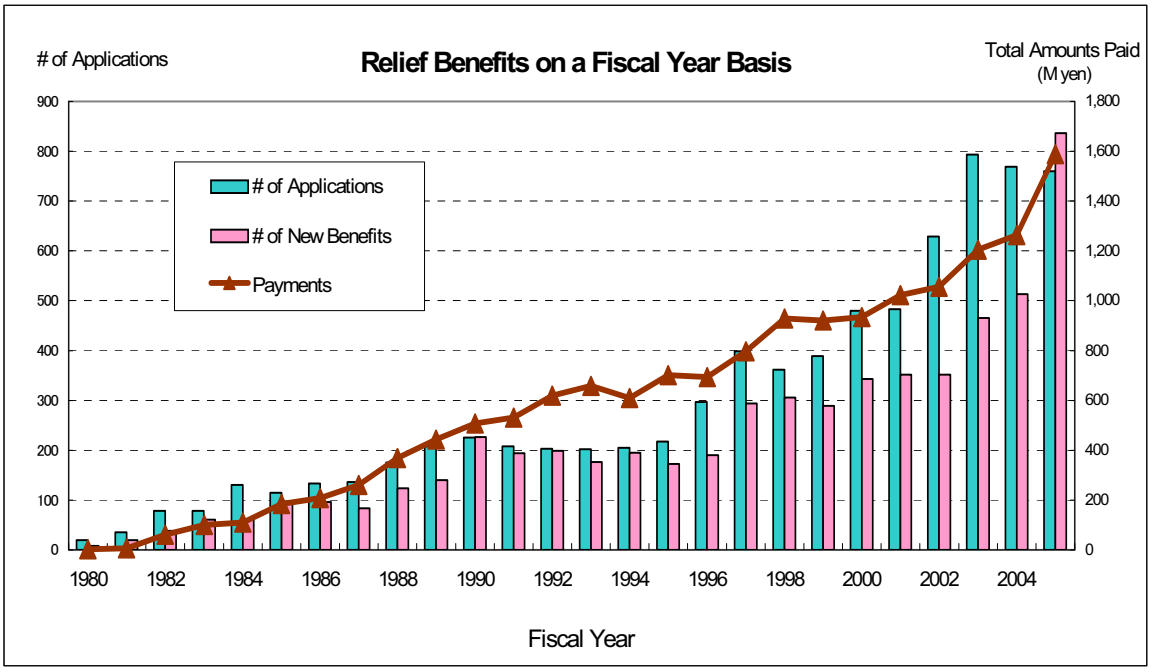
In order to speedily proceed with the administrative process of relief benefit applications, the Agency investigates and organizes the fact alleged in the applications before requesting the Minister of Health, Labour and Welfare (MHLW) to make medical and pharmaceutical judgment on the applications for relief payment. For this purpose, the Agency conducted the following tasks in this fiscal year:

1. Conducting fact-finding investigations of the applied cases, 2. Developing a summary chart of the case over time, 3. Creating the investigation reports.

Improvement of Adverse Health Effect Relief Services



＊In FY 2005, the Agency received 760 new applications total for the ADR relief service, and 1,035 cases were judged (including applications submitted in FY 2004 but judged in FY 2005, and 836 of them were judged as payable). On the other hand, 5 new applications to the infectious disease relief service were filed, and 6 cases were judged (3 of them were judged as payable).



The Agency also aims to judge applications on benefit eligibility within eight months of the standard administrative process time since their submission, including the time required for medical and pharmaceutical judgment by MHLW. In collaboration with MHLW, the Agency is expected to process applications for the benefits smoothly and complete the judgment within the targeted standard administrative process time for 60% or more of the cases filed in FY 2008, the end of the Agency's Midterm Targets period,.

For this target, the Agency, consulting with MHLW, made a clear allocation of the administrative process time for medical and pharmaceutical judgments between the two organizations, 2.5 months for MHLW and 5.5 months for the Agency, excluding the pending period when MHLW or PMDA cannot proceed with the process because applicants and/or medical institutions are required to develop additional or supplementary materials. The Agency also periodically renewed the list of the applications in process and requested MHLW to deliver a speedy judgment.

However, the number of the applications in process has recently shown a dramatic increase because a significant number of new applications for the benefits were submitted. As a result, the accomplishment rate of the standard administrative process time has continuously dropped. Therefore, the Agency increased the staff of the Office of Relief Funds to provide speedy service

and started consultations with experts from various fields who appointed by the Chief Executive of the Agency in order to support investigations for MHLW's judgment, along with the start of the Dual Judgment Committee of MHLW in October 2005.

In fiscal 2005, the achievement rate of the standard administrative process time dropped because backlogs of the benefit applications were processed; however, the total number of processed applications substantially increased.

[Number of Applications and Judgments for ADR Relief] (Cases)

Fiscal Year	FY 2003	FY 2004	FY 2005
# of applications	793	769	760
Judged cases	566	633	1,035
Withdrawn cases (breakdown)	2	1	4
Applications in process*	820	956	681
Accomplishment rate **	17.6%	14.5%	12.7%
Administrative process time (Median)	10.6 months	12.4 months	11.2 months

[Number of applications for infectious disease relief]

The number of filed applications for infectious disease relief was 5, and the number of cases judged for the relief was 6. (Accomplishment rate** was 50%)

* "Cases in process" show the numbers obtained at the end of each fiscal year.

** "Accomplishment rate" indicates the percentages of the cases judged within 8 months of the standard administrative process time out of the total number of the cases judged during the fiscal year.

(2) Unified Management of Information through Database

In fiscal 2005, the Agency upgraded its existing database, established in fiscal 2004, on the relief services in order to further improve efficiency and capacity of the services.

(3) Promotion of Appropriate Communication of Information through Interdepartmental Collaboration

The Agency has sought interdepartmental collaboration in the organization. As part of the effort, the information of judged cases on eligibility for ADR relief benefit in FY 2005, excluding personal information, was reported to the post-marketing safety department so that the post-marketing safety department can utilize the information.

The information of infectious disease relief benefits in FY 2005, 5 applications and 6 judged cases, was also reported to the post-marketing safety department.

(4) Surveys on Actual Damages from Adverse Drug Reactions (ADRs)

It is legislated that the Agency is to provide necessary health and welfare services to take speedy measures in the case of ADR occurrence, besides the relief benefit payments to the sufferers from adverse health effects. (Article 15, Pargraph 1, Item 1-2: the Law on Incorporated Administrative Agency, Pharmaceuticals and Medical Devices Agency (PMDA))

Specifically, the Agency continued to carry out the "Survey on Actual Damages from ADRs" and the "Study on Indicators for Recognition of Eye Disorders under the ADR Relief System" in the fiscal year.

"Survey on Actual Damages from ADRs" (FY 2004 and 2005)

The Agency established this panel, headed by Dr. Hisao Sato, Professor of Social Welfare Department, Japan College of Social Work, and the panel discussed questionnaire items for the survey and scope of groups/individuals to be studied. Then, the Agency carried out the survey in August 2005 in order to grasp actual damages from ADRs and take measures for better quality of life and necessary services for the ADR sufferers. The result of the survey was compiled and reported to the "Committee on Relief Services" and posted on the website for the public.

(5) Expansion of Consultation Service

The Agency assigned its staff in charge of consultation service. The consultation office is open from 9:00 to 17:30 (without lunch break) in order to respond to the inquiries about the relief services and how to apply for ADR relief and infectious disease relief benefits.

The Agency also introduced a toll free number for better access of the public to the service.

Toll Free Number: 0120-149-931
Phone: 03-3506-9411
E-mail address of the relief consultation service: kyufu@pmda.go.jp

Fiscal Year	FY 2003	FY 2004	FY 2005	Year-on-year ratio compared with FY 2003	Year-on-year ratio compared with FY 2004
# of consultations	5,338	3,911	4,307	Down 19%	Up 10%
# of web accesses	35,726	41,947	37,655	Up 5%	Down 10%

During the fiscal year, the Agency actively implemented public relations activities for the relief services and targeted to increase the number of requests for relief consultations and of web accesses by about 10% over the level of FY 2003, which is specified in the fiscal plan for FY 2005.

The Agency recognized a decline in the number of requested consultations for the relief in FY 2005 over FY 2003, but a 10% increase in the fiscal year over FY 2004. It is considered that higher availability of publication of the Agency' toll free number in newspapers, on the website, and on Yakutais (small paper bags containing prescribed drugs that is given to patients in hospitals or pharmacies) increased the number of calls from the public to ask about the service. On the other hand, the Agency experienced a 5% increase in number of web access in FY 2005 over FY 2003, but a 10% decrease in the fiscal year over FY 2004. However, 3 months of public relations activities on the website, informing the public of the service, resulted in 42,714 total accesses to the web page that specifically advertises the Agency's adverse health effect relief service. The Agency considers the resulted number shows its active public relations activities fully contributed to informing the public of the service.

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

1. Disclosure of judged cases on relief benefit payment on website

The Agency plans to release information about the relief services and other operations achieved in FY 2005 on the website for providing more helpful information to the public and enhancing transparency of the Agency. In addition, the Agency has just posted information on the cases judged on relief benefit eligibility in FY 2004 on the website with due consideration to protecting personal information. The Agency will continue to provide such information of FY 2005 successively on the website.

Information is available on judged cases on relief benefits payment at http://pmda.go.jp/help/information.html.

2. Improvement of pamphlets and other communication tools

The Agency took the following 3 actions to create better pamphlet and instruction manual about application for the relief benefit payments, which explains to doctors and patients about the system clearly and help reduce the numbers of flawed applications that disturbs the administrative process for the services;

1. The content of the pamphlet for the bio-derived product-caused infection relief service was reviewed for clearer and easier descriptions.
2. The toll free number for the relief services has been put in the pamphlet and on the website for better recognition and convenience for the public.
3. Applications and other forms for the relief services, which were available only by mail on request in fiscal 2004, can now be downloaded from the website at http://search.pmda.go.jp/fukusayo_dl/.

(7) Proactive Public Relations Activities

The Agency purposed to widely inform the public of the relief services through a series of effective and proactive public relations activities as follows;

1. Publicity about the services have been displayed in the newspapers (30 local newspapers and 3 block newspapers that cover a wider area than local newspaper), on websites (banner advertisement on 4 expert websites for medical professionals and keyword-linked advertisement on 6 general website), and on Yakutais.
2. Publicity on the infectious disease relief service were placed in 6 medical/pharmaceutical magazines, and publicity on the relief benefit payments for the HIV-positives and other ADR sufferers was placed in 5 medical/pharmaceutical magazines.
3. The staff of the Agency visited 21 medical institutions to explain the services.
4. The Agency displayed the posters at the 19th annual meeting of the “Japanese Society for AIDS Research” and distributed the leaflets that explain the overview of the service to the participants of the meeting.

The Agency also launched the following public activities in fiscal 2005 with the cooperation of relevant groups;
1. The publicity about the relief service of the Agency was placed in the magazine that is issued by the Federation of Pharmaceutical Manufacturers’ Associations of Japan to provide drug safety information, and the magazines were distributed to all the medical institutions.
2. The pamphlets to introduce the service were distributed to medical institutions through the Blood Center of the Japanese Red Cross Society.
3. The publicity about the service was posted in the medicine notebook issued by the Japanese Pharmaceutical Association.

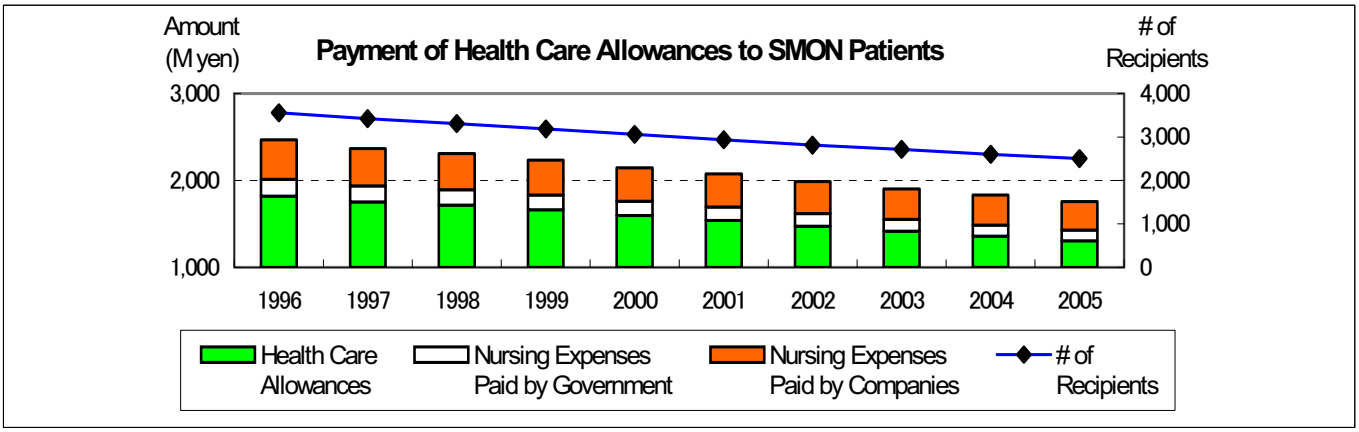
[Publicity in Newspaper]

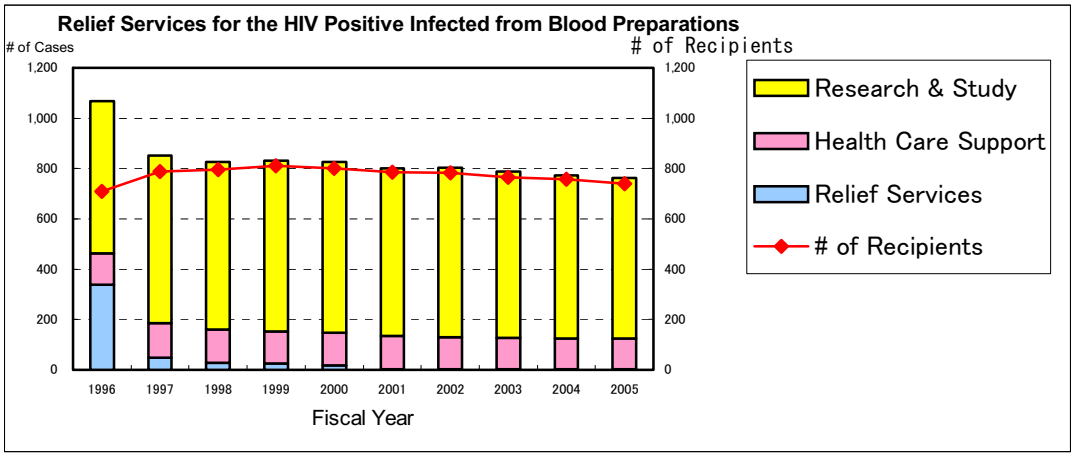
[Advertisement in Yakutai]

In order to directly inform patients taking prescribed medicines about the relief services, the Agency has taken advertising opportunities given at the back of a Yakutai (a small paper bag containing prescribed drugs, which is given in hospitals or pharmacies). Specifically, the Agency entrusted a ad agency on commission with design and print of the ad and selection of the areas and pharmacies for its distribution. Then, the Agency distributed, across Japan, approximately 4.42 million Yakutais with the advertisement to 460 health insurance pharmacies.

