Pharmaceutical Affairs Japan

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CHAPTER 1

Organization and Function of the Ministry of Health, Labour and Welfare

The **Ministry of Health, Labor, and Welfare** (**MHLW**) (**Koseirodosho** in Japanese) was established by a merger of the Ministry of Health and Welfare (**MHW**) and the Ministry of Labor, on January 6, 2001 as part of the government program for reorganizing government ministries. The MHLW, which was originally established in 1938, has been in charge of the improvement and promotion of social welfare, social security and public health, and the new organization has the same tasks. It consists of the ministry proper, affiliated institutions, councils, local branches, and an external organization. The ministry proper includes the Minister's Secretariat, 11 bureaus, and the Director-General for Policy Planning and Evaluation. Councils include the Social Insurance Council, Pharmaceutical Affairs and Food Sanitation Council (PAFSC), and other organizations. Affiliated institutions include national hospitals, the National Institute of Health Science. Local branches are regional bureaus of health and welfare and prefectural labor bureaus. The external organizations are the Social Insurance Agency and the Central Labor Relations Commission (**Fig. 1.** Organization of Ministry of Health, Labour, and Welfare).

The MHLW is in charge of pharmaceutical regulatory affairs in Japan, and the **Pharmaceutical and Food Safety Bureau** (**PFSB**) undertakes main duties and functions of the Ministry: it handles clinical studies, approval reviews and post-marketing safety measures, i.e., approvals and licensing. The **Health Policy Bureau** handles promotion of R&D, and production, distribution policies and drug pricing, i.e., functions related to pharmaceutical companies. The **Pharmaceuticals and Medical Devices Evaluation Center** (**Evaluation Center**) in the **National Institute of Health Sciences** was established to strengthen approval reviews on July 1, 1997.

To confirm the reliability of reviews and application data, the Organization for Pharmaceutical Safety and Research (OPSR) conducted compliance reviews on application data. The OPSR also began offering consultation services on protocols at the clinical trial stage.

This was followed by the integration of the aforementioned Evaluation Center, OPSR and part of the Medical Devices Center on April 1, 2004, to form a new independent administrative organization, the Pharmaceutical and Medical Devices Agency (PMDA, SOGO-KIKO). The role of the PMDA is to provide consultations concerning the clinical trials of new drugs and medical devices, and to conduct approval reviews and surveys of the reliability of application data.

Following this reorganization, the MHLW and PMDA handle a wide range of activities from clinical studies to approval reviews, reviews though the post-marketing stage, and safety measures (**Fig. 2.** Organization of Pharmaceutical and Food Safety Bureau (PFSB)

and Pharmaceuticals and Medical Devices Agency (PMDA).

1. PHARMACEUTICAL AND FOOD SAFETY BUREAU (PFSB)

The Pharmaceutical and Food Safety Bureau (PFSB) (except for the Department of Food Safety) is one of the 11 bureaus of the MHLW. In addition to polices to assure the efficacy and safety of drugs, quasi-drugs, cosmetics and medical devices, and policies for safety in medical institutions, the PFSB tackles problems directly related to the lives and heath of the general public including policies related to blood supplies and blood products, and narcotics and stimulant drugs. This new bureau consists of a Secretary-General, Councilor in charge of drugs, five divisions, and one office* (Fig. 2. Organization of Pharmaceutical and Food Safety Bureau (PFSB) and Pharmaceuticals and Medical Devices Agency (PMDA). These divisions have the following functions.

1.1 General Affairs Division

The functions of this division are as follows:

1) Overall planning and coordinating activities for the Pharmaceutical and Food Safety Bureau
2) Matters related to pharmacists
3) Supervision of the PMDA (excluding areas under the control of the Evaluation and Licensing Division, Safety Division, and Compliance and Narcotics Division)
4) Issues related to PFSB not governed by other divisions

- **Office of Drug Induced Damages**
  1) Matters related to the PMDA (clerical work related to damage caused by adverse drug reactions [ADRs] and infections)
  2) Measures for handling health injury caused by adverse effects of drugs, quasi-drugs, cosmetics and medical devices (“drugs, etc.”)

1.2 Evaluation and Licensing Division

The functions of this division are as follows:

1) Technical guidance and supervision concerning the production of drugs, quasi-drugs, cosmetics and medical devices (“drugs, etc.”)
2) Manufacturing/distribution business licenses and approvals to manufacture and distribute drugs, etc.
3) Reexamination and reevaluation of drugs and medical devices
4) Business license and approvals to distribute, rental, or repair medical devices (excluding areas under the control of Health Policy Bureau [“HPB”])
5) Issues related to the Japanese Pharmacopoeia (JP)
6) Standards and specific precautions concerning drugs, etc.
7) Designation of orphan drugs and orphan medical devices
8) Enforcement of laws pertaining to poisonous and deleterious substances

(excluding areas under the control of the Compliance and Narcotics Division)

9) Regulations related to evaluation of chemicals that might cause damage to the health of humans, animals, and plants in living environment from the standpoint of the environment and public health, as well as regulations concerning the manufacture, import, use, and other handling of such chemicals
10) Control of household products containing harmful substances
11) Establishment of tolerable daily intake (TDI) of dioxins and related compounds
12) Work related to the PMDA (SOGO-KIKO) (limited to approval and license to manufacture and distribute drugs, medical devices, etc.)
13) Control and dissemination of Industrial standards for medical devices and other hygiene products and other industrial standards

- **Office of Medical Devices Evaluation**

1) Technical guidance and supervision concerning the production of medical devices
2) Manufacturing/distribution business licenses and approvals to manufacture and distribute medical devices
3) Reexamination and reevaluation of drugs and medical devices
4) Business license and approvals to distribute, rental, or repair medical devices
5) Standards and specific precautions concerning medical devices
6) Designation of orphan medical devices
7) Work related to the PMDA (SOGO-KIKO) (limited to approval and license to manufacture and distribute medical devices)
8) Control and dissemination of Industrial standards for medical devices and other hygiene products and other industrial standards

- **Office of Chemical Safety**

1) Enforcement of laws pertaining to poisonous and deleterious substances (excluding areas under the control of the Compliance and Narcotics Division)
2) Regulations related to evaluation of chemicals that might cause damage to the health of humans, animals, and plants in living environment from the standpoint of the environment and public health, as well as regulations concerning the manufacture, import, use, and other handling of such chemicals
3) Control of household products containing harmful substances
4) Establishment of tolerable daily intake (TDI) of dioxins and related compounds

1.3 Safety Division

The functions of this division are as follows:

1) Planning and drafting of policies to assure the safety of drugs, quasi-drugs, cosmetics and medical devices (drugs, etc.)
2) Manufacturing/distribution business licenses and approvals to manufacture and distribute drugs, etc.
3) Reviews of the safety of drugs, etc. (excluding items handed by the Evaluation and Licensing Division)
4) Guidance and advice concerning preparation and storage of records of biological products and designated medical devices
5) Work related to the PMDA (SOGO-KIKO) in handling matters related to improve safety of drugs, etc. (excluding items handed by the Evaluation and Licensing Division)

1.4 Compliance and Narcotics Division

The functions of this division are as follows:

1) Control of poor quality or falsely labeled drugs, quasi-drugs, cosmetics and medical devices (drugs, etc.)
2) Guidance and supervision related to advertising of drugs, etc.
3) Testing and government certification of drugs, etc.
4) Matters related to pharmaceutical inspectors
5) Control of substances designated by the Pharmaceutical Affairs Law
6) Matters related to inspectors of poisonous and deleterious substances
7) Control of narcotics, psychotropics, cannabis, opium and stimulants
8) Duties of narcotics control officers and staff as judicial police officials
9) Cooperation with international criminal investigations concerning narcotics, psychotropics, cannabis, opium and stimulants
10) Work related to the PMDA (SOGO-KIKO) in handling matters related to compliance (limited to work related to compliance inspection by the PMDA)

1.5 Blood and Blood Products Division

The functions of this division are as follows:

1) Regulation of blood collection services
2) Promotion of blood donation
3) Assurance of proper use of blood products and assurance of stable supply of blood products
4) Maintenance of stable supply of blood products
5) Promotion, improvement, and coordination concerning production and distribution of biological products

2. HEALTH POLICY BUREAU

With the aging of society, changes in disease structure, and increasing demands from the public for better quality health care, the Health Policy Bureau is drafting policies aimed at achieving a high quality, efficient health care supply system for the 21st century.

The Economic Affairs Division and the

Research and Development Division, the two divisions most closely related to the pharmaceutical industry, have the following functions.

2.1 Economic Affairs Division

The functions of this division are as follows:

1) Promotion, improvement and coordination related to production, distribution and consumption of drugs, quasi-drugs, medical devices, sanitary materials and other hygiene-related products (drugs, etc.) (excluding items handed by PFSB and the Research and Development Division)
2) Advancement, improvement and coordination of manufacturing of drugs, etc. (excluding items handed by the Research and Development Division)
3) Matters related to foreign trade (import and export) of drugs, etc.
4) Matters related to outsourcing the work of managers of hospitals, clinics and maternity clinics (hospitals, etc.)
5) Guidance on enterprises related to the improvement of the management of hospitals, etc. (excluding those governed by the national and local governments)
6) Issues related to hygiene inspection offices

This Division includes the Office of Direction for Health-Related Services with the following functions.

- **Office of Direction for Health-Related Services**

1) Matters related to outsourcing the work of managers of hospitals, etc.
2) Guidance on enterprises related to the improvement of the management of hospitals, etc. (excluding those governed by the national and local governments)
3) Issues related to hygiene inspection offices

2.2 Research and Development Division

The functions of this division are as follows:

1) Matters related to research and development of drugs, etc. (excluding items handed by PFSB)
2) Matters related to the cultivation and production of medicinal plants
3) Promotion, improvement and coordination of manufacturing business of drugs, etc. (items related to research and development)
4) Matters related to installation and use of medical devices (excluding medical supplies, dental supplies and hygiene-related products) (excluding items handled by the Guidance of Medical Service Division of PHB)
5) Matters related to the improvement of health care information-processing and management system
6) Matters related to the evaluation of medical technology (excluding those handled by other bureaus of MHLW)

- **Japan Health Sciences Foundation**

This foundation was established in 1986

by the MHW (currently MHLW) and related companies, etc. with the aim of promoting advanced technology in the field of the health sciences. It promotes joint public and private research and development on advanced and fundamental technology, undertakes surveys and studies to contribute to such promotion, assures the supply of research resources such as cells and genes, and conducts exchanges with related organizations in Japan and overseas.

3. NATIONAL INSTITUTE OF HEALTH SCIENCES

In July 1997, the name of the former National Institute of Hygienic Sciences was changed to the National Institute of Health Sciences. In addition to its long-standing work related to testing and research on drugs, quasi-drugs, cosmetics, medical devices, foods, poisonous and deleterious substances, the Institute supervised the Pharmaceuticals and Medical Devices Evaluation Center to undertake the reviews required for approval to manufacture or import drugs, quasi-drugs, cosmetics and medical devices, as well as the reexamination and the reevaluation of drugs and medical devices. Thereafter, the Evaluation Center was incorporated into the Pharmaceuticals and Medical Devices Agency (PMDA, SOGO-KIKO) in April 2004.

4. PHARMACEUTICALS AND MEDICAL DEVICES AGENCY (PMDA, SOGO-KIKO), AN INDEPENDENT ADMINISTRATIVE ORGANIZATION

In accordance with the special corporation rationalization plan passed by the Cabinet in December 2001, and enactment of the Pharmaceuticals and Medical Devices Agency Law in December 2002, the PMDA (SOGO-KIKO) was established in April 2004, through the integration of the Pharmaceutical and Medical Devices Evaluation Center in the National Institute of Health Sciences, the OPSR and part of the Medical Devices Center.

Until that time, the Evaluation Center reviewed drugs and medical devices, while the OPSR handled consultations and reviews related to clinical trial protocols, but from April 2004, the PMDA started handling all consultation and review work from the preclinical stage to approvals and post-marketing surveillance.

The PMDA consists of 15 departments and 3 offices, namely the Office of General Affairs, Office of Planning and Coordination, Office of Relief Funds, Office of Review Administration, Office of New Drug I, Office of New Drug II, Office of New Drug III, Office of New Drug IV, Office of Biologics I, Office of Biologics II, Office of OTC and Generic Drugs, Office of Medical Devices, Office of Conformity Audit, Office of Safety, Office of Compliance and Standards, Audit Office, Information and Technology Promotion Group, etc. (**Fig. 2.** Organization of Pharmaceutical and Food Safety Bureau (PFSB) and Pharmaceuticals and Medical Devices Agency (PMDA)). The duties of the departments are indicated below. R&D promotion activities that were handled in the past were transferred to the National Institute of Biomedical Innovation, which was established in

April 2005.

1) Drug ADR Relief Work

- Provision of medical benefits to cover healthcare expenses, disability pensions and survivor's pensions for individuals suffering disease or disability due to adverse drug reactions or bioderived infections.
- Provision of medical allowances for treatment of myelo-optico-neuropathy (SMON) patients and for HIV carriers and AIDS patients infected through blood products.
- Provision of medical allowances for treatment of hepatitis C patients infected through specified fibrinogen concentrates or specified coagulation factor XI concentrates.

2) Review Related Work

- Approval reviews of new drugs and medical devices based on the Pharmaceutical Affairs Law
- Guidance and advice related to clinical trials
- Reviews of GLP and GCP compliance of attached data of approval applications and reexamination and reevaluation applications
- Reviews of manufacturing facilities, processes and quality control by GMP inspections
- Confirmation of reexaminations and reevaluations based on the Pharmaceutical Affairs Law

3) Safety Measures

- Collection, analysis and dissemination of information related to the quality, efficacy and safety of drugs and medical devices
- Consultations with consumers and other parties concerning drugs and medical devices
- Guidance and advice for manufacturers, etc. to improve the safety of drugs and medical devices

The work of the review and safety departments is detailed below.

4.1 Office of New Drug I

This department confirms clinical trial notifications and adverse drug reactions and conducts reviews required for approval, reexaminations and reevaluation of gastrointestinal drugs, dermatologic drugs, new anti-malignant neoplasm drugs, antibacterial drugs, and anti-HIV or AIDS agents.

4.2 Office of New Drug II

This department confirms clinical trial notifications and adverse drug reactions and conducts reviews required for approval, reexaminations and reevaluation of new cardiovascular drugs, urological and anal drugs, reproductive system drugs, metabolism-improvement drugs, *in vivo* diagnostics and radiopharmaceuticals.

4.3 Office of New Drug III

This department confirms clinical trial notifications and adverse drug reactions and conducts reviews required for approval, reexaminations and reevaluation of new central nervous system drugs, peripheral nervous system

drugs, sensory organ drugs (other than drugs for inflammatory diseases) and narcotics.

4.4 Office of New Drug IV

This department confirms clinical trial notifications and adverse drug reactions and conducts reviews required for approval, reexaminations and reevaluation of new respiratory tract drugs, anti-allergy drugs sensory organ drugs (limited to drugs for inflammatory diseases), hormone products and metabolic disease drugs (other than combination drugs).

4.5 Office of Biologics I

In the Office of Biologics, the PMDA confirms clinical trial notifications and adverse drug reactions and conducts reviews required for approval, reexaminations and reevaluation of blood coagulation factor products, etc.

This office also undertakes preliminary reviews for applications for verification of drugs for gene therapy and medical devices using cells and tissues, preliminary reviews for applications for approval or verification based on the Cartagena Protocol, and quality review of antibody preparations.