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

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




Relief Services for the HIV Positive Infected from Blood Preparations
# of Cases
# of Recipients
1,200
1,000
800
600
400
200
0
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
Fiscal Year
Research & Study
Health Care Support
Relief Services
# of Recipients

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

In order that the public can safely use the pharmaceuticals and medical devices that have the required international level and that such pharmaceuticals and medical devices can enhance the public health in the long term, the Agency considers it necessary to adequately conduct the review and related operations and the post-marketing safety operations by ensuring the followings; better pharmaceuticals and medical devices are provided to medical practice settings faster and with greater safety, pharmaceuticals and medical devices are used properly, and that health hazards are prevented or addressed properly and promptly. Therefore, the Agency has taken the following specific measures to strengthen the systems for consultation/review and post-marketing safety measures, and make both of the operations organically function to achieve the Midterm Targets and the fiscal year plan for 2005.

(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 is required to ensure that the public and healthcare professionals swiftly enjoy the maximum benefits of innovative, yet safe, pharmaceuticals and medical devices, that the pharmaceutical and medical device industry are benefited from the swift review system of the Agency.

a. Clinical trial consultations and reviews

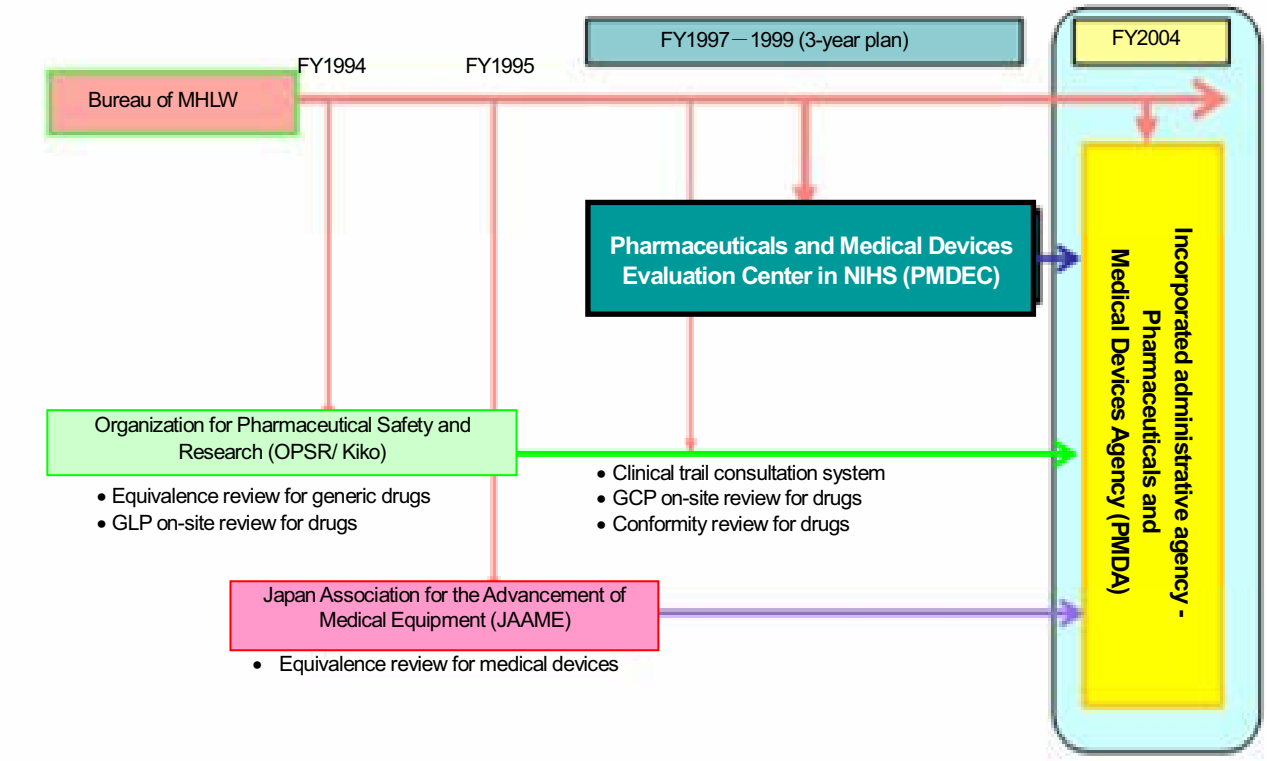
・The review system for pharmaceuticals and medical devices has been improved significantly since 1997. In 2004, the Pharmaceuticals and Medical Devices Agency (PMDA) was founded for the improved review system by independent organization integrating previously separated review operations, while leaving the authority for approval and final judgment on applied pharmaceuticals and medical devices in MHLW. The followings are the measures taken for the improvement of the system;

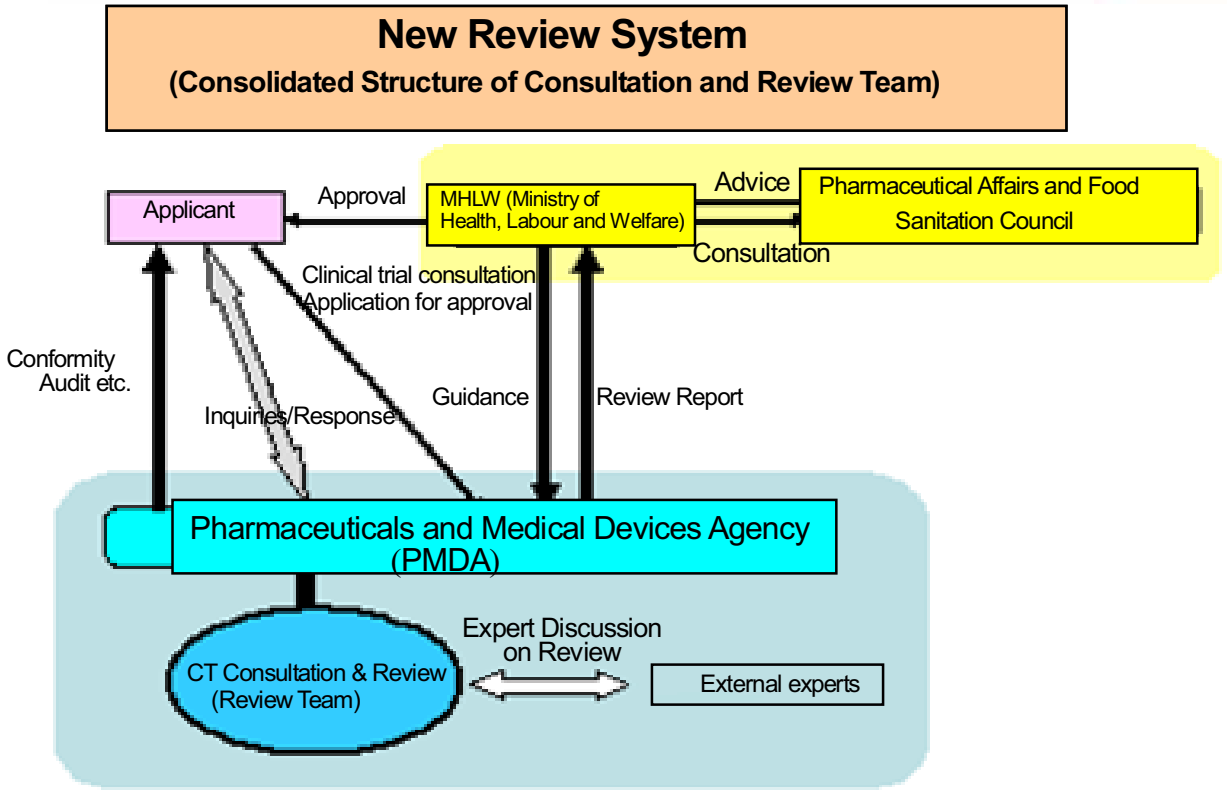
i) In order to provide consistency across the operations and improve their efficiency, a new incorporated administrative agency, Pharmaceuticals and Medical Devices Agency (PMDA) was established integrating three separate organizations in charge of review work operations.
ii) The Agency decided to greatly increase in the number of its staff by about 100, including reviewers, during the Midterm Targets period.
iii) Under the new system of the Agency, the entire review range process including of work clinical trial consultation is conducted by one team for consistency and coordination in a review process. (Clinical trial consultation and review operations were done by different organizations and staff under the previous system, which caused organizations discrepancies in opinions and policies in

review process and guidelines.)

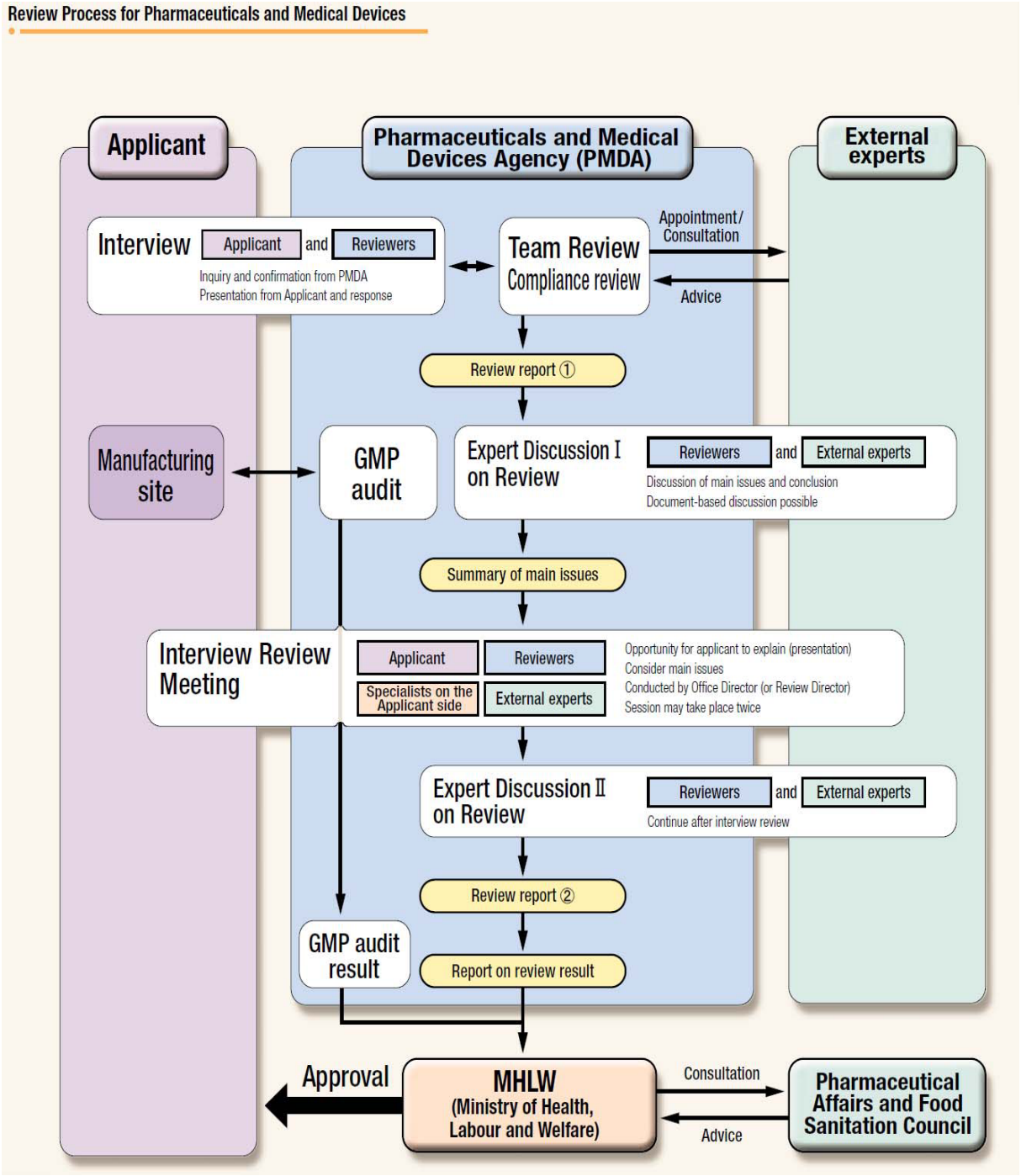
iv) The Agency strengthens its function to review biological and biotechnology-derived products and medical devices in order to respond to increasing needs in these fields in the future.