4.6 Office of Biologics II

This department confirms clinical trial notifications and adverse drug reactions of vaccines, antidotes and drugs for cell therapy and performs the reviews required for approval, reexamination or reevaluation.

The department also performs preliminary reviews for approval applications of drugs and medical devices using cells and tissues.

4.7 Office of OTC and Generics

This department conducts reviews required for the approval, export certification and quality reevaluations of generic prescription drugs, non-prescription drugs, quasi-drugs and cosmetics.

4.8 Office of Medical Devices

In the Office of Medical Devices, the PMDA undertakes reviews required for approval of medical devices and in vitro diagnostics, confirmation required for reexamination or reevaluation, and examination of clinical trial protocols

4.9 Office of Compliance and Standards

In the Office of Compliance and Standards, the PMDA reviews the documentation included with applications for approval, reexamination or reevaluation of drugs and medical devices to assure that the data complies with GLP, GCP, etc. both ethically and scientifically to determine if the documents have been prepared appropriately and accurately based on the study results in accordance with the Criteria for Reliability of Application Data (Article 43 of the Enforcement Regulations, Pharmaceutical Affairs Law) (“Reliability Criteria” hereinafter).

4.10 Office of Safety

With the cooperation of the Ministry of Health, Labor and Welfare, this office undertakes primary collection and compilation of information related to the quality, efficacy and safety of drugs and medical devices, and conducts scientific analysis

and examination of collected information. It also undertakes consultations and information dissemination work.

5. THE NATIONAL INSTITUTE OF BIOMEDICAL INNOVATION（INDEPENDENT ADMINISTRATIVE AGENCY）

The National Institute of Biomedical Innovation was established in April 2005 based on the Law for the National Institute of Biomedical Innovation which was approved by the 159th National Diet Session and promulgated in 2004 to make a major contribution to drug research and development by integrating basic research, research on bioresources and promotion of research and development.

Research promotion and orphan drug development promotion, which had been conducted by the PMDA, were transferred to the institute.

6. PHARMACEUTICAL AFFAIRS AND FOOD SANITATION COUNCIL (PAFSC)

The Pharmaceutical Affairs and Food Sanitation Council (PAFSC) serves as an advisory body to the MHLW, and reviews and discusses important pharmaceutical and food sanitation-related matters (**Fig. 3.** Organization of the Pharmaceutical Affairs and Food Sanitation Council. PAFSC). This council was created by merging of the Central Pharmaceutical Affairs Council (**CPAC**) and the Food Sanitation Investigation Council. It is divided into a **Pharmaceutical Affairs Committee** and a **Food Sanitation Committee**. The latter comes under the Food Sanitation Law and the former under other laws.

The Council has as members experts in various fields[1)] including the medical and pharmaceutical sciences whose duty is to examine and review important pharmaceutical matters.

The frequency of committee meetings differs. For example, the First Committee on New Drugs[2)] and the Second Committee on New Drugs[2)], which review new drug applications, each meet approximately eight times a year and the Committee on Non-prescription Drugs[3)] meets four times a year.[4)] New drugs are then reviewed or reported and approved[5)] by the Pharmaceutical Affairs Committee that meets four times a year 4.[6)]

Note 1) Nursing, life sciences, applied biochemistry, mathematics and statistics, law and economic.

Note 2) The Second Committee on New Drugs discusses antiviral drugs, chemotherapeutic agents, anti-malignant tumor agents, blood products and biological products while the First Committee discusses agents in the remaining therapeutic categories.

Note 3) The Committees on Non-prescription Drugs reviews new non-prescription drugs which are apparently different from existing non-prescription drugs in active ingredient, strength, dosage/administration, indications, etc.

Note 4) The First and Second Committees on New Drugs meet in January, February, April, May, July, August, October and

November in principle. The Committees on Non-prescription Drugs meets in February, May, August and November in principle.

Note 5) For recent new drugs, refer to the homepage on drug information. http://www.info.pmda.go.jp/

Note 6) The Pharmaceutical Affairs Committee meets in March, June, September and December in principle.

7. NATIONAL INSTITUTE OF INFECTIOUS DISEASES

In April 1997, the name of the National Institute of Health was changed to the National Institute of Infectious Diseases. The institute undertakes basic and applied research, reference and surveillance activities, and collection, analysis and supply of information pertaining to infectious diseases, performs research on the quality control of antibiotics and other biological products, and undertakes national certification and testing, and activities related to international cooperation.

- **Infectious Diseases Information Center**

  This Center was established in April 1997 to undertake surveys and research, and collect and supply information on infectious diseases, etc.

- **AIDS Research Center**

  This Center was established in April 1988 to undertake HIV basic research and to develop methods of prevention and treatment of AIDS.

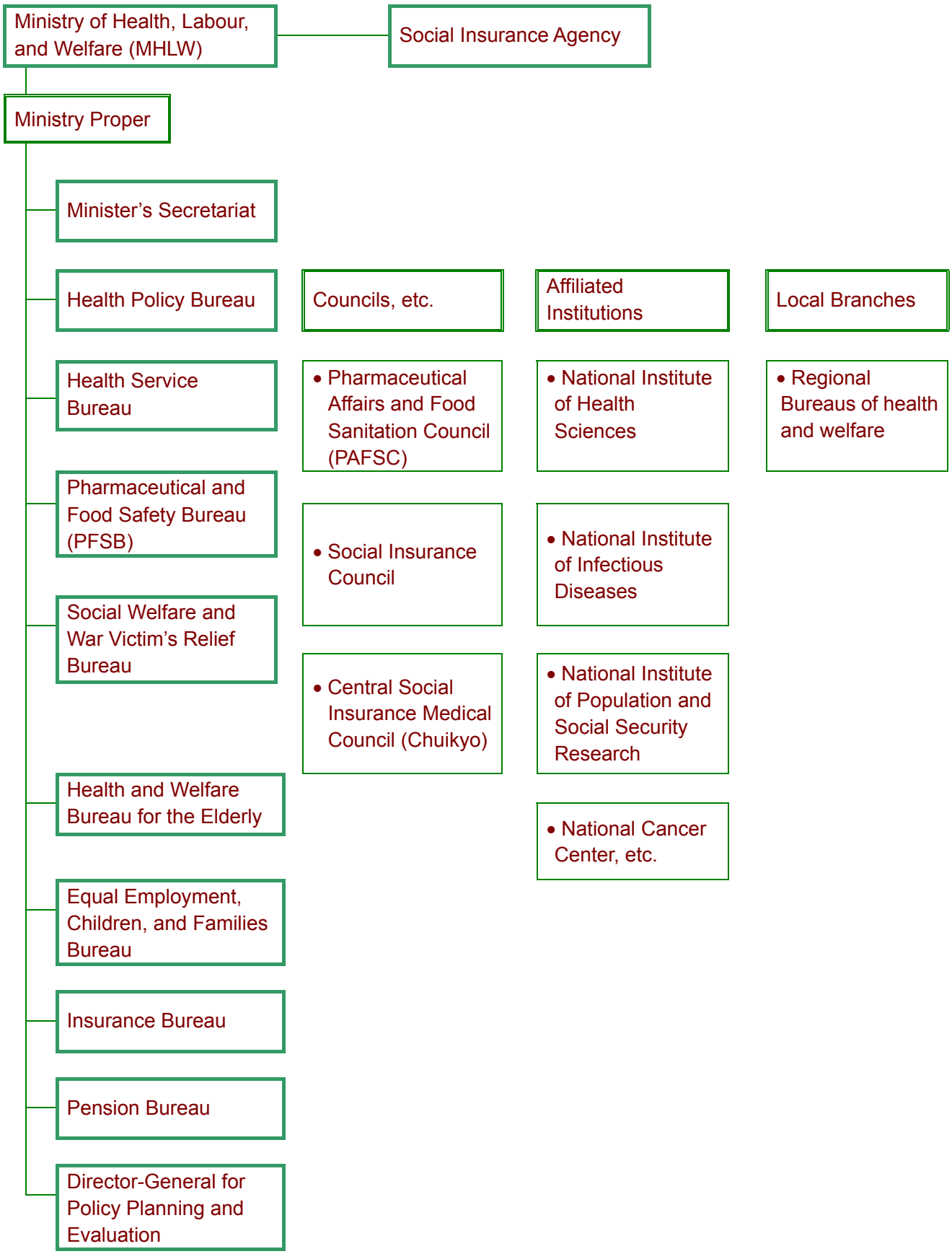


Fig. 1 Organization of Ministry of Health, Labour, and Welfare (Health-related organizations)