Transition of Approval Review System on Drugs and Medical Devices





Flowchart of Review Process for Approval



[Results in review operations in FY 2005]

Review related operations:

Drugs

1) Expert discussions conducted meetings:121 (87 Document reviews, 34 Face-to-face reviews)
2) Applications discussed at the Drug Committee meetings (PAFSC):46
   Review reports made to the Drug Committee (PAFSC)21

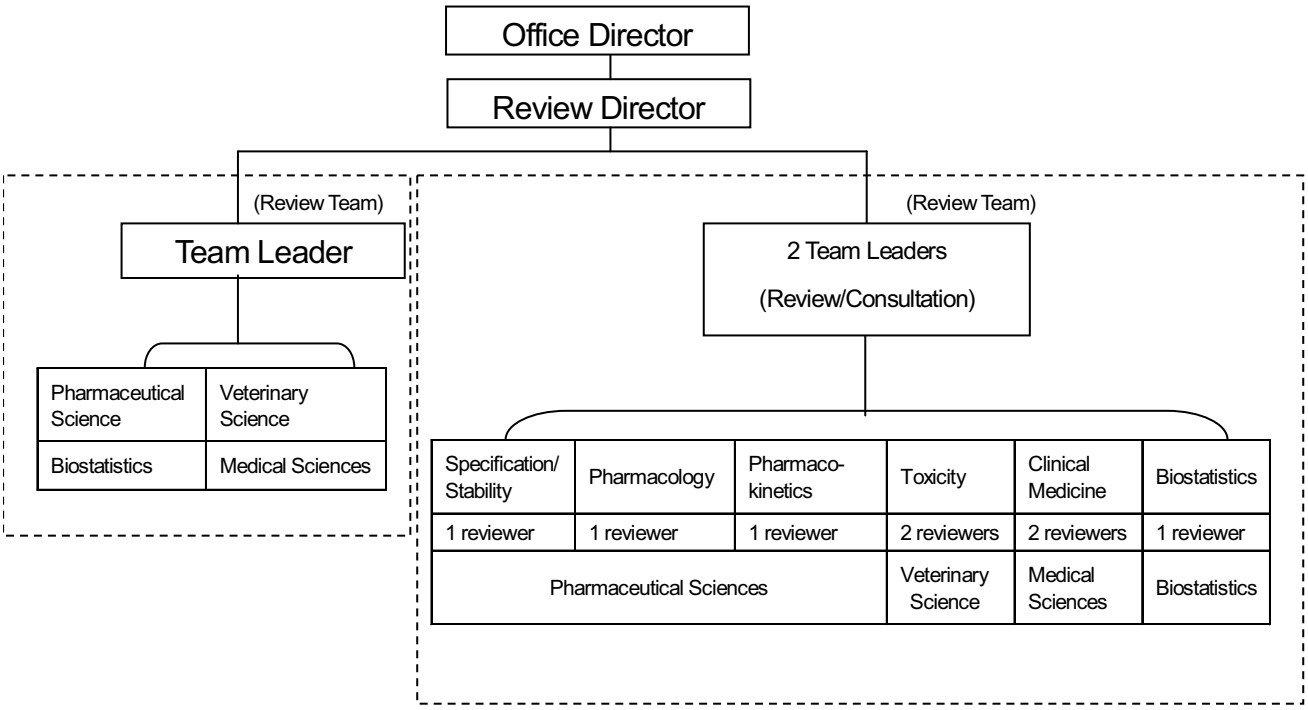
Medical Devices and In-vitro Diagnostics

1) Expert discussions conducted with specialists: 174 (152 Document reviews, 22 Face-to-face reviews)
2) Applications discussed in the Drug Committee (PAFSC):7
   Review reports made to the Drug Committee (PAFSC):107
   (90 cases for medical devices, 17 cases for in-vitro diagnostics)

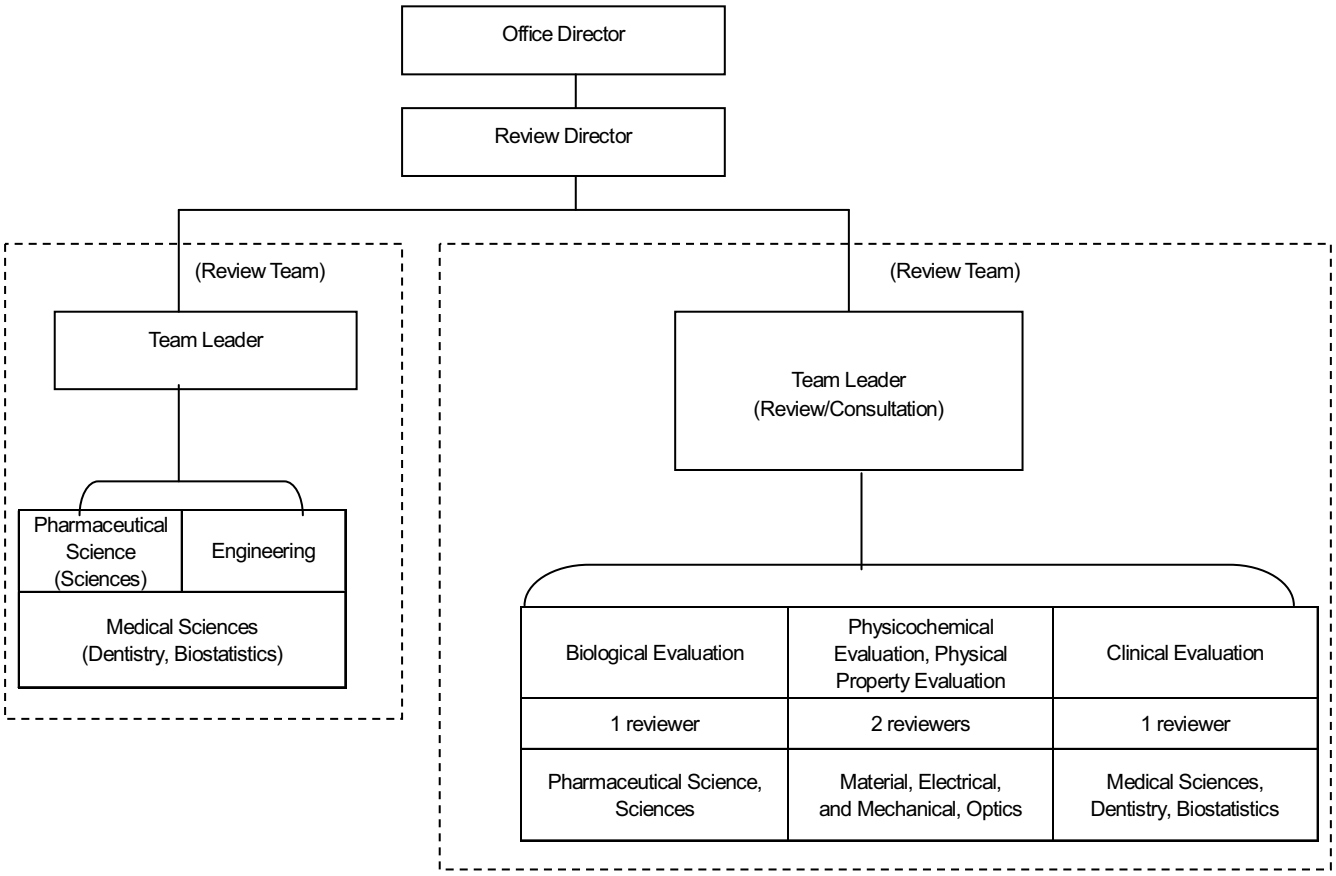
・As provided in the following, review of new drugs was conducted by review teams with experts who have academic degrees in pharmaceutical science, medical science, veterinary science, biostatictics and other specialties. The review team basically consists of an office director, a review director, team leader(s), deputy team leader(s), and reviewers respectively specialized in quality, toxicity, pharmacology, pharmacokinetics, clinical medicine and biostatistics.

・Similarly, review of new medical devices was conducted by review teams with experts who have academic degrees in engineering, pharmaceutical science, medical science, dentistry, veterinary science, statistics and other specialties. The review team basically consists of an office director, a review director, team leader, and reviewers respectively specialized in biological, physicochemical/physical property, and clinical evaluations.

[Structure of a review team for NDAs]



[Structure of review team for new medical devices]



・For more efficient and systematic review of new drugs, the Agency assigned a dedicated office and team to each therapeutic category shown as below. (13 teams in total by December 2005, and 14 from January 2006)

[Therapeutic categories assigned to each new drug review department office of new drug]

Name	Therapeutic Category	
Office of New Drug I	Category 1	Gastrointestinal drugs, dermatologic medicines
	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 3	Central/peripheral nervous system drugs, sensory organ drugs (except drugs classified in Category 6-1), narcotics
	Category 6-1	Respiratory tract drugs, anti-allergy drugs, sensory organ drugs for inflammatory diseases
	Category 6-2	Hormone drugs, Drugs for metabolic disorders (excluding combination drugs)
Office of Biologics	Biological products	Vaccines, antitoxic serum
	Blood products	Serum globulin, blood coagulation factors
	Cellular and Tissue-derived products	Products for cell therapy

* In April 2005, the Agency split Category 3 into two and newly established Category 6. Then, the Agency also split Category 1 into two, added Category 6-2, and changed the name of Category 6 into Category 6-1 in January 2006.

・On the other hand, for approval review of medical devices, the Agency assigned a dedicated office and team to each therapeutic category shown as below.

[Therapeutic categories in the office of medical devices]

Therapeutic Category	
Category 1	Mainly for Ophthalmology and Otorhinolaryngology
Category 2	Mainly for Dentistry
Category 3	Mainly for Cerebral, Cardiovascular, Respiratory, Psychoneurologic (materials)
Category 4	Mainly for Cerebral, Cardiovascular, Respiratory, Psychoneurologic (mechanical)
Category 5	Mainly for Gastrointestinal and Urinary systems, Obstetrics and Gynecology
Category 6	Mainly for Orthopedic surgery, Plastic surgery, Dermatology
Category 7	Mainly for Clinical test (In-vitro diagnostic)
Category 8	Mainly for Multicategory medical devices, Advanced electronic medical devices, Other uncategorized medical devices

・For clinical trial consultations for new drugs, Review Director and Chief Reviewer in charge and Deputy Reviewer in charge appointed from a review team drafted its policies on advice, and then the team discussed the policies and gave clinical trial consultations to applicants and made consultation reports.

・Clinical trial consultations for new medical devices were also conducted in the same way as consultations for new drugs.

b. Grasping the needs of public and healthcare professionals

・Through dialogue with healthcare professionals at academic conferences, the Agency has endeavored to grasp the needs for pharmaceuticals and medical devices. While attending domestic and international academic conferences, the Agency has actively exchanged ideas with healthcare professionals.

* In total, more than 700 members of the Agency people attended more than over 300 domestic and international academic conferences and seminars.

・Based on the report of the Investigative Committee on Combination Therapy of Anticancer Drugs (chaired by Dr. Kiyoshi Kurokawa, Adjunct Visiting Professor, Research Center for Advanced Science and Technology, the University of Tokyo) set up in MHLW that sought for prompt approval of unapproved indications, pre-review assessments on approval of anticancer

drugs were conducted at the meetings of the PAFSC in May and August 2004. The Agency approved all the five cases filed by companies were also approved in this fiscal year within 4 months of target review process time, of the target review process time following the similar accomplishments last fiscal year.

・Moreover, in order to periodically grasp the needs of academic societies and patients for the drugs approved in the US and/or the EU, but not in Japan, the “Investigative Panel study group on Use of the problems concerning Unapproved Drugs” (chaired by Dr. Tomomitsu Hotta, Director of National Hospital Organization Nagoya Medical Center Adjunct) has investigated about the needs since the panel was established in MHLW in January 2005. The Agency has applied the investigation results when providing clinical trial consultations to companies and reviewing new drug applications.

・The result of the investigation conducted to grasp the needs in the review operations by the Agency clearly revealed opinions and expectations of the public and medical professionals to the Agency in terms of expediting the access to cutting-edge drugs and medical devices in line with the medical practices present and the Agency’s role in regulatory system of drugs and medical devices. The Agency is willing to take the opinions and expectations into consideration for its better performance.

2. Efforts for efficient and prompt reviews

・PMDA needs to improve its operations by establishing an efficient review structure and target times* to reduce the review process time** for applications submitted since PMDA was established on April 1, 2004.

* Target time means a period set under normal conditions except in cases when significant changes happen in the review system or in social conditions.
* Review process time means the period consumed by MHLW and PMDA for review of products that were approved in the fiscal year”

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

a. Approval Review for new pharmaceuticals

・In new pharmaceuticals, the Agency aims to review and act on 70% of all filed NDAs within 12 months of review process time during the Midterm Targets period, aiming at the 80% accomplishment in FY 2008. In order to attain the target, the Agency: (i) strengthened its review system and improved its operational efficiency by increasing the number of reviewers especially for NDA categories in which process of the applications were considered to be difficult due to the

excessive concentration of applications submitted; (ii) regularly discussed its review policy with MHLW and managed the review process through the progress management committee for review related operations in PMDA so that review operations can be smoothly conducted; (iii) made efforts to properly manage the review process by taking concrete measures such as observing guidelines for review and investigation, keeping reviewers informed about review related information, and developing standard operating procedures.

・With regard to applied new pharmaceuticals which are distinctly different from already approved drugs in terms of active ingredients, quantities, administration and dosage, indications and effects, the review teams consisting of expertise in pharmaceutical science, medical science, veterinary science, biostatistics, etc. conducted approval reviews.

・As to review operations for NDA, in order to ensure consistency among the review teams and carry out review work promptly and appropriately, the Agency developed the implementation manual for NDA reviews and related procedures and the standard operating procedures for its related operations.

・In order to attain its performance target throughout the Midterm Targets period and conduct review related work promptly and appropriately, the Agency established the progress management committee for review related operations in January 2005 so that the chief executive and other executives of the Agency were able to grasp operational progress surely and improve the progress management. The committee held meetings to monitor and examine operational progress at the end of every month. In the review department, directors of the Office of Review grasped the operational progress on daily basis, and based on the reports from the directors, Director of the Center for Product Evaluation and Associate Center Directors provided necessary instructions at the liaison meeting of the review related offices.

(Results of overall NDA reviews)

・In FY 2005, for approval of the NDAs submitted on and after April 1, 2004, the Agency attained 83% as the performance target by processing 20 of 24 applications within 12 months. Nine out of the 24 approved applications, however, were those for priority review, and the achievement rate was 50%, 30 out of 60 applications, when including NDAs submitted before April 1, 2004.

・Compared to the previous year, the number of approved NDAs somewhat increased from 49 applications due to advancement in the review system in FY 2005. However, the median of total review process time took longer because the Agency had to continue processing applications filed before the establishment of PMDA.

[Number of approved NDAs] (cases)

	FY 2002*	FY 2003	FY 2004	FY 2005	Applications filed in and after FY 2004***
No. of approval cases & review process time (median)	52 (10.8 months)	51 (11.3 months)	49 (8.6 months) [65%]**	60 (12.0 months) [50%]**	24 (8.6 months) [83%]

*) 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. The figure in FY 2005 includes the number of NDAs filed before April 2004 which are out of the target period of the Midterm Targets.

***) The data indicate the number of applications filed in and after FY 2004, and approved in FY 2005. These figures are breakdown of the result in FY 2005.

・As for 139 and 146 applications submitted before and after the establishment of PMDA in April 2004 respectively, the Agency processed these reviews in the order of the submission, fully considering the targeted review time. However, the Agency has called for pharmaceutical companies to withdraw their applications which were considered to be difficult to approve because they had not replied to our inquiries.

・As to the applications submitted before the establishment of the Agency, 85 of them were approved or withdrawn during FY 2004 and 2005. However, in order to achieve the target on review process time, it is necessary for the Agency to vigorously process backlog of applications so that we can concentrate all our resources on the applications submitted on and after April 1, 2004 as soon as possible.