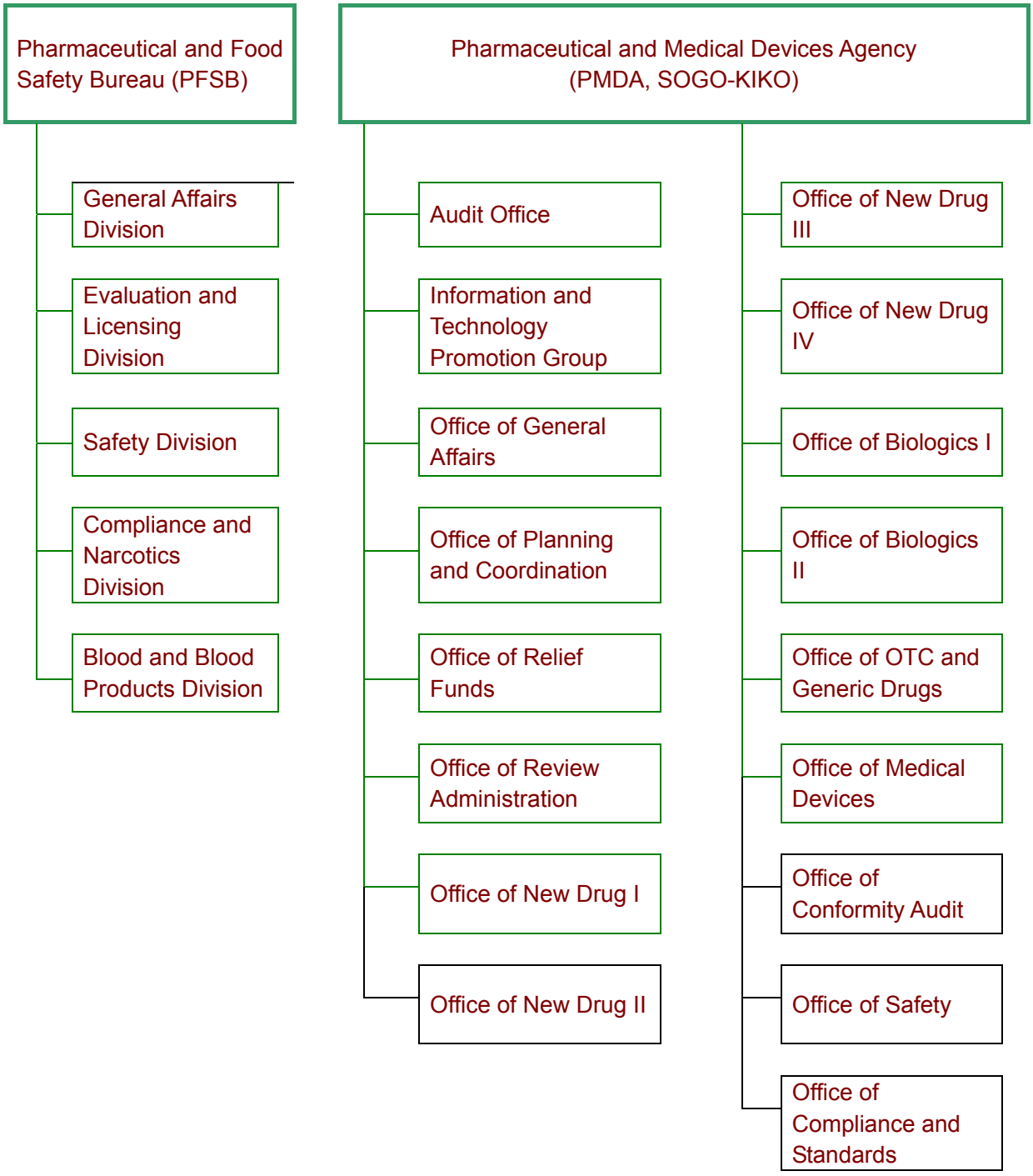


Fig. 2 Organization of Pharmaceutical and Food Safety Bureau (PFSB) and Pharmaceuticals and Medical Devices Agency (PMDA [SOGO-KIKO])

Committee on Japanese Pharmacopoeia	・ Subcommittee on Japanese Pharmacopoeia
First Committee on Judgment of Sufferers from Adverse Drug Reactions and Infections	・ Subcommittee on Evaluation of Adverse Effects of Biological Products
Second Committee on Judgment of Sufferers from Adverse Drug Reactions and Infections	
First Committee on New Drugs	
Second Committee on New Drugs	
Committee on Blood Products	・ Subcommittee on Supply of and Demand for Blood Products ・ Subcommittee on Safety of Blood Products ・ Subcommittee on Proper Use of Blood Products
Committee on Medical Devices and *in vitro* Diagnostics	
Committee on Medical Materials	
Committee on Reevaluation of Drugs	
Committee on Handling Regulations for Biological Products	・ Subcommittee on Medicinal Products for Animals by Application of recombinant DNA Technology
Committee on Non-prescription Drugs	
Committee on Cosmetics and Quasi-Drugs	
Committee on Safety of Drugs	・ Subcommittee on Transmissible Spongiform Encephalopathy ・ Subcommittee on Safety Measurements
Committee on Safety of Medical Devices	・ Subcommittee on Safety Measurements
Committee on Poisons and Powerful Drugs	・ Subcommittee on Handling Regulations for Poisons and Powerful Drugs ・ Subcommittee on Poisons and Powerful Drugs
Committee on Safety of Chemical Substances	・ Subcommittee on Chemical Substances ・ Subcommittee on PRTR substances

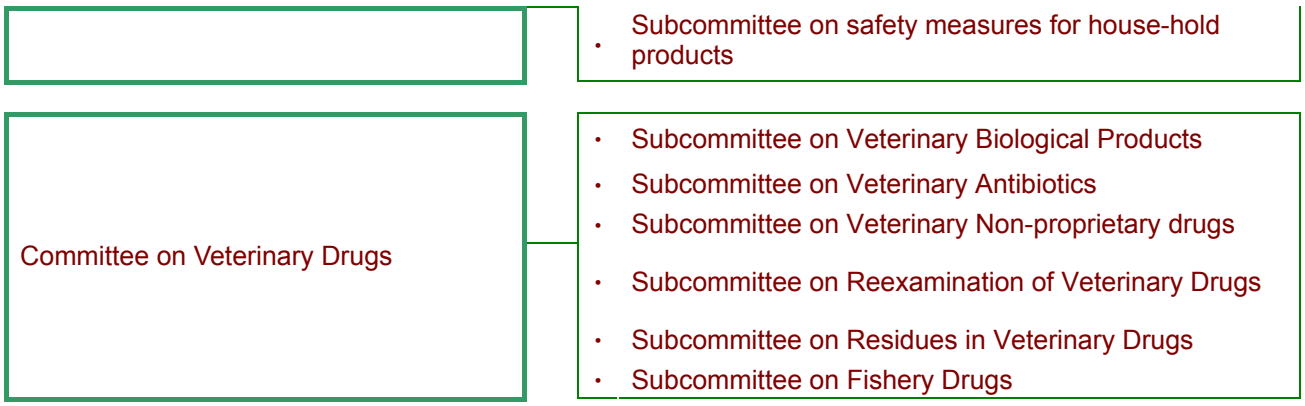


Fig. 3 Organization of the Pharmaceutical Affairs and Food Sanitation Council (PAFSC) (17 Committees and 20 Subcommittees, October 1, 2007)

CHAPTER 2

Pharmaceutical Laws and Regulations

1. PHARMACEUTICAL LAWS

Pharmaceutical administration in Japan is based on various laws and regulations, consisting mainly of: (1) the Pharmaceutical Affairs Law, (2) Pharmacists Law, (3) Law Concerning the establishment for Pharmaceuticals and Medical Devices Organization, (4) Law Concerning Securing a Stable Supply of Blood Products, (5) Poisonous and Deleterious Substances Control Law, (6) Narcotics and Psychotropics Control Law, (7) Cannabis Control Law, (8) Opium Law, and (9) Stimulants Control Law.

For the enforcement and management of these laws, detailed regulations are prepared by the government in the form of ministerial ordinances and notices, such as the Enforcement Ordinance and the Enforcement Regulations of the Pharmaceutical Affairs Law, and notifications issued by the Director General of the bureau or the directors of the Divisions in charge in the Ministry of Health, Labor, and Welfare.

2. PHARMACEUTICAL AFFAIRS LAW

The objective of the Pharmaceutical Affairs Law is to improve public health through regulations required to assure the quality, efficacy, and safety of drugs, quasi-drugs, cosmetics and medical devices, and through measures to promote R&D of drugs and medical devices that are especially essential for health care.

Modern pharmaceutical legislation originated in Japan with the enactment of the Regulations on Handling and Sales of Medicines in 1889. The Pharmaceutical Affairs Law was enacted in 1943 and has been revised several times since then. The current Pharmaceutical Affairs Law is the result of complete revisions (Law No. 145) in 1948 and 1960. Subsequent revisions have included that related to the reexamination of new drugs, the reevaluation of drugs, notification of clinical study protocols, and items required for sponsoring clinical studies in 1979, that related to direct manufacturing approval applications by overseas pharmaceutical manufacturers, and the transfer of manufacturing or import approvals in 1983, and that related to promotion of R&D of orphan drugs and **priority reviews** for such drugs in 1993.

In 2002, the Pharmaceutical Affairs Law was revised (Law No. 96, July 31, 2002) based on demands for augmentation of safety assurance in keeping with the age of

biotechnology and genomics, augmentation of post-marketing surveillance policies, revision of the approval and licensing system (clarification of the responsibility of companies for safety measures and revision of the manufacturing approval system in accordance with international coordination) and a radical revision of safety policies for medical devices. In the revised Law, provisions on the enhancement of safety measures for biological products, investigator-initiated clinical trials and safety reports from medical institutions came into effect on July 30, 2003 (Cabinet Order No. 212, April 23, 2003), and law to establish the PMDA was enacted on April 1, 2004 to revitalize the review system. Provisions related to the manufacturing/distribution approval system, manufacturing/distribution businesses and manufacturing businesses, as well as provisions related to medical devices came into effect on April 1, 2005.

Thereafter, the Law for Partial Amendment of the Pharmaceutical Affairs Law (Law No. 69) to revise the OTC drug selling system and strengthen the control of illegal drugs was announced on June 14, 2006 and will be enforced from 2009. For enforcement of the amended Pharmaceutical Affairs Law, notifications on risk classification of non-prescription drugs (type 1: especially high risk, type 2: relatively high risk, and type 3: relatively low risk) (Notifications No. 033037 and 0330007 of the PFSB dated March 30, 2007) and a notification on implementation of registered marketer tests to confirm the characters of registered marketers to type 2 and type 3 drugs (Notification No. 0808001 of the General Affairs Division, PFSB dated August 8, 2007) were issued.

The Pharmaceutical Affairs Law has 11 chapters and 91 articles as follows:

Chapter 1: General Provisions (Articles 1 and 2) (Purpose and definitions of drugs, quasi-drugs, cosmetics, medical devices, specially controlled medical devices, controlled medical devices, general medical devices, specially designated medical devices requiring maintenance, biological products, specified biological products, pharmacies, manufacturing and distribution, in vitro diagnostics, orphan drugs, orphan medical devices and clinical trials)

Chapter 2: Prefectural Pharmaceutical Affairs Councils (Article 3) (Establishment of Prefectural Pharmaceutical Affairs Councils)

Chapter 3: Pharmacies (Article 4 - Article 11) (License standards, restrictions on designation of pharmacies, supervision of pharmacies, duty of supervisors, supply of information, etc. on pharmacy by proprietors, requirements observed by proprietors, notification of suspension or discontinuation of business, etc.)

Chapter 4: Manufacturers/Distributors and Manufacturers (Article 12 - Article 23) (License standards for manufacturers/ distributors, licenses for manufacturers, surveys by the PMDA, accreditation of foreign manufacturers, manufacturing/distribution approvals, approval reviews performed by the PMDA (SOGO-KIKO), restrictive approvals, reexamination, reevaluation, transfers, notification of manufacture/distribution, receipt of manufacture/distribution notifications by the PMDA, drug master files, registration by the PMDA, appointment of distribution supervisors-general, items requiring compliance by manufacturers/distributors, notifications of suspension or discontinuation, manufacturing approvals for drugs manufactured overseas, notifications of changes in appointed manufacturer/distributors, restrictive approvals of drugs manufactured overseas, exceptions for drugs manufactured/distributed in pharmacies, etc.)

Chapter 4-2: Third-party Certification Bodies (Article 23-2 - Article 23-19) (Certification of manufacturing/distribution of designated controlled medical devices, appointment of manufacturer/distributors by overseas manufacturers of designated controlled medical devices, cancellation of certification, submission of reports, registration, standards for registration, disclosure of registration, duties for reviews of criteria conformity certification, operational standards manual, etc.).

Chapter 5: Retail Sellers of Drugs and Retail Sellers of Medical Devices

Section 1 Retail sellers of drugs (Article 24 - Article 38) (First-class and second-class licenses for selling drugs, prohibition of selling designated drugs, license for selling drugs by household distribution, restrictions on drugs sold by household distribution, third-class license for selling drugs, restrictions on drugs sold by third-class sellers, categories of non-prescription drugs, etc.)

Section 2 Retail Sellers, Leasers and Repairers of Medical Devices (Article 39 - Article 40-4) (License for selling and leasing specially control medical devices, appointment of managers, submission of notifications on selling and leasing businesses of controlled medical devices, license for repairing medical devices, etc.)

Chapter 6: Standards and Government Certification for Drugs (Article 41 - Article 43) (Japanese Pharmacopoeia and other standards, etc.)

Chapter 7: Handling of Drugs

Section 1 Handling of Poisonous and Deleterious Substances, (Article 44 - Article 48) (Labeling, restrictions on selling unsealed products, transfer procedures, restrictions on supply, storage and exhibition)

Section 2 Handling of drugs (Article 49 - Article 58) (Selling of prescription drugs, items included on immediate containers and in package inserts, prohibited entries, prohibition of manufacturing, giving and distribution of drugs, etc.)

Section 3 Handling of quasi-drugs (Article 59 - Article 60) (Items included on immediate container, etc.)

Section 4 Handling of cosmetics (Article 61 - Article 62) (Items included on immediate container, etc.)

Section 5 Handling of medical devices (Article 63 - Article 65) (Items included on immediate container, etc., prohibition of selling and manufacture)

Chapter 8: Advertising of Drugs (Article 68-2 - Article 68-11) (False advertising, restrictions on advertising of drugs for designated diseases, prohibition of advertising of drugs before approval, etc.)