[Review status of NDAs in FY 2005](Cases)

	Cases*	Withdrawn	Approved	Under Review
Applications submitted by March 31, 2004	139 (-1)	17 (5)	68 (36)	54 [-42]
Applications submitted in FY 2004	88 (-1)	8 (4)	37 (20)	43 [-25]
Applications submitted in FY 2005	57	0	4	53 [53]
Total	284 (55)	25 (9)	109 (60)	150 [-14]

Note 1: The number of “Cases*” is obtained based on the number of review reports discussed at and reported to the Drug Committees of Pharmaceutical Affairs and Food Sanitation Council (PAFSC)

2: The figures in parentheses indicate the number of applications which were completed its process in FY 2005. They are breakdown of the figures above.

3: The figures in brackets are increase and decrease in number of cases under review of each fiscal year compared with that of FY 2004.

4: The number of applications submitted before April, 2004 was modified to 139 from 140 reported in the previous annual report because the Agency considered two separate applications for one ingredient as one application.

5: According to the review report which was released in February 2006, the number of applications submitted in FY 2004 was corrected to 88 from 89 because the Agency considered two separate applications for one ingredient as one application.

・In NDAs submitted on and after April 2004, the number of the applications treated in each review process and the total review process time* consumed in FY 2005 are as follows (Median):

* Total review process time is a period consumed by reviewer and applicant sides for approval of products.

Review Process	1. From receipt of applications to first consultation	2. From first consultation to expert discussion	3. From expert discussion to notification of review result	4. From notification of review result to approval
Number of processed cases/ total review process time (median)	58 cases 80 days	22 cases 407 days	25 cases 23 days	24 cases 4.5 days

Note 1: The days shown in each review process are the median of total review process time (the sum of reviewers' and applicants' time clocks).

2: One of the 58 applications in the first review process was withdrawn after the first consultation.

3: The figures for processed cases in the process 2 exclude 5 cases which had the expert discussion without the first consultation.

4: The figures in the process 3 exclude 6 cases whose review result notifications were issued without the expert discussion after the first consultation.

(Results of priority NDA review)

・As to priority review for NDAs specified by the Minister of Health, Labour and Welfare, the Agency aimed to process 50% of all priority NDAs within review process time of 6 months by the end of the effective Midterm Target period.

・Applications for orphan drugs and other drugs that are regarded as highly medically needed, that is, drugs for serious diseases and with distinctly superior efficacy or safety to existing drugs or

treatment, were reviewed on a priority basis.

[Number of approvals in priority NDAs] (cases)

Fiscal Year	2001	2002	2003	2004	2005	Applications filed in and after FY 2004, but approved in FY 2005***
No. of approvals & review process time (median)	21	4	10	22 (2.8 months)* [86%]**	18 (8.9 months)* [28%]**	9 (2.8 months)* [56%]**

* The months shown in parenthesis in each review process are the median of review process time.

** The percentage in bracket [ ] indicates the ratio of the number of applications processed within 6 months of review process time. The results in FY 2005 include priority NDAs filed in and before March 2004 which are out of the target period of the Midterm Targets.

*** The data indicate the number of applications filed in and after FY 2004, and approved in FY 2005. These figures are breakdown of the result in FY 2005.

b. Review of new medical devices

・The Agency aimed to review and complete on 70% of all filed applications for new medical devices within 12 months in FY 2004, aiming at 80% accomplishment 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 to improve and accelerate its operations, such as establishing operating procedures for review and examination.

・As to review of new medical device, in order to carry out its operation promptly and appropriately, the Agency established the implementation manual for approval review of new medical devices as well as the standard operating procedures for the other related work. The Agency also collected monthly data on achievement level of the targeted process time and informed the results to the review staff. The progress management committee for review and related operations had monthly meetings to monitor and examine the operational progress. In the review department, Director of Office of Medical Devices grasped the operational progress on a daily basis, and at the liaison conference of the review related offices, Director of the Center for Product Evaluation and Associate Center Directors provided necessary instructions.

・With the enforcement of the revised PAL in April 2005, the Agency changed the classification of applications for medical devices based on whether they are required to be applied with clinical trial data and whether there are the approval criteria. Low risk medical devices with certification

criteria are currently certified by the third party body but not approved by the Minister.

・As with the medical devices mentioned above, established application categories for *in vitro* diagnostics were revised based on the risk level of the diagnostic information along with the revision of the PAL in April 2005. In addition, *in vitro* diagnostics whose risk level of the diagnostic information is extremely low are currently certified without any approval by the Minister but by the applicant itself. Low risk *in vitro* diagnostics with certification criteria are currently certified by the third party body and not approved by the Minister.

(Review results of new medical devices)

・For the applications for new medical devices submitted in and after April 2004, the Agency approved all of them (5/5 cases) within 12 months, which was the aim in the Midterm targets and FY2005 plan. The median of the review process time was 1.8 months. However, the achievement ratio of the new medical device approvals including applications submitted in and before March 2004 decreased to 82% (9/11 applications), and the median of the review process time was 7.7 months.

[Number of approved new medical devices and median review process time]

Fiscal Year	2002	2003	2004	2005	Applications filed in and after FY 2004, but approved in FY 2005**
No. of approvals & review process time (median)	3 cases (2.9 months)	13 cases (8.9 months)	8 cases (12.7 months) [50%]*	11 cases (7.7 months) [82%]*	5 cases (1.8 months) [100%]**

* The percentage in bracket [ ] indicates the ratio of the number of applications processed within 12 months of review process time. The figure in FY 2005 includes applications filed in and before March 2004, which is excluded from the Midterm Targets.

** The data indicate the number of applications filed in and after FY 2004, and approved in FY 2005. These figures are breakdown of the result in FY 2005.

・For the 132 and 64 applications submitted before and after the establishment of PMDA in April 2004 respectively, the Agency processed these reviews fully considering the targeted review process time. However, the Agency called for medical device companies to withdraw their applications which were considered to be difficult to approve because they had not replied to our inquiries.

・As to the applications submitted before the establishment of the Agency, 94 of them were processed during FY 2004 and 2005. In order to achieve the target on review process time, it is

necessary for the Agency to vigorously process backlog of reviews so that we can concentrate all our resources on the applications submitted after the establishment of PMDA as soon as possible.

[Review results of new medical devices in FY 2005](cases)

	Cases applied	Withdrawn	Approved	Under Review
Applications submitted by March 31, 2004	132	64 (26)	30 (22)	38 [-48]
FY 2004	56	14 (12)	5 (4)	37 [-16]
FY 2005	8	0	1	7 [7]
Total	196 (8)	78 (38)	36 (27)	82 [-57]

Note 1: The figures of “Cases applied” are the number of applications for new medical devices.

2: The figures in parentheses indicate the number of applications that were completed processing in FY 2005. They are included in the number above.

3: The figures in brackets show increase and decrease in number of cases under review of each fiscal year compared with that of the Annual Report FY 2004.

4: Among 36 cases of the total of “Approved” were 21 approved as improved medical devices. Seventeen approved improved medical devices are included in total 27 of “Approved” in parenthesis. In addition, one application which was applied as an improved medical device but approved as a new medical device is excluded.

・In applications for new medical devices submitted on and after April 2004, the number handled and the median of total review process time* consumed in each review process in FY 2005 are as follows:

(* Total review process time is the total time consumed by reviewers and applicants’ side for approval of products.)

Review Process	1. From receipt of applications to first consultation	2. From first consultation to first expert discussion	3. From first expert discussion to notification of review result	4. From notification of review result to approval
Number of processed cases/ median of total review process time	31 cases 57 days	7 cases 294 days	2 cases 262 days	5 cases 12 days

Note 1: The days in each review process is the median of total review process time (the sum of reviewers and applicants time clocks).

2: In this table, one application was not included because its review result notification was issued without the first consultation and first expert discussion.

3: Two applications whose review result notifications were issued without the expert

discussion after having the first consultation were not included.

4: The Expert discussion on review was held several times as needed.

(Results of priority review for new medical devices)

・As to priority review applications for medical devices specified by the Minister of Health, Labour and Welfare, the Agency aims to attain its performance target of reviewing 70% of them within review process time of 9 months by the end of the effective period of the Midterm Targets.

・The Agency reviews applications for approval of orphan medical devices and other devices that are regarded as highly medically needed, that is, medical devices for serious indications and with distinctly superior efficacy or safety to existing medical devices or treatment on a priority basis.

In FY 2005, there were no priority applications.

[Number of approved priority applications for medical devices] (Cases)

	FY 2001	FY 2002	FY 2003	FY 2004	FY 2005
No. of approvals	5	4	4	2	0

c. Compliance review of application materials, GLP, GCP and GPMSP review

・The Agency aims to efficiently conduct on-site and document examinations on 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.

・Moreover, the Agency conducted on-site and document examinations on the materials included in new drug and medical device applications to determine if the tests supporting these 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 properly and accurately in accordance with the reliability criteria.

[Number of conducted conformity reviews]

	FY 2001	FY 2002	FY 2003	FY2004	FY 2005
Document conformity review	151	189	173	161	136
GLP review	24	40	24	20	37
GCP review	120	118	143	73	131
GPMSP review	116	102	66	27	82

* The figures of GCP and GPMSP reviews since FY 2004 show the number of notifications after the evaluation.

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

1) Dissemination of interpretation of GCP operations/ improvement of consultation service
The Agency made efforts to conduct consultations on GCP inspections in any way possible for medical institutions where the inspections were carried out, and encouraged the dissemination of the knowledge on the GCP operation by enriching information such as Q&As and case commentary and points to consider with respect to conduct of clinical trials on the “Operations of Office of Conformity Audit” page of PMDA’s website. In Tokyo and Osaka, the Agency held workshops on GCP and quality assurance for people in charge of drug development and pharmaceutical affairs at companies, clinical research associates (CRAs), auditors, site management organizations (SMOs), and medical professionals; moreover, PMDA staff made lectures in academic conferences for health personnel in order to give them better understanding about GCP.

2) Enhancement and improvement of GCP on-site inspections
・The Agency increased the number of GCP on-site inspections for medical institutions considering assignment of our staff for the service.

・Although a standard process time of conformity audit has not been placed, the Agency made efforts for the audit not to interrupt approval review process, and thus there was no delay in these reviews in FY 2005.

d. Approval review for generic drugs, over-the-counter (OTC) drugs and quasi-drugs
・According to “Standard Administrative Process Time for Approval Review”, Notification No. 960 of Director-General Pharmaceutical Affairs Bureau (PAB), MHW; dated October 1, 1985, the Agency set the standard review process time of applications for generic drugs and others 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 implementation manuals for approval review of generic drugs, OTC drugs, insecticide and rodenticide and quasi-drugs as well as the standard operating procedures for these operations. The committee on progress management of review related operations monthly collected data on the achievement level of targeted process time and informed the results to the review staff.

・The number of generic drugs, OTC drugs and quasi-drugs approved from FY 2001 to FY 2005 was as follows:

[Results of approved generic drugs and others]

	FY 2001	FY 2002	FY 2003	FY 2004	**FY 2005**
Generic drugs	3,159	1,831	2,243	3,476	**1,919**
- Number of approved applications filed in and after April 2004 (breakdown)	—	—	—	1,468	**1,782**
- Median of review process time (for the applications filed in and after April 2004)	—	—	—	3.3 months	**7.3 months**
- Achievement rates on target process time (for the applications filed in and after April 2004)	—	—	—	100%	**98%**
OTC drugs	4,865	2,956	1,934	1,781	**1,570**
- Number of approved applications filed in and after April 2004 (breakdown)	—	—	—	270	**1,163**
- Median of review process time (for the applications filed in and after April 2004)	—	—	—	8.7 months	**7.8 months**
- Achievement rates on target process time (for the applications filed in and after April 2004)	—	—	—	83%	**84%**
Quasi-drugs	5,260	3,605	2,992	2,972	**2,611**
- Number of approved applications filed in and after April 2004 (breakdown)	—	—	—	1,431	**2,575**
- Median of review process time (for the applications filed in and after April 2004)	—	—	—	5.6 months	**5.3 months**
- Achievement rates on target process time (for the applications filed in and after April 2004)	—	—	—	89%	**86%**
Total	13,284	8,392	7,169	8,229	**6,100**
- Number of approved applications filed in and after April 2004 (breakdown)				3,169	**5,520**

・During FY 2005, as to achievement ratio of the target standard review process time for applications applied on and after April 1, 2004, the Agency achieved 98% by reviewing 1,737 of 1,782 applications for generic drugs within 12 months, 84% by reviewing 980 of 1,163 applications for OTC drugs within 10 months, and 86% by reviewing 2,212 of 2,575 applications for quasi-drugs within 6 months; the Agency attained the targeted standard process time (median) indicated in the MHW Notification No. 960 issued by Director of PAB dated October 1, 1985.

【Review results of generic and other drug reviews】

	No. of Total Applications	Withdrawals*	Approvals	Under Review
Generic drugs	4,299 (1,829)**	221	1,919	2,159
OTC drugs	3,921 (1,131)	144	1,570	2,207
Quasi-drugs	4,244 (2,286)	118	2,611	1,495

*) The number of withdrawals includes applications that were changed to another review category in review process.

**) The figures in parentheses of the “No. of Total Applications” indicate applications submitted in FY 2005, which are included in the figures above.

・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, etc.

【The number of document compliance review of generic drugs from FY 2001 to FY 2005】

	FY 2001	FY 2002	FY 2003	FY 2004	FY 2005
Number of audits	1,129	1,228	1,425	1,090	941

3. Reinforcement of clinical trial consultation system

The Agency is required to improve its pre-application consultation system and give priority to conducting clinical trial consultations for drugs and medical devices expected to be highly useful in order to shorten the period of time for their approval.

a. Establishment of priority consultation system

・The Agency established the priority clinical trial consultation system in FY 2004 to expedite review and approval for the products with high social needs; thereby, enabling consultation on conformity to reliability criteria and increasing opportunities to provide guidance and advice on approval applications before the submission.

・As for the priority CT consultation system for drugs considered to be especially important from a medical standpoint, the Agency received the applications for 20 ingredients and conducted the priority consultations on 17 ingredients (including 2 ingredients applied in FY 2004) of them that were designated as subjects of such consultations in FY 2005. For these designated ingredients, the Agency provided a total of 12 clinical trial consultations on a priority basis in FY 2005.

The Agency received applications neither for priority consultations of medical devices nor for face-to-face consultations regarding compliance review on application materials of drugs and medical devices designated as priority consultation items.

b. Acceleration of clinical trial consultations for drugs

・The Agency worked to expedite clinical trial consultation procedures through shortening the duration from application for clinical trial consultation to face-to-face consultation and to the 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 manual, making self-check-up on compliance with the manual and informing the relevant staff about the observance situations.