Chapter 8-2: Exceptions for Biological Products (Article 69 - Article 77)

(Manufacturing supervisors, items included on immediate containers, package inserts, etc., prohibition of selling and manufacture, explanation of specified biological products by appointed health professionals, regular reports on infectious diseases, preparation and retention of records on biological products, guidance and advice, complication and examination of information on regular reports on infectious diseases by the PMDA).

Chapter 9: Supervision (Article 69 - Article 76-3) (On-site inspections, on-site inspections by the PMDA, emergency orders, disposal, test orders, orders for improvement, orders for replacement of distribution supervisors-general, supervision of household distributors, cancellations of approvals and licenses, approvals to distribute drugs manufactured overseas, restrictive approvals and accreditation of overseas manufacturers, procedures for refusal of renewal of licenses, exceptions for hearings, pharmaceutical affairs inspectors)

Chapter 9-2: Handling of Designated Drug Substances (Article 76-4 - Article 77) (Prohibition of manufacture, restriction of advertisement, inspection, etc. of goods suspected of containing designated drug substances, disposal and other measures, on-site and other

inspections, and special handling of designated procedures

Chapter 9-3: Designation of Orphan Drugs and Orphan Medical Devices (Article 77-2 - Article 77-2-6) (Designation, securing funds, tax relief measures, notification of suspension of research and development, cancellation of designations)

Chapter 10: Miscellaneous Provisions (Article 77-3 – Article 83-5) (Supply, etc. of information, promotion and enlightenment of proper use of drugs, etc., prevention of hazards, reporting of adverse reactions, reporting of recall, reporting, etc. to PAFSC, compilation and examination by the PMDA of data from adverse reaction reports, preparation and retention of records on specially designated medical devices, guidance and advice, fees, conditions for licenses, etc., application exemptions, etc., handling of clinical trial, review of clinical trial applications by the PMDA, duties of prefectural governments, duties of the Minister in emergencies, classification of clerical works of government agencies, delegation of authority, interim measures, drugs for animals, prohibition of manufacture/import of drugs for animals, prohibition of use, regulations on the use of drugs for animals and regulations on the use of other drugs)

Chapter 11: Penal Provisions (Article 83-6 - Article 91)

3. OUTLINE OF PHARMACEUTICAL REGULATIONS

Various regulations apply to the development, manufacture, import, marketing, and proper use of drugs and medical devices in the form of the Pharmaceutical Affairs Law, cabinet orders, MHLW ordinances, etc. An outline of the main regulations affecting pharmaceuticals is presented here.

3.1 Definition of Drugs

Drugs subject to the regulations in the Pharmaceutical Affairs Law are defined as follows in Article 2, Paragraph 1 of the Pharmaceutical Affairs Law. The term "drug" refers to the following substances.

1) Substances listed in the Japanese Pharmacopoeia.
2) Substances (other than quasi-drugs), including dental materials, medical supplies and sanitary materials, which are intended for use in the diagnosis, treatment or prevention of disease in humans or animals, and which are not equipment or instruments.
3) Substances (other than quasi-drugs or cosmetics) which are intended to affect the structure or functions of the body of humans or animals, and which are nor equipment or

instruments.
The specifications used to judge whether or not a substance ingested orally corresponds to a drug were specified in Notification No. 476 of the PAB, MHW dated June 1, 1971, but the "Specifications on the range of drugs" were revised (Notification No. 0331009 of the Pharmaceutical and Food Safety Bureau (PFSB), MHLW dated March 31, 2004).

3.2 Classification of Drugs

Drugs can be classified as follows based on the regulatory provisions in the Pharmaceutical Affairs Law, etc.

1) Classification according to use and supply

(1) **Prescription drugs**
Drugs intended for use by a physician or dentist or under the prescription or instructions of a physician or a dentist

(2) **Non-prescription (OTC) drugs**
Drugs other than prescription drugs that are intended for use at the discretion of general consumers by direct purchase in a pharmacy or drug store under guidance by pharmacist

* The Law for Partial Amendment of the Pharmaceutical Affairs Law (Law No. 69, enforcement expected in 2009) announced on June 14, 2006 to define non-prescription (OTC) drugs as the drugs not having pronouncedly strong intended actions (indications) in humans and those to be selected by users based on information provided by pharmacist or other medical personnel and to classify them in three types based on the degree of risk: Type 1 (highly risky), Type 2 (moderately risky) and Type 3 (relative low risky).

2) Classification according to handling regulations related to safety

Drugs include those that are highly poisonous, which have serious adverse reactions, and which are addictive or habit forming. They are classified as follows in related laws such as the Pharmaceutical Affairs Law (the Law) or the Stimulants Control Law (**Table 1.** Main regulatory drug classification).

(1) Poisonous substances (Article 44 of the Law).
(2) Deleterious substances (Article 44 of the Law).
(3) Drugs requiring a prescription (Article 49 of the Law).
(4) Habit-forming drugs (Article 50 of the Law).
(5) Designated drugs (Article 29 of the Law).
(6) Drugs with restrictions on advertising (Article 67 of the Law).
(7) Drugs manufactured in pharmacies (Article 22 of the Pharmaceutical Affairs Law)

(8) Narcotics (Narcotics and Psychotropics Control Law).
(9) Psychotropic drugs (Narcotics and Psychotropics Control Law).
(10) Opium and powdered opium (Opium Law).
(11) Cannabis (Cannabis Control Law).
(12) Stimulants (Stimulant Control Law).
(13) Clinical study drugs (investigational products) (GCP).
(14) Investigational products for post-marketing clinical trials (GCP).
(15) Biological products (Article 2, Paragraph 9 of the Law)
(16) Specified biological products (Article 2, Paragraph 10 of the Law)

3) Biological products and specified biological products

Biological products were classified as follows based on the definition by the Pharmaceutical Affairs Law and risk of infection as specified in Notification No. 0731011 of the PFSB, MHLW dated July 31, 2002, from the standpoint of augmentation of safety measures in keeping with advances in science and technology including biotechnology and genomics.

(1) Biological products
Drugs, quasi-drugs, cosmetics, or medical devices using materials manufactured from humans or other organisms (excluding plants) as raw materials or packaging materials, which are designated as requiring special precautions in terms of public health and hygiene.

(2) Specified biological products
Biological products designated as requiring measures to prevent the onset or spread of risk to public health and hygiene due to the biological product concerned after selling, leasing or giving.

Biological products and specified biological products are specified by the Minister of Health, Labor and Welfare in Notice No. 209 2003 of the MHLW and these specifications came into effect on July 30, 2003 (Notification No. 0520001 of the PFSB, MHLW dated May 20, 2003). Biological products designated by the Minister of Minister of Health, Labor and Welfare (Article 2, Paragraph 9 of the Law) are the drugs, quasi-drugs, cosmetics or medical devices shown in Attached Table 1. Specified biological products (Article 2, Paragraph 10 of the Law) are biological products shown in Attached Table 2 that require measures to prevent the onset or spread of risk to public health and hygiene due to the biological product concerned after selling, leasing or giving.

Based on the provisions in the Law for biological products and specified biological products, the “Manufacturing supervisors and import and distribution supervisors for biological products,” “Labeling on the

immediate container or packaging," "Entries in the package inserts (Notification No. 0515005 of the PFSB dated May 15, 2003)","Periodic infection reporting system (Notification No. 0515008 of the PFSB dated May 15, 2003)","Records and their retention," "Outsourcing of records and their retention," "Dissemination of information" and "Manufacturing control and quality control" are specified in Notification No. 0515017 of the PFSB dated May 15, 2003 and Notification No. 0520004 of the PFSB dated May 20, 2003, etc.

3.3 Licenses for Marketing Businesses and Manufacturing Businesses

1) Licenses for marketing businesses

Person wishing to start marketing business for drugs, quasi-drugs, cosmetics or medical devices must obtain a marketing business license depending on the type of business. These licenses are of the following seven types.

(1) Type 1 drug marketing business license: marketing of prescription drugs
(2) Type 2 drug marketing business license: marketing of drugs other than prescription drugs
(3) Quasi-drug drug marketing business license: marketing of quasi-drugs
(4) Cosmetic drug marketing business license: marketing of cosmetics
(5) Type 1 medical device marketing business license: marketing of specially controlled medical devices
(6) Type 2 medical device marketing business license: marketing of controlled medical devices
(7) Type 3 medical device marketing business license: marketing of general medical devices

The licensing requirements for drug marketing businesses include the appointment of a general marketing compliance officer, who is a pharmacist, and compliance with Good Quality Practice (GQP) for quality control and Good Vigilance Practice (GVP) for postmarketing safety surveillance.

The general marketing compliance officer, the quality assurance supervisor of the quality assurance unit in charge of GQP and the safety management supervisor of the general safety management division in charge of GVP are known as the "manufacturing/marketing triumvirate" and are at the center of the marketing system.

In an Office Communication dated April 9, 2007, the Safety Division of the PFSB issued a collection of case reports on pharmaceutical manufacturing and marketing business licenses.

2) Manufacturing business licenses

Persons wishing to establish a business for the manufacture of drugs, quasi-drugs,

cosmetics or medical devices must obtain a manufacturing business license in accordance with the manufacturing category as specified by MHLW ordinance.

3.4 Marketing Approvals

Formal approvals and licenses are required in order to marketing drugs in Japan, and formal approval and/or licenses must first be obtained from the Minister of the MHLW or prefectural governor.

The approval and licensing system has been revised in the amended Law and manufacturing (import) approvals became marketing approvals from April 2005. Product licenses have been abolished and GMP compliance for each product has been specified as an approval condition.

Marketing approvals require a review to determine whether or not the product in the application is suitable as a drug to be marketed by a person who has obtained a marketing business license (marketing authorization holder) for the type of drug concerned and confirmation that the product has been manufactured in a plant compliant with GMP.

3.5 Good Manufacturing Practice (GMP)

GMP specifies that compliance with the Regulations for Buildings and Equipment of Pharmacies, etc. that specify standards for structures and equipment in manufacturing plants for each manufacturing category without relation to the products manufactured is a requirement for a manufacturing business license. Compliance with the GMP ordinance that specifies standards for structures and equipment required for the product concerned as well as standards for manufacturing control and quality control for each manufactured product is a condition for approval of the drug concerned (refer to Chapter 3).

3.6 Drug Master File (MF)

With the amendment of the Pharmaceutical Affairs Law enforced on April 2005, approvals for drug substances that had been necessary the past were no longer required (except for products listed in the Japanese Pharmacopoeia) and it is possible to omit documentation on drug substances attached to applications if the marketing authorization holder presents a certificate in writing of MF registration. The drug master file system aims at protecting intellectual property of relevant information and facilitating review work by allowing a registrant (master file registrant) other than an applicant to separately submit information on quality and the manufacturing method at the time of approval reviews of drug substances to be used in drug products (Notification No. 0210004 of the Evaluation and Licensing Division, PFSB dated February 10, 2005).

When an overseas drug substance manufacturer submits an MF registration application, it is necessary to appoint a

drug substance manager to handle the activities of the MF registrant in Japan.

When the registered contents of the drug master file (MF) are changed, an application to change the MF or a slight modification notification must be submitted. However, new registration applications are required in cases where there is concern that the change in registered items will alter the basic nature of the registered items.

When an application to change of the MF is submitted, the marketing authorization holder must submit a partial change application or a slight modification notification for the MF depending on the contents of the change. However, when an MF slight modification notification is submitted, the marketing authorization holder is not required to submit a partial change application or a slight modification notification of the approval form. In both cases, MF registrants must notify the marketing authorization holder or the manufacturing approval holder.

When approval applications are filed using MF registration, a copy of the registration certificate and a copy of the contract with the registrant related to MF utilization are required. When inquiries concerning MF registration arise in the course of the review, inquiries directly from the PMDA are made to the registrant or the drug substance manager. When changes are made in the registered contents as a result of the review, the MF registrant must submit an application for a change in registered content or a slight modification notification without delay.

3.7 Accreditation of Overseas Manufacturers

Persons wishing to manufacture drugs, quasi-drugs, cosmetics or medical devices exported to Japan from overseas (overseas manufacturers) must receive accreditation from the Minister (enforced from April 1, 2005).

The specifications for accreditation are the same as those for manufacturing licenses for domestic manufacturers.

The following items are taken from “Q&A on Accreditation of Overseas Manufacturers” in an office communication of the Evaluation and Licensing Division, PFSB dated February 14, 2006. Refer to the PMDA homepage for reference.

http:www.pmda.go.jp/pdf/application.pdf

(1) Applicants for accreditation of overseas manufacturers and their agents

- When the applicant is a corporation, the representative (director with representative authority) makes the application.
- The marketer, etc. who acts as the agent for the application files the application after confirming from the applicant the type of corporation of the applicant, name, address and agent. The contact information for the agent,

and whether the agent is a marketing authorization holder or a manufacturer is entered in the Remarks section of the application form.

(2) Timing of applications for accreditation of overseas manufacturers

The application should be submitted by the time of the marketing approval application. When accreditation is not obtained beforehand, “under application” should be entered in the marketing approval application form. (Marketing approval can not be obtained without accreditation approval.

(3) Outline of the structure and facilities of the manufacturing plant required for accreditation of overseas manufacturers and attached documentation

- The outline of the structure and facilities of the manufacturing plant should be based on that in the manufacturing business license application in Japan. A list of the structures and facilities must be included.
- When Japanese can not be used as the language in the attached documentation under special circumstances, a foreign language can be used, but a Japanese translation must be attached in such cases. If the foreign language is not English, certification of the translator must be attached.
- A medical certificate from a physician must be submitted when the applicant is a corporation for the executives involved in the business, namely the executive with representative authority and executives involved in the business without representative authority, and a table showing the duties of the executives must be attached. When it is difficult to submit medical certificates for physicians for unavoidable reasons in countries where the overseas manufacturer has received authorization, it is possible to submit documents verifying that the executives involved do not correspond to the provisions of Article 5, Item 3(d) (excluding the part related to adult wards) and (e) in place of the medical certificates for physicians.

(4) On-site surveys for accreditation of overseas manufacturers

When a GMP compliance survey is performed simultaneously with the accreditation, the structures and facilities are required for accreditation to be confirmed in the GMP compliance survey, as a rule.

3.8 Drug Retail Seller Licensing

A license must be obtained from the Prefectural Governor, etc. in order to sell or supply drugs. Licenses of drug retail selling businesses are divided into the following four types:

(1) First-class seller of drugs
(2) Second-class seller of drugs
(3) Seller of drugs by household distribution
(4) Third-class seller of drugs

* In the revised Pharmaceutical Affairs Law announced on June 14, 200 (Law No. 69, enforcement in 2009), the types of drug retail business licenses have been amended to three types: retail store sellers, home distribution sellers and wholesale sellers of drugs.

3.9 Quality Standards and Government Certification

The Japanese Pharmacopoeia, Japanese Pharmaceutical Codex, Japanese Pharmaceutical Excipients, and other similar standards have been specified as quality standards. Certain specified drugs such as biological products must not be marketed or supplied without government certification based on batch tests.

3.10 Labeling and Package Inserts

Specified items must be entered on the immediate container of drugs. The package inserts must contain indications, dosage and administration, precautions and precautions for handling.

All ingredients used as excipients must be included in the package inserts of prescription and non-prescription drugs. Entries in the package inserts of biological products are specified in Notification No. 0515005 of the PFSB dated May 15, 2003 and labeling on the immediate container or packaging of biological products is specified in Notification No. 0515017 of the PFSB dated May 15, 2003. These specifications came into effect from July 30, 2003. According to the Pharmaceutical Affairs Law amended on April 1, 2005, a new regulatory category for prescription drug labeling “Caution: use only with a prescription from a physician” and a labeling item for manufacturer/distributor business instead of manufacturer or importer were added (refer to Chapter 5).