・Concretely, as for 10% of all applications submitted, the Agency aims to confirm records on face-to-face consultations within 30 business days since the consultations are made, and as to 50% of priority consultation applications, the Agency intends to carry out the first priority consultation for clinical trial within 30 business days since the consultations are requested.

・The number of clinical trial consultations for drugs conducted in FY 2005 was 218 which excluded 14 withdrawn applications. The Agency attained 13% in confirming records on face-to-face consultations within 30 business days since the consultations were made (25 of 193 cases), and reached 57.1% in conducting the first CT consultation within 30 business days since the consultations were requested (12 of 21 cases); thereby the Agency succeeded in our goal in FY 2005.

・Reservations of CT consultations for NDAs were always fully booked by half a year ahead because expectations and demands for clinical trial consultations significantly increased due to the integration of the consultation and approval review operations. Therefore, in March 2005, PMDA temporarily suspended receipt of the reservation requests for the consultations scheduled in and after October 2005. Then in April 2005, as the provisional measure which is effective by the end of FY 2007, the Agency posted on PMDA's website four months ahead the monthly schedule regarding available dates for the consultations of each application category. In addition, the Agency has introduced the new scoring system to arrange consultation schedule. In this system, PMDA grades the applications according to their importance in "Consultation Category" and "Development Stage Category", and the applicants for the consultations who gain higher scores in total can be prioritized in receiving the consultation service. The determination is made three months before the consultation. The new system established in July 2005 is applied to applications for clinical trial consultations to be conducted this October.

・In March 2006, learning from the situation of the new CT consultation system for 6 months, PMDA modified the scoring system for the CT consultations scheduled in and after July 2006. Concretely speaking, the Agency is going to give additional scores to applications every time they are left out of the previous selections, and applications for new active ingredients which are developed in collaborative multinational clinical trials with a purpose of expediting these developments. Besides, the Agency started the document consultation on a trial basis, and introduced a simpler list format to record dialogue between reviewer and applicant in face-to-face consultations in addition to the full report.

As mentioned in “Priority Issues of PMDA in FY 2005”, the Agency aimed to have 220 consultations approximately in FY 2005, which were up 10% from the previous year, and attained the goal by conducting 232 consultations. In FY 2006, we are targeting 240 consultations.

[Number of clinical trial consultations]

	FY 2002	FY 2003	FY 2004	FY 2005
Applications for CT consultation	246	185	334	243 (339)*
Conducted CT consultations	225	206	193	218
Withdrawn	-	-	23	14
Total	225	206	216	232

* The parenthesis ( ) indicates the total number of applications including reapplications because of rejection.

4. Promotion of international harmonization

・The Agency needs to make efforts to accelerate review process for new drug approvals 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 process time (process time of the reviewer side plus that of the applicant side for products approved in a year) for the next Midterm Targets period.

・Approach to international harmonization in ICH and others

・In the FY 2005 plan, the agency targeted to actively attend ICH Steering Committee Meetings and Expert Working Groups, and to promote the consistency and harmonization of Japanese standards with international standards for the development of review data which were agreed among Japan, US, and EU in ICH Meetings.

・Toward the global harmonization and development of the shared standards, the Agency actively attended the Steering Committee Meetings and Expert Working Groups of ICH and GHTF, etc.

* ICH: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

* GHTF: The Global Harmonization Task Force for Medical Devices

【International conferences on drugs】

・The Agency attended the following ICH expert working group on review and post-marketing safety measures for drugs and relevant issues:

ICH Expert Working Groups

・Electronic Standards for the Transfer of Regulatory Information (M2)

・Data Elements for Transmission of Individual Case Safety Reports (E2B)

・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)

・MP Quality Systems (Q10)

Regulatory Acceptance of Pharmacopoeial Interchangeability (Q4B)

Data Elements and Standards for Drug Dictionaries (M5)

The Pharmacopoeial Discussion Group (PDG)

MedDRA (Medical Dictionary for Regulatory Activities) Steering Committee Meeting

OECD Pharmacogenetics workshop

・In order for PMDA to substantially develop an information exchange system for consultation, review and (post-marketing) safety measures in cooperation with US and EU, the Agency held discussions with FDA and EMEA in collaboration with MHLW.

【International conferences on medical devices】

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

・ISO/TC/194//WG 4 (June and July, 2005)

・ISO/TC/194 meeting in Berlin (December, 2005)

・GHTF SG1TF, SG1, IVD subgroup

・GHTF, SG2

・GHTF, SG4

・GHTF, SG5

b. Introduction of total review process time (system/ idea)

・The Agency monitors and manages total review process time taking into account international

trends in order to improve its operations.

・The median total review process time for 60 NDAs and 11 new medical device applications approved in FY 2005 were both 22.4 months.

・The Agency reinforced the clinical trial consultation function to solve as many basic problems as possible before application submission, and advised applicants to withdraw their applications whose review was suspended for any reason caused by the applicants themselves.

(2) Improvement of Reliability in Operations

1. Planned recruitment of staff with advanced expertise and systematic provision of training opportunities

a. Staff recruitment

・In order to ensure smooth enforcement of 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 expertise, mainly through open recruitment ensuring its impartiality as an incorporated administrative agency. (refer to “PART1, (5), 4. Securing human resources through open recruitment” on page 25).

b. Systematic support for training

・The Agency worked to improve quality and capability of its staff members by providing them with training opportunities through internal/external training organizations in a systematic fashion according to the quality and ability of each individual. (refer to “PART1, (5), 2. Systematic implementation of staff training” on page 23).

2. Development of GMP on-site review system

・The revised PAL that came into effect on April 1, 2005 requires the manufacturing establishments to comply with requirements specified in the newly established/revised GMP Ministerial Ordinance on drugs and quasi-drugs, and QMS Ministerial Ordinance on Medical Devices and *In Vitro* Diagnostics as a pre-requisite for marketing authorization.

・Therefore, in addition to the manufacturing establishments licensed by the Minister, following manufacturing establishments became subjects of the GMP/QMS on/off-site reviews to be conducted by the Agency,: 1) foreign manufacturing establishments related to all products that require regulatory approval; 2) domestic manufacturing establishments related to new drugs, new medical devices and Class IV medical devices (high-risk medical devices such as pacemakers).

* GMP Ministerial Ordinance on drugs and quasi-drugs:
“Standards for Manufacturing Control and Quality Control of Drugs and Quasi-drugs”, MHLW

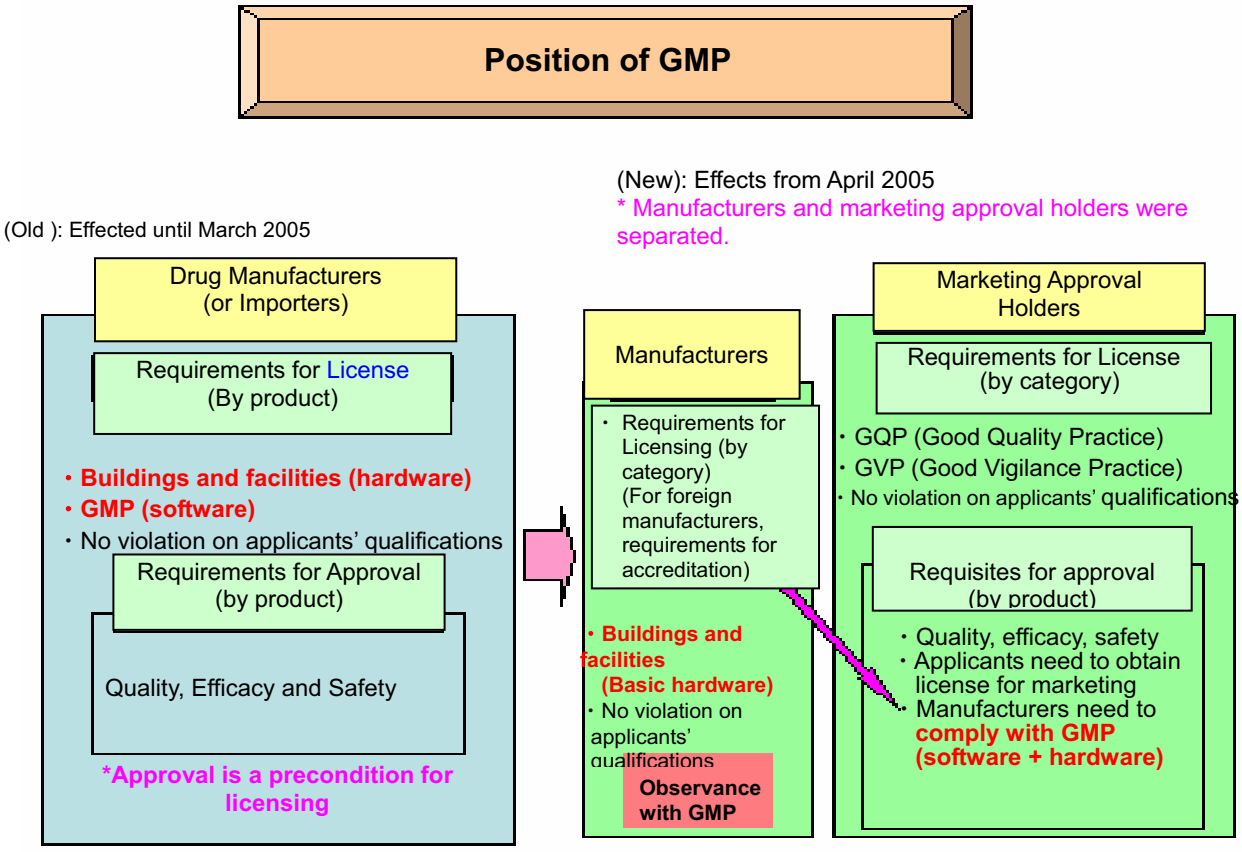
Ministerial Ordinance No. 179 revised in December, 2004

* QMS Ministerial Ordinance on Medical Devices and *In Vitro* Diagnostics:
"Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostics", MHLW Ministerial Ordinance No. 169 revised in December, 2004

* QMS: Quality Management System

・The number of GMP/QMS inspectors including advisers and temporary staff was 7 when the Office of Compliance and Standards was established on April 1, 2004. As a result of the continued recruiting, their number increased to 18 and 26 in April 1, 2005 and April 1, 2006, respectively. At the same time, in order to reinforce their expertise, the inspectors participated in training programs domestically and abroad including seminars hosted by Pharmaceutical Inspection Cooperation Scheme (PIC/S), the Europe-based international organization on GMP inspection.

・In the first half of fiscal 2005, no on-site inspections were conducted abroad. In the second half of the year, 13 on-site inspections on compliance with GMP/QMS were conducted on foreign manufacturing establishments of new drugs and new medical devices and 2 on-the-spot inspections (based on the PAL) were conducted on foreign manufacturing establishment.



3. Effective use of external experts

・The Agency assigned external experts to advisers in order to utilize their knowledge on scientifically important matters, especially for the highly specialized fields of review operations. The number of the assigned advisors was 847 as of March 31, 2006.

4. System development for efficient review operations

In reviews and related operations, PMDA mainly uses a new computer management system for application and review shared with the Pharmaceutical and Food Safety Bureau of MHLW, Regional Bureau of Health and Welfare, local prefectural governments, pharmaceutical companies, etc. Other specific operational/support systems that PMDA uses for review, examination and management of fees are the following systems; i) Drug review support system, ii) New drug database system, iii) Device system, iv) Conformity review support system, v) Medical device review support system, vi) Clinical trial database system, vii) Electronic common technical document (eCTD) viewer system, viii) Medical device malfunction reporting system (only for reference), ix) ADR reporting system (only for reference).

・With this new application and review system, the Agency sequentially manages whole process

from acceptance of applications and notifications to their authorization for marketing approval and business license on new drugs, quasi-drugs, cosmetics and medical devices. In addition, the system is utilized in a series of related operations for official license, such as development of application data using application software, acceptance of the application data, data exchange among review institutions, recording of review note, preparation of approval certificate, and management of approval registration list.

・In fiscal 2005, in order to attain the goals set in the Midterm targets and plan by promptly and efficiently promoting review and examination operations, there is the urgent need for the Agency to develop the following systems:

1) Development of review support system to conduct approval review smoothly and efficiently with the eCTD system introduced in April 2005
2) Reflection of information on GMP and its progress, GLP and GCP reviews for approval application to the new application review system
3) Development of review support system in which reviewers from any office can access to the review related systems by the authority to refer to database of approval review managed by other offices
4) Improvement of a system to grasp attainment level of goals such as reviewers' processing time and establishment of a statistics tabulation system specified in the Midterm targets and plan
5) Development of a system to manage historical information on reviewers in charge of each application, to organize inquiry information and to calculate the cost by inputting review time

5. Strengthening of partnership with foreign regulatory authorities

・In review-related and post-marketing safety operations, 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 more clinical trials are conducted, by establishing a new division dedicated to international operations and promoting the exchange of trainees (visitors) with foreign regulatory authorities.

・The Agency promoted 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 post-marketing safety operations at the APEC conference in Taipei and other conferences to improve international recognition of the Agency and to take the first step for establishment of cooperative framework with Asian countries (refer to Part 2, 2, (1), 4. on page 58). The Agency also implemented the following measures to further strengthen its relationships with foreign regulatory authorities:

1) The Agency collected information on review and post-marketing safety operation systems in the US FDA (Food and Drug Administration), EMEA (European Medicines Agency), etc. In addition, the Agency also exchanged information with them on their methods of conducting operations and other matters.
2) Based on the “Administrative Rule on Overseas Training on a Long-term Basis”, the Agency dispatched one employee each to FDA and EMEA respectively after screening the applicants.
3) The Agency accepted two trainees from the Singaporean regulatory authority.

6. Evaluation of such advanced technologies as biotechnology and genomics/ Cooperation in developing 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 utilizes external experts with high knowledge effectively to review these technologies and cooperates in developing the government guidelines for reviewing new technology-based products.

・The Agency compiled the points to consider in preparing application dossier and provided the information to industry and academia through academic conferences to facilitate guidance and review in PMDA.

・In order to expedite the review operation for new influenza vaccine using recombinant DNA technology, the Agency offered guidance to companies from its development stage as necessary and sent the staff to WHO and other conferences for the information collection.

・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, Pharmacogenomics is expected to be applied to drug development. However, since there are still many things to be considered, such as how to apply Pharmagenomics to clinical trials and review operations, the Agency officially established the “Pharmacogenomics Discussion Group (PDG)” internally to collect scientific information. Based on the government’s “notification regarding information provision to administrative agencies related to development of the guideline for the use of Pharmacogenomics in clinical trials of drugs” issued in March 2005, the Agency scrutinized the information regarding Pharmacogenomics submitted to MHLW, and commenced to consider toward developing the concrete guideline in concert with MHLW.

7. Promotion of appropriate clinical trials

・To improve the quality of domestic clinical trials, the Agency educates healthcare professionals and patients about appropriate clinical trials through its website and public relations, taking into

consideration the results of on-site inspections of clinical trials at medical institutions, etc.

・The Agency updated information on the number of notifications of clinical trials and ADR reports posted on its website starting fiscal 2004 on an as needed basis.

・In order to help improve clinical trial systems at medical institutions, the Agency provided pharmacists and nurses of the medical institutions with training for Clinical Research Coordinators, lectures in September 2005 and practical training from October 2005 to February 2006.

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

・In FY 2005, middle year of the three-year plan period, the Agency subsidized the same two facilities as last year:
- 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 suggestions often made on PMDA's GCP inspections on the website. Also, we delivered lectures at academic conferences so that it would help improve the quality of clinical trials.

8. Prompt provision of information such as review reports

・In promoting transparency of approval review operations and appropriate use of drugs by patients, the Agency has, with understanding of and in cooperation with related companies, and also in cooperation with MHLW, posted information on approval of new drugs etc. on our Information Website, in the following manner:

(Review reports on new drugs)

・Based on the contents of the submitted 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 (PAFSC) (hereinafter referred to as the "Applications to be Discussed" and "Applications to be Reported" respectively). Among data on newly approved drugs, with regard to the "Applications to be Discussed", the Agency disclosed "Review Reports" which describe the process and results of the reviews, plus "Summaries of Application Dossier" submitted by applicants; with regard to the "Applications to be Reported", the Agency disclosed

“Review Reports”.

・Based on the Notification of the Evaluation and Licensing Division of MHLW (Shinsa Kanri Kacho) the Agency disclosed the information on each application after conferring with the related companies about its content.

・In FY 2005, the Agency finalized 74 review reports and 57 summaries of application dossier to be officially disclosed.

(Review reports on new medical devices)

The Agency also disclosed sequentially review reports on new medical devices according to the procedures specified in the Notification of Office of Medical Devices Evaluation, Evaluation & Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW dated September 22, 2005.

The Agency disclosed review reports of all the 9 applications approved in FY 2004 and 2005, and also provided review reports on the medical devices approved from FY 2001 to FY 2004.

・In order to help related companies understand the quality standard of application materials which are required for new medical devices review, the Agency posted the seminar documents on its web page, “Information for those who consider taking pre-application consultations or submitting approval application for medical devices” (http://www.pmda.go.jp/shonin/iryoshinseisoudan.html).

(3) Reinforcement of Post-marketing Safety Operations including information management and risk management system

1. Basic direction of post-marketing safety measures

The agency seeks to improve safety of marketed drugs and medical devices, and to enable patients and medical professionals to appropriately use them. To achieve these goals, the Agency is required to: make efforts in efficient collection and examination of safety information; to expeditiously process the information; to plan adequate safety measures; and to promptly disseminate easy-to-understand safety information. We are also improving operational functions of review and safety operations so that they can smoothly work as an inseparable pair.

The number of reports on ADRs (Adverse Drug Reaction) and malfunctions of medical devices reported to PMDA domestically and internationally is around 90,000 and 10,000 cases respectively a year. This information is registered into PMDA’s database to share with MHLW. The Agency is making efforts to take effective safety measures for marketed drugs and medical devices by strengthening cooperation between its review and safety offices, and between its

safety and relief funds offices.

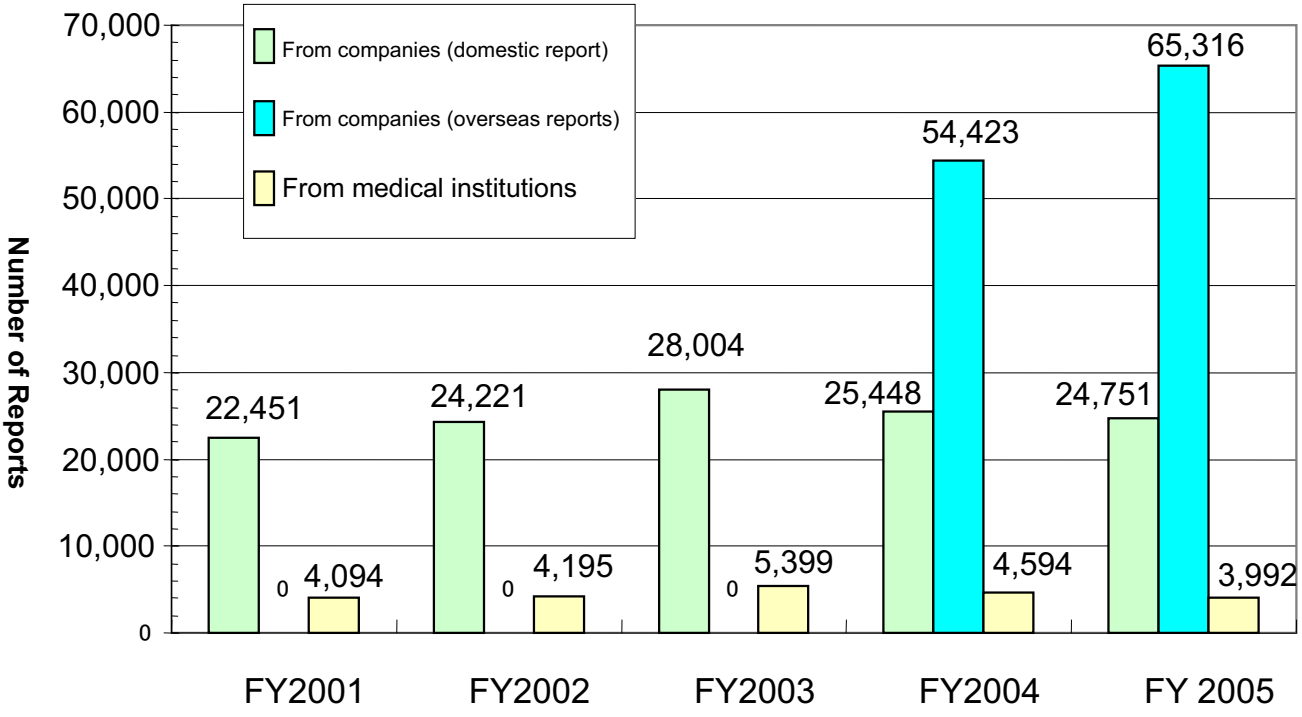
・With matters examined daily by the PMDA staff regarding ADR and medical device malfunction reports and information on safety measures taken abroad, the Agency contacts and coordinates with MHLW every week. Then, based on experts' opinions gathered about once every five weeks, we report to MHLW on the proposed safety measures including revision of precautions. As for issues of urgency, the Agency responds immediately without going through the process mentioned above.

・The Agency distributes important safety information such as revision of precautions to medical professionals and related companies by e-mail when it is issued by MHLW, and also we are working hard for reinforcing the information service by posting safety information about package inserts, revision of precautions, recall, and drug guides for patients on our Information Website (http://www.info.pmda.go.jp/).

The Agency is on the process to develop the method (Data-Mining Technique) to analyze the enormous amount of compiled reports on ADR and medical device malfunction by using computer technology and statistical techniques and thereby to take measures, to forecast and prevent risks at an early stage. This technique is scheduled to be introduced into PMDA's operations by FY 2008.

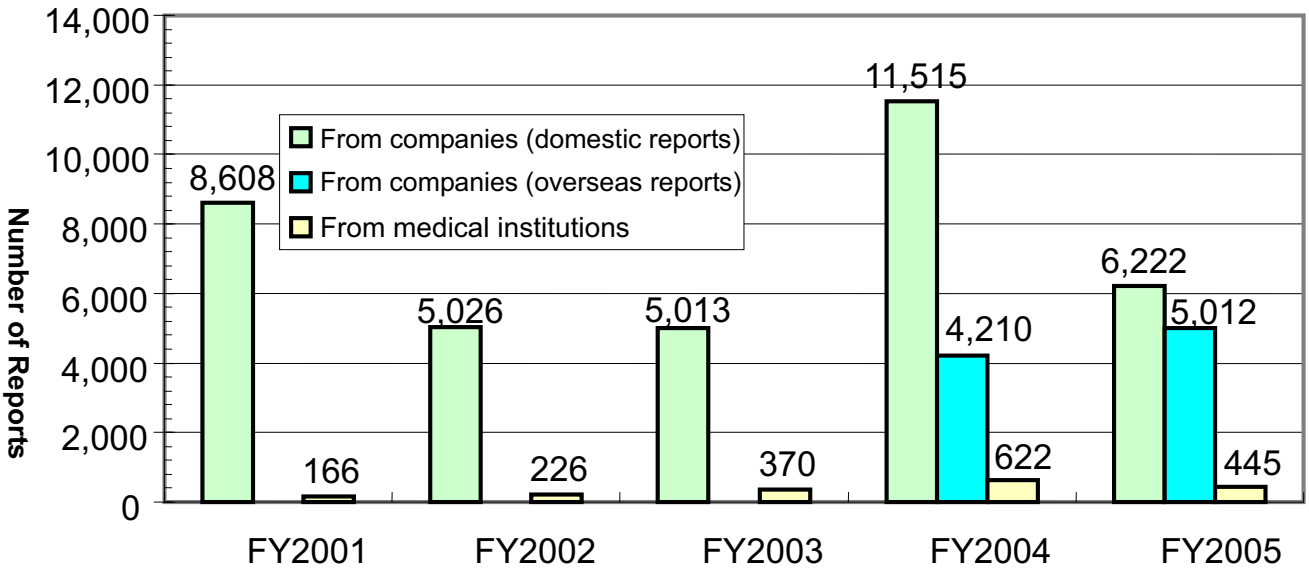
・As for post-marketing safety operations, the Agency aims to take proactive safety measures by predicting and preventing risks through scientific evaluation and analysis. The Agency is also enhancing the safety measures by establishing a division which conducts the signal extraction operation by setting up a sentinel medical institution network and introducing data mining technique.

Change in the number of ADR/Infectious Disease Reports

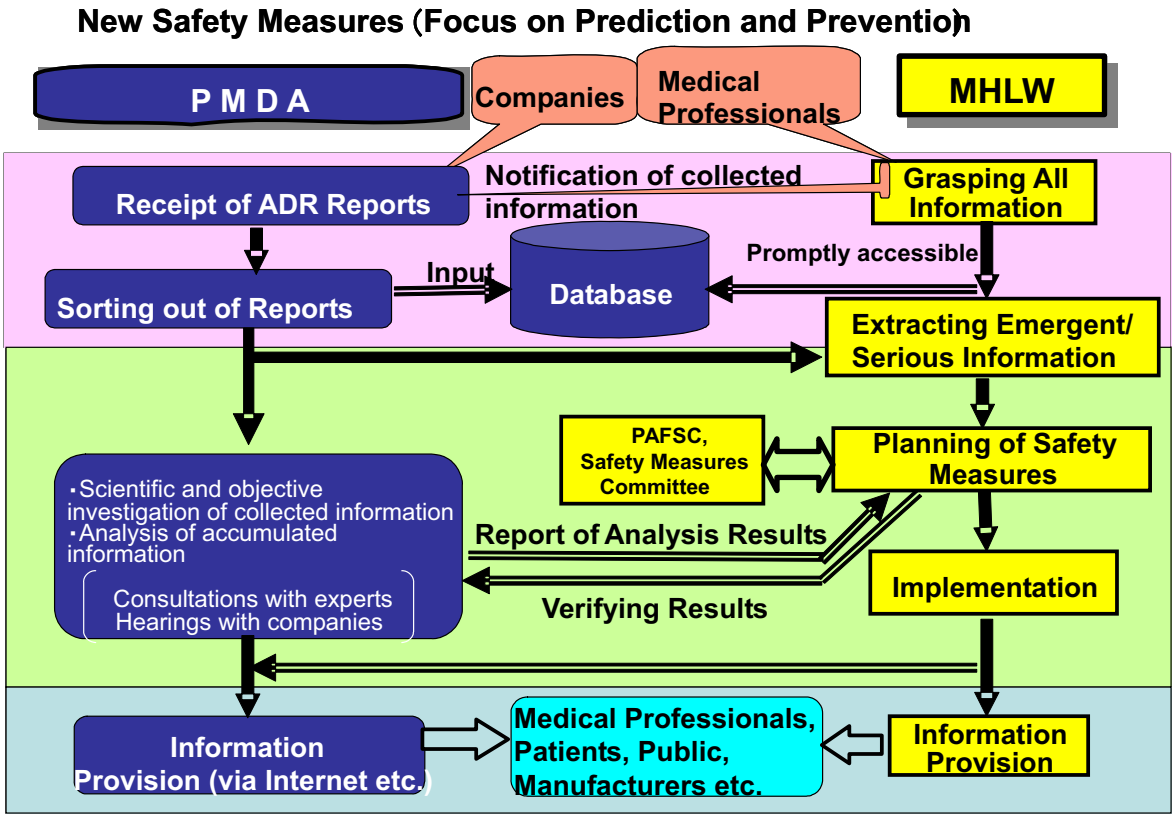


Note: The overseas company reports were not tallied before FY2004.

Change in the number of Device Malfunction Reports



Note: The Company Reports submitted by FY2003 include overseas reports.



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

The Agency is driving for introducing the data mining technique by the end of the Midterm Targets period in order to find new relevancy among multiple adverse reaction information, to study and introduce techniques for the detection and analyses of new safety information, and to take preventive measures for adverse reactions.

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.

◆ What is data mining technique?

The data mining technique is a method to extract events that occur frequently and simultaneously as highly correlative events from a large amount of data accumulated in a database. The word “data mining” means the activity of retrieving only useful information by accessing very large volumes of data (=database) like taking ore from mines.

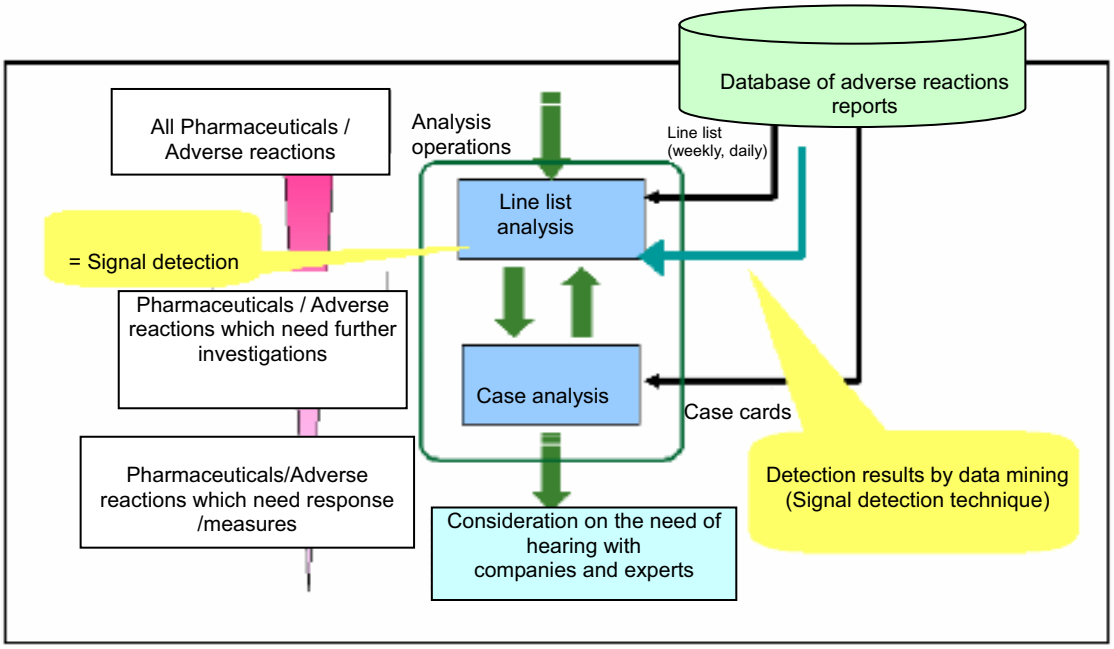
Specifically, the data mining method is to detect combination (signals) of drugs and ADRs with likely causality from the database of ADR reports. The retrieved signals are evaluated by clinical and other experts and utilized for taking appropriate measures. This new technique is expected to become an operational support tool which enables staff in charge of post-marketing safety measures to find signals at an early stage.

・In FY 2004, the Agency mainly examined the signal extraction method as the data mining technique to be introduced to PMDA and sought its sophistication to contribute to post-marketing safety operations. The development plan, effective until FY 2008, was established to achieve this goal.

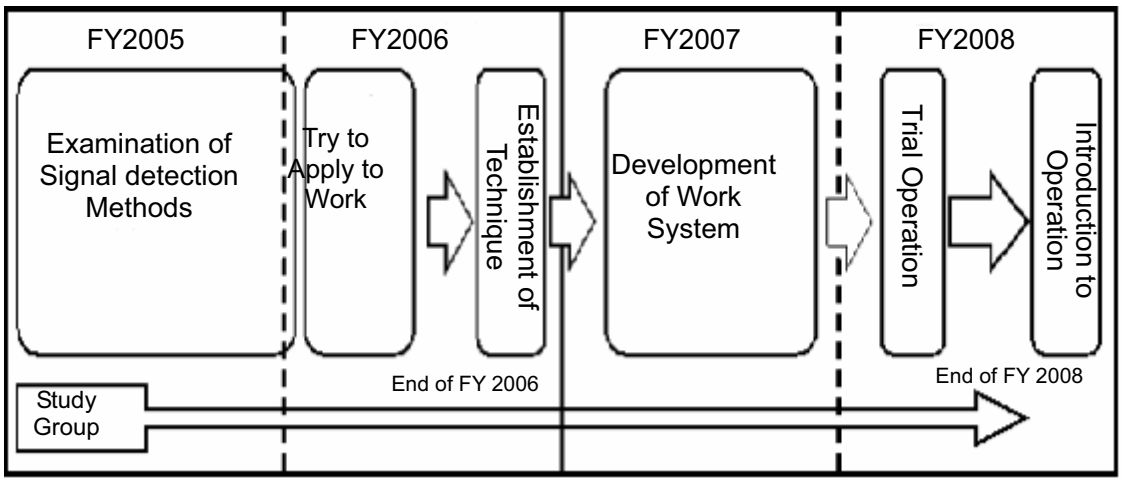
・In FY 2005, the Agency examined various signal extraction methods which are introduced in regulatory authorities such as US FDA, MHRA (UK) and WHO based on consideration of the issue in FY 2004. At the same time, we considered compatibility of those methods, such as validity of detected signals, and timing of the detection by applying these methods used in foreign countries to Japanese data.

In FY 2006, the Agency aims to establish more advanced and accurate methods that can detect signals from information on concomitant drugs and demographics of patients (e.g. sex and age), etc. among collected ADR reports based on the study in FY 2005. By the end of the Midterm Target period (FY 2008), the Agency will introduce the methods into post-marketing safety operations.

Application of Data Mining Method to Post-marketing Safety Operations



Schedule Plan for Introduction of Data Mining Technique to Operations

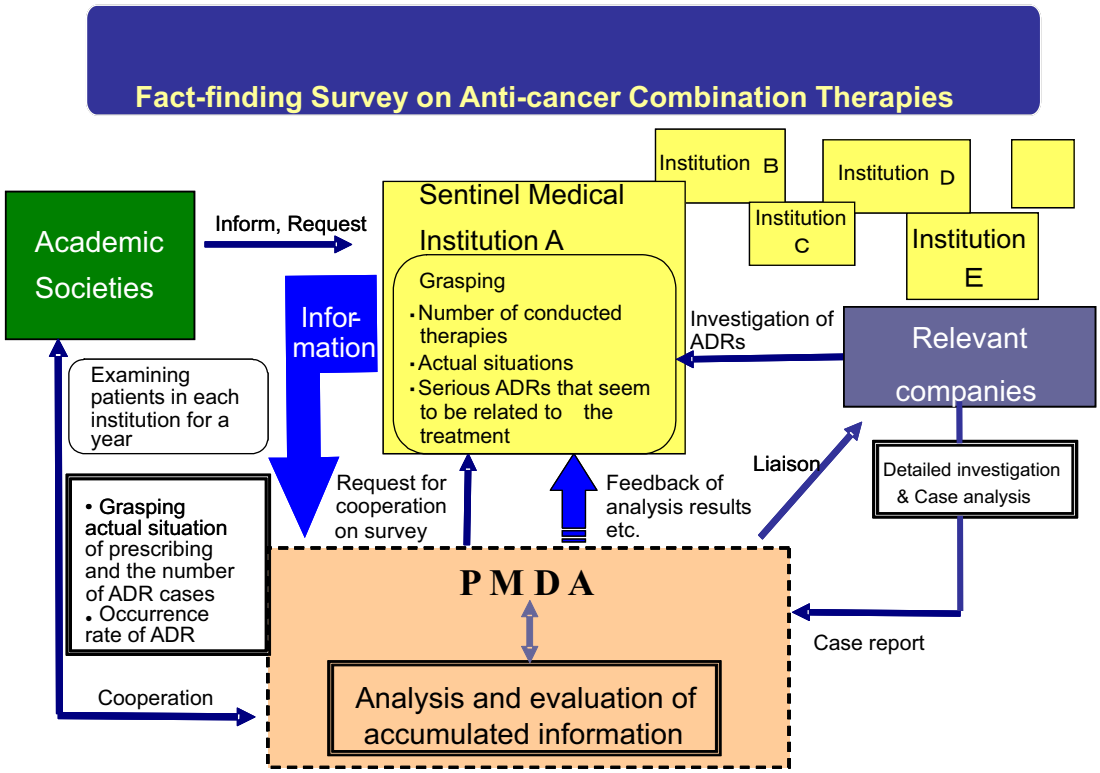


3. Establishment of sentinel medical institution network

During the Midterm Plan period, the Agency plans to establish a new Sentinel Medical Institution Network to focus its post-marketing safety measures. This network aims to collect information intensively within a certain period of time from the medical institutions organized by specific therapeutic categories, products and diseases in cooperation with the review department to improve the accuracy of analysis of ADR information.

・In June 2005, the Agency started to conduct a fact-finding survey to investigate usage and ADRs of 22 anti-cancer combination therapies. With approval by the ethical review board of each trial site, 74 institutions joined the network, and around 2,200 patients were registered by the end of March 2006. The Agency received 260 ADR reports by the end of March 2006; however, there were no reports which required early action.

・The Agency will complete the fact-finding survey in FY 2006, and conduct counting and analyzing the results in FY 2007.



[Reference] Surveyed anti-cancer combination therapies (22 therapies)

*The 22-therapy categorization is based on the PMDA's own categorization applied for the survey.

1	AC therapy (Breast cancer)
2	Pamidronate Disodium (Breast cancer)
3 (1)	Ifosfamide single therapy (Bone and soft tissue tumor)
(2)	Doxorubicin single therapy (Bone and soft tissue tumor)
(3)	Ifosfamide and doxorubicin combination therapy (Bone and soft tissue tumor)
4 (1)	Ifosfamide (Pediatric solid tumor)
(2)	Doxorubicin (Pediatric solid tumor)
(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)
(2)	DHAP (Malignant lymphoma)
12 (1)	Cisplatin (Pediatric solid tumor)
(2)	Carboplatin (Pediatric solid tumor)
(3)	Cisplatin (Medulloblastoma)
13	Actinomycin (Ewing's sarcoma family of tumors)
14 (1)	EC therapy (Breast cancer)
(2)	CEF therapy (Breast cancer)

・The Agency plans to conduct a research in order to grasp problems in collecting safety information in the pediatric field and to confirm safety of medication for children. This research will be conducted in cooperation with "Supporting Information Collection Project on Medication for Children" of MHLW and drugs which were designated to be surveyed in the project will be studied in terms of safety. In addition, the Agency is going to designate the following drugs as subjects of the research: 1) among drugs whose package inserts include the description that "its safety for children has not been confirmed", those drugs on which academic societies request to change the description; 2) drugs whose safety information for children needs to be collected from multiple companies.

・In FY 2005, the Agency held the orientation for 29 major medical institutions including pediatric hospitals that were asked to cooperate for the research, coordinated between relevant academic

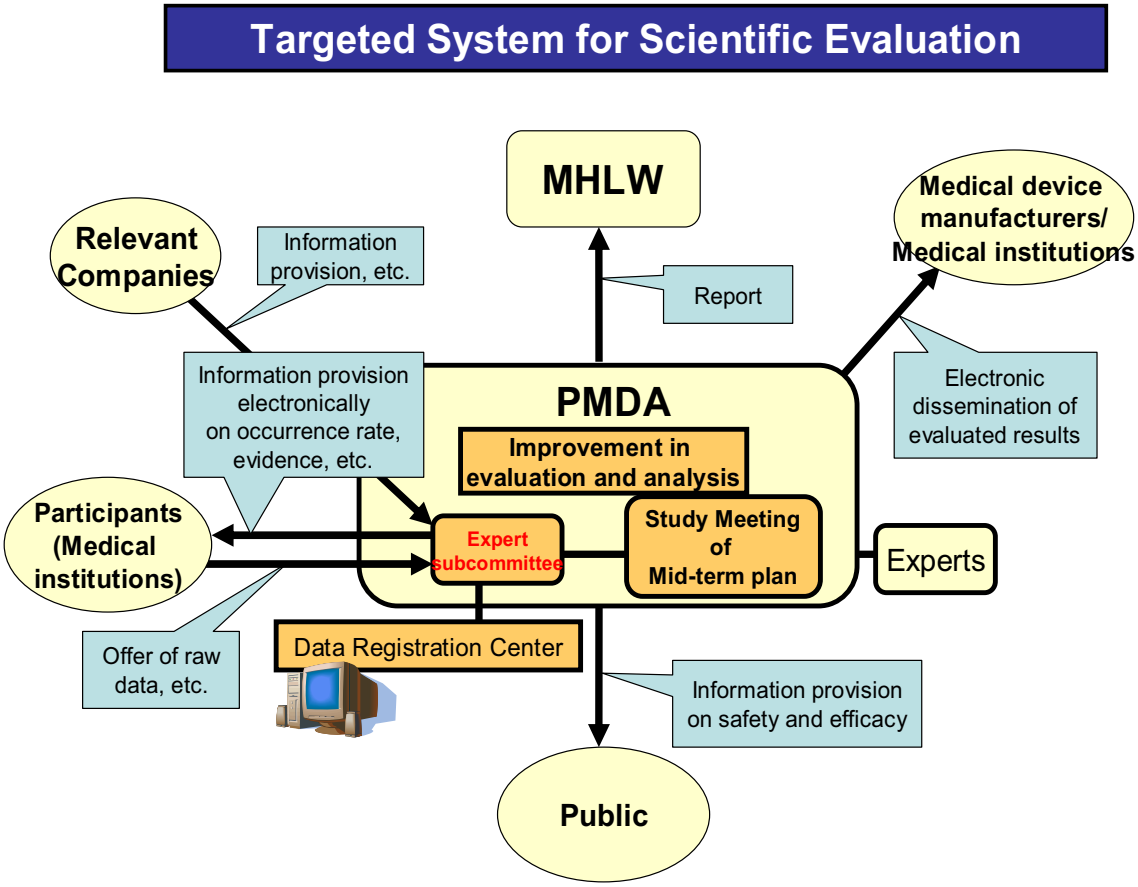
societies and industry, and prepared for implementation of the research with MHLW.

4. Study on system for collection and evaluation of information/reports on medical device malfunctions

・The Agency has been making efforts to comprehend the certain level of occurrence rate of medical device malfunctions that are not attributable to structural defects but would occur at a certain rate due to their characteristics. In order to consider developing a system for scientific evaluation on such malfunctions, the Agency held the review meeting consisted of medical professionals and experts. Based on remarks made by the committee, the Agency selected two medical devices for the pilot study, coronary stents and implantable drug infusion instruments whose occurrence frequency of malfunction is relatively high. In FY 2005, the Agency established the expert committee on implantable drug infusion instruments. In the committee, the implementation guideline was developed and participating institutions for the study were confirmed. As to selecting members of the expert committee for coronary stent, the Agency is coordinating with the relevant academic societies.

・For high-risk medical devices such as implantable pacemakers that require tracking*, the Agency plans to establish a system to collect and evaluate data regarding the operational status of medical devices including information on the malfunction rates over time. The Agency has gathered the information by attending meetings of a scientific research team under MHLW as the observer. Additionally, for collecting the temporal data on malfunction rate of implantable leads which are connected to pacemakers, the Agency has just started to select members of the expert committee and developed the guideline.

* Medical devices to be tracked:
The marketing approval holders (MAH) of such devices are obliged to develop and maintain contact information lists of the users so that they can take action promptly and appropriately in case of the malfunction occurrence, etc.
Under the Pharmaceutical Affairs Law, such devices are categorized to as specially designated medical devices.



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

・Under the Pharmaceutical Affairs Law (PAL), marketing approval holders of drugs and medical devices are required to directly report to PMDA ADRs, medical device malfunctions and infectious diseases in and after April 2004. These reports have been stored in PMDA's database and managed for information-sharing with MHLW.

・In addition, those reports which medical professionals such as doctors and pharmacists submit to the Ministry— that was made obligatory under the PAL since July 2003—also have been stored in PMDA's database and managed for information-sharing with MHLW.

・Regarding investigation of ADR and malfunction reports, the Agency has been working closely and holding regular meetings with Safety Division of MHLW. Moreover, we are gathering opinions from experts about once every 5 weeks, and reporting safety measure plans such as revision of precautions to MHLW. As for a matter of urgency, the Agency responds immediately without going through the process mentioned above.

・As for cooperation with review department within PMDA: Review Department has been working supportively for investigation on ADR cases of drugs subject to early postmarketing-phase

vigilance (EPPV), and member of staff of Office of Safety has been participating in review operations for new drugs and medical devices, such as expert discussions. As for cooperation with the office of Relief Fund, names of drugs and ADRs and other information on eligible and ineligible cases are provided in order to make use of them for safety measures.

・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) For efficient reception/data entry operation, the Agency:
a. raised online reporting rate to 86.4 % on a full-year basis by having consultations for companies that had not yet introduced the system, and thereby was able to reduce the workload associated with data entry;
b. improved efficiency of receiving ADR reports by employing online data entry tools;
c. increased the number of staff designated to input data;
d. updated the master files of drug and company names.
2) To improve the quality of staff in charge of collecting/arranging/examining reports, the Agency encouraged such staff to attend academic conferences (a total of 13 staff members attended 10 conferences) and gathered information through the conferences.
3) While cooperating with MHLW efficiently, the Agency established standard operating procedures for efficient operations.
4) The Agency regularly held liaison meetings on drugs and on medical devices every week respectively to exchange information and discuss the matter with MHLW.

6. Online reporting system on ADRs and medical device malfunctions

a. Improvement of online reporting rate from companies

・In order to effectively and efficiently collect safety information from companies by utilizing IT, the Agency improved the environment for the online reporting system for ADRs and infectious diseases, which was commenced from October 2003, adopting the forms specified by ICH standards. The target rate of online reporting in FY 2005 was 75% by asking companies for their cooperation.

・For this, while improving environment for electronic transmission of information by introducing and providing an online reporting tools on its website, the Agency monitored the electronic reporting rate monthly and directly asked major companies that had not yet reported online for their cooperation, and also promoted the system through lectures at academic conferences. As a result, the reporting rate in FY 2005 reached 86.4% on a full-year basis exceeding targeted 75%.

b. Development of online reporting system for medical institutions and pharmacies

・MHLW started a system that allows medical institutions, pharmacies and others to report their information on ADRs and infections conveniently via the internet in April 2005.

7. Establishment of postmarketing safety system through information feedback

a. Feedback to companies

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

・In order to contribute to improve the risk management system of companies, the Agency is strengthening a system that enables a company to secure access to information on ADR reports that pertain to its own products, which were reported by medical institutions and other companies. In FY 2005, the Agency decided to post on its website about all ADR information reported by companies since PMDA was established in 2004, and started to sequentially release the ADR line list in January 2006.

ii) Consultations for companies

・In order to contribute to improve safety measures of companies, the Agency provided companies with consultations concerning drugs, medical devices and medical safety. The issues covered in this consultation were about revision of package inserts, risk management plans for marketed products, development of drug guide for patients, and improvement of products to prevent medical accidents based on analyses of near-incident (hiyari-hatto) cases.

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

・In order to implement appropriate consultations, the Agency provided meetings to explain drug summaries subject to EPPV in cooperation with industry. Also, the Agency reinforced its internal organization to analyze hiyari-hatto incidents collected from the medical arena by holding four review sessions.

・The Safety Department of PMDA cooperatively responded to inquiries from the Review Department to confirm similar names of new drugs.

b. Feedback to health professionals

・During FY 2005, the Agency took the following measures to disseminate safety information on drugs and medical devices to the public as well as health professionals via internet etc:

1) Period from getting information to posting it on website

The Agency aimed at posting information on revision of package inserts of ethical drugs on its

website within two days receiving the electronic information of MHLW directives. As a result, the Agency achieved this target for the second consecutive year.

2) Package Insert (PI) Information of ethical drugs

The PI information on ethical drugs is accessible on PMDA's website. Besides, the Agency improved the functionality of its website so that the users can follow the link from PI information to MHLW notifications of directives or to safety information including ADR line lists, etc.

3) Labelling information of medical devices

The Agency started online information service on Labelling of medical devices on its website in July 2005.

4) Dissemination of medical safety information through database management

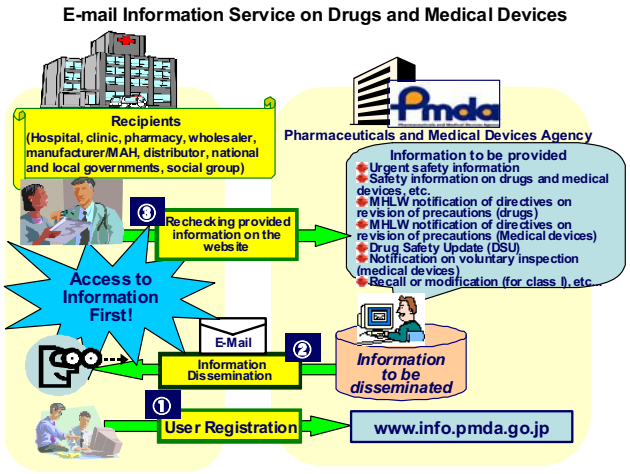
Regarding medical accidents and hiyari-hatto incidents collected and analyzed by the Japan Council for Quality Health Care since April 2004, the Agency compiled the database of the information by providing professional evaluation and consideration of safety measures to disseminate the information through internet.

・This database is retrievable by categories such as "name of drug or medical device" that caused malpractice and hiyari-hatto incidents, "name of distributor" or "circumstances of the incidents".

5) E-mail information service for drugs and medical devices

・In August 2005, the Agency launched the information service for medical professionals etc. via email as to safety information such as PI revision and voluntary recall of drugs and medical devices of class I*. Enrollment in the service registration reached about 3,000 as of the end of March 2006.

(* The classification of voluntary recalls, class I to III, is arranged based on a risk level of the recalled products to human health. Class I products refer to drugs and medical devices which may cause significant human health damage or death in their use.)



6) Publication of ADR cases

・On all ADR reports submitted by companies since April 2004, the Agency started to publish information on “Reported fiscal year”, “Sex”, “Age”, “Primary disease, etc.”, “Suspected drug”, “Adverse event”, “Suspected concomitant drug”, “Outcome” sequentially on the Information Website in January 2006.

Note: For those cases with fatal outcome, the causality between the suspected drug and death is classified into the following three categories, and published in the website.

A: “Cases for which causality between the suspected drug and death cannot be denied.”

Those cases for which it is undeniable that the adverse event supposed to be associated with the suspected drug caused the death after comprehensive judgement from medical and pharmaceutical points of view.

During the judgement, various factors such as relationship between the primary disease and the death, its pharmacological viewpoint and the time elapsed were considered.

B: “Cases for which causality between the suspected drug and death cannot be found.”

Those cases for which it is not recognized that the adverse event supposed to be associated with the suspected drug caused the death after comprehensive judgement from medical and pharmaceutical points of view.

During the judgement, various factors such as relationship between the primary disease and the death, its pharmacological viewpoint and the time elapsed were considered.

C: ”Cases for which causality between the suspected drug and death cannot be evaluated due to lack of information etc.”

Those cases for which the causality between the suspected drug and death cannot be evaluated because of lack of information or inappropriateness of the intended use or usage of the drug etc.

7) Publication of medical device malfunction cases

・On all reports on medical device malfunction submitted by companies since April 2004, the Agency started to publish information on “Reported fiscal year”, “Sex”, “Age”, “Outcome”, “Generic name”, “Condition of the medical device”, “Adverse effect on patients, etc.” sequentially on the Information Website in March 2006.

Note: For those cases with fatal outcome, the causality between the medical device used and death is classified into the following three categories, and published in the website.

A: “Cases for which causality between the medical device used and death cannot be denied.”

Those cases for which it is undeniable that the adverse event supposed to be associated with the medical device used caused the death after comprehensive judgement from medical, pharmaceutical and engineering points of view.

During the judgement, various factors such as relationship between the primary disease and the death, circumstances when malfunction happened, situations of maintenance and the time elapsed were considered.

B: “Cases for which causality between the medical device used and death cannot be found.”

Those cases for which it is not recognized that the adverse event supposed to be associated with the medical device used caused the death after comprehensive judgement from medical, pharmaceutical and engineering points of view.

During the judgement, various factors such as relationship between the primary disease and the death, circumstances when malfunction happened, situations of maintenance and the time elapsed were considered.

C: “Cases for which causality between the medical device used and death cannot be evaluated due to lack of information etc.”

Those cases for which the causality between the medical device used and death cannot be evaluated because of lack of information or inappropriateness of the intended use or use method of the device etc.

8) Publication of Drug Guide for Patients (see C)

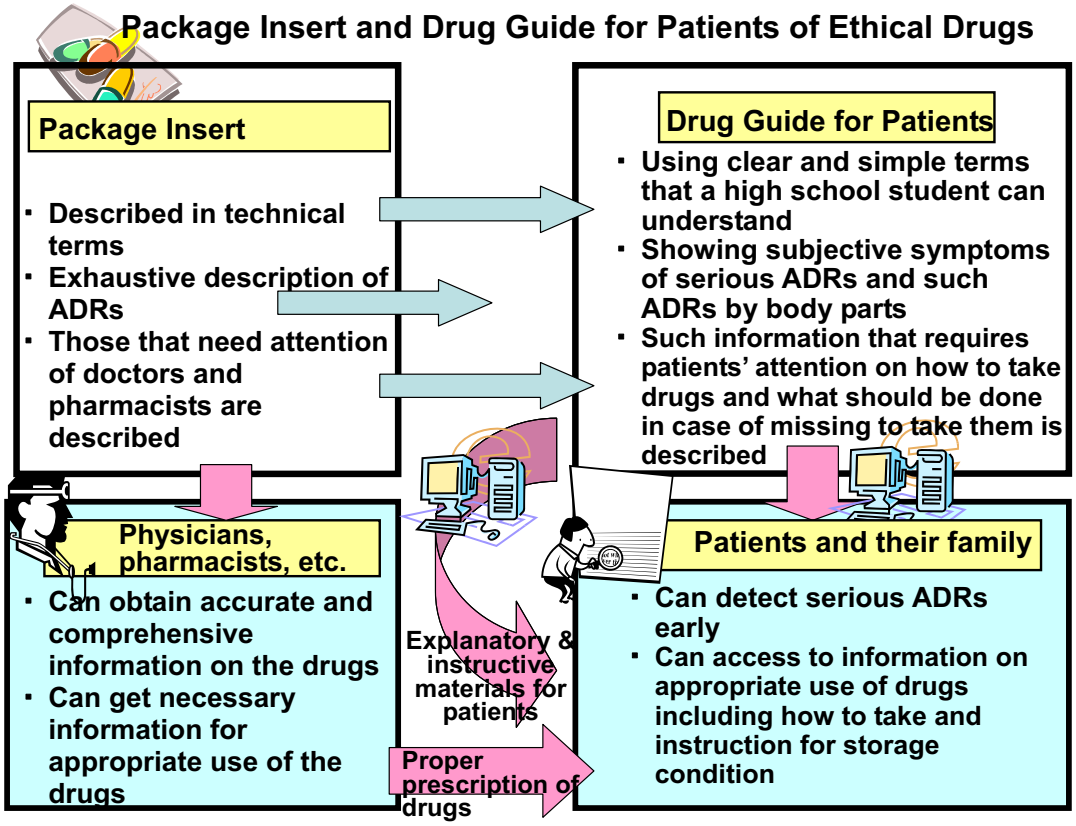
C. Telephone consultation service for general consumers and patients

・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 telephone consultation service for them regarding those products. As for consultations on drugs, which have been conducted since July 1994 when former Kiko existed, the Agency started the service even during the lunch break in February 2005. The counseling service on medical devices was launched in July 2005, as well.

・Publication of drug guide for patients

・Cooperating with a scientific research group of MHLW, “Research on how to provide patients and people with drug safety information”, the Agency initiated to post “Drug guide for patients” on its website in January 2006, in accordance with the notification of “Guidelines for developing drug guide for patients” announced by Director-General, Pharmaceutical and Food Safety Bureau, MHLW dated June 30, 2005. This guide is intended to help patients understand ethical drugs

correctly and detect serious ADRs at an early stage. Additionally, the guide cover information on ethical drugs whose package inserts includes “warnings”, or for which information on their appropriate use is provided specifically to patients. By around March 2007, it is scheduled to cover all the information on target drugs.



【Number of access to the webpage, “Information Website”】

(Million)

	FY 2001	FY 2002	FY 2003	FY 2004	FY 2005
Number of access	76	87	107	233	289

For the number of information posted on Information Website as of March 2005, please refer to “PART III, 7, (3), “Providing safety information” on page 114.

d. Improvement of content and its quality of disseminating information

・In order to facilitate cooperation with the Review Department and Office of Relief Funds with due consideration to protection of personal information, Safety Department examined a concrete

method for cooperation and aimed to consistently conduct safety evaluations in the process from approval to relief with this method. To achieve this aim:

1) The Department established the standard operating procedures for related collaborative operations;

2) The Safety Department examined the needs of safety measures considering information on cases that were eligible or ineligible for relief offered by the Office of Relief Funds.

・In order to ensure optimal cooperation between the Safety Department and the Review Department:

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 applications 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) In the study meeting on ADRs found in clinical trials, it was decided that the Drug Safety Division provides ADR information reported in the early postmarketing-phase vigilance (EPPV).

3) The Agency established standard operating procedures for related collaborative operations.

・In advance of the study to be conducted during FY 2006 for improving the information service for general consumers and health professionals, in March 2006 the Agency surveyed through its website in order to grasp the current situation of the service by analyzing the recipients' needs and their satisfaction. The respondents of the questionnaire consisted of pharmacists (39.8%), drug manufacturers and marketing approval holders (22.8%), general consumers (8.3%), manufacturers and marketing approval holders of medical devices (7.4%), and others (21.9%). (For more details about the questionnaire's results, please refer to PART III, 7, (4), "Consultation service for consumers" on page 83.

・The Agency has just enhanced and improved the server functionality and performance for the search ability on its website, responding to the requests such as being inaccessible to the website and slow searching speed.