* The revised Pharmaceutical Affairs Law announced on June 14, 200 (Law No. 69, enforcement in 2009) specifies matters regulated by Ministry order be described according to the risk classification.

To prevent medical accidents due to misunderstandings and assure traceability, implementation of barcode labeling for prescription drugs (excluding in vitro diagnostics) (Notification No. 0915001 of

the Safety Division, PFSB dated September 15, 2006) and preparation of medication guides for patients so that the patient understands the prescription drug correctly and serious adverse drug reactions can be discovered at an early stage (Notification No. 0228001 of the Safety Division, PFSB and No. 0228002 of the Compliance and Narcotics Division, PFSB dated February 28, 2006) are being promoted.

3.11 Restrictions and Prohibition of Advertising

The following restrictions on advertising are enforced to ensure proper use of drugs: prohibition of advertising of prescription drugs aimed at the general consumer, advertising of the name, manufacturing method and/or indications of a drug before approval, and false or exaggerated statements.

With the recent increased awareness of the public concerning health and the spread of the Internet, there have been cases of advertisement of unapproved drugs by persons acting as importers. Therefore, a notification has been issued concerning guidance and control of individual importers including items related to drug advertising (Notification No. 0828014 of the PFSB dated August 28, 2002).

3.12 Good Laboratory Practice (GLP)

GLP specifies standards that must be met by testing facilities for nonclinical safety tests on drugs from the viewpoint of the structure/equipment and the operation/management of the facilities. The first GLP guideline was issued as a PAB notification in 1982, but was changed to a MHW ordinance in 1997 (Ordinance No. 21: GLP dated March 26, 1997) that was enforced on April 1, 1997 to assure greater reliability of application data (refer to Chapter 3).

3.13 Good Clinical Practice (GCP)

Previously, any prospective sponsor requesting permission to conduct a clinical trail had to comply with the standards outlined in Article 67 of the old Enforcement Regulations of the Law and in "Standards for the Conduct of Clinical Trials on Drugs" (PAB Notification No. 874 dated October 2, 1989 [Old GCP]). These standards were established for an ethically correct and scientifically accurate implementation of clinical studies and applied to those clinical studies conducted according to study protocols prepared after October 1990. However, from April 1, 1997, an MHW Ordinance specifying the Standards for the Conduct of Clinical Studies (Ordinance No. 28, GCP dated March 27, 1997) was enacted to cover not only ordinary clinical studies but also post-marketing clinical trials. This ordinance was issued to protect the human rights of subjects, to

assure safety, and to assure the reliability of clinical study data. (Refer to Chapter 3.)

In June 1999, the Study Group on the Efficient Conduct of Clinical Trials reported recommendations to improve systems for actively encouraging voluntary participation of human subjects in clinical studies and for establishing clinical research facilities in hospitals. These recommendations are summarized as follows:

(1) Actively publicize the importance of clinical studies to the public.
(2) Promote the publicity of planned or scheduled clinical studies for efficient recruitment of prospective subjects.
(3) Be equipped to provide adequate treatment to subjects during the study period.
(4) Reduce the burden on the subjects.
(5) Train and secure clinical research coordinators (CRCs).

Based on these recommendations, several measures were taken to improve the conduct of clinical trials. Such measures included establishing guidelines for the improvement of clinical research facilities and equipment, education and training of CRCs, and rules concerning appropriate dissemination of information for efficient recruitment of subjects (Notification No. 65 of the Inspection and Guidance Division, PMSB dated June 30, 1999); and for ways to reduce the financial burden on study centers, including national hospitals and national universities (Notification No. 196 of the Medical Professions Division, Health Policy Bureau dated July 2, 1999 and Notification No. 20 of the Medical Education Division, Higher Education Bureau, Ministry of Education, Culture, Sports, Science and Technology dated July 2, 1999).

The new GCP was enacted on October 4, 1998. However, the Study Group on the Efficient Conduct of Clinical Trials indicated the need for standard operating procedures (SOP) for the proper conduct of clinical studies. One of the working groups started to investigate standard operating procedures, in particular the acceptance of monitoring and audits by medical institutions that presents a problem in clinical practice (Notification No. 889 of the Evaluation and Licensing Division, PMSB dated July 24, 2000). Because of increasing use of site management organizations (SMOs) for clinical trials in medical institutions, the Report of the SOP Study Group on Utilization of SMO was published in November 2002.

Part of the revision of the Pharmaceutical Affairs Law in July 2002 came into effect in 2003. This included the establishment of a system for clinical studies performed for future approval applications by physicians and medical institutions (so-called investigator-initiated clinical trials). It has become possible to conduct clinical studies on unapproved drugs obtained by physicians and medical

institutions and clinical studies on off-label applications of approved drugs (MHLW Ordinance No. 106 dated June 12, 2003, the revised GCP). Application of the revised GCP is specified in Notification No. 0722014 of the Evaluation and Licensing Division, PFSB dated July 22, 2004. In March 2005, the Council on Efficient Conduct of Clinical Trials was established to evaluate and find ways to efficiently conduct clinical trials securing reliability of the conduct of clinical trials and safety of study subjects and discussed procedures necessary for proper conduct of investigator-initiated clinical trials and for improvement of quality and performance of institutional review board. On September 19, 2007, a report was compiled by the MHLW Council of Ideal Registration-directed Clinical Trial. Based on this report, the Evaluation and Licensing Division of PFSB issued Notification No. 1002002 dated October 2, 2007 to reevaluate and rationalize the type and scope of documents necessary for the conduct of clinical trials. The GCP regulations are to be revised accordingly.

3.14 Good Post-Marketing Study Practice (GPSP)

GPMSP specified the system and scope of activities to be conducted by companies to assure proper implementation of post-marketing surveillance and the reliability of the data obtained. The GPMSP was originally issued as a PAB notification in June 1991 and applied in April 1993. It was issued as an MHW Ordinance in 1997 (Ordinance No. 10: the new GMPSP dated March 10, 1997), which was enforced on April 1, 1997 to further strengthen post-marketing surveillance.

With the enactment of the revised Pharmaceutical Affairs Law, the GPMSP was divided into Good Vigilance Practice (GVP, standards for post-marketing safety management) and Good Post-marketing Study Practice (GPSP). The GPSP Ordinance was enforced from April 1, 2005 (refer to Chapter 4).

The reexamination period for drugs with new active ingredients had been six years as a rule, but it was prolonged to eight years as a rule from April 1, 2007 (Notification No. 0401001 of the PFSB dated April 1, 2007).

Note: Reexamination period: Period of protection of data in Japan during which applications for generics cannot be filed.

3.15 Reexamination and Reevaluation

Marketers must perform post-marketing surveys on new drugs so that efficacy and safety can be reconfirmed by reexamination by the MHLW for a specified period after marketing approval. All drugs, including those that have completed reexamination must undergo reevaluation to recheck their efficacy, safety, and quality in accordance with progress in medical and pharmaceutical sciences.

Data submitted with applications for reexamination or reevaluation must be collected and compiled in accordance with the GPSP.

Since April 1, 1997, periodic safety reports must be submitted to the Minister until completion of the reexamination period, when the Ministry designates drugs for reexamination.

The reexamination period for drugs with new active ingredients had been six years as a rule, but it was prolonged to eight years as a rule from April 1, 2007 (Notification No. 0401001 of the PFSB dated April 1, 2007).

3.16 Adverse Drug Reaction (ADR) and Infection Reporting

When marketers of drugs are informed of any adverse reactions, infections, etc. as specified by MHLW ordinance for trial products or their marketed products, they must report it to the Minister within the specified period (Notification No. 0317006 dated March 17, 2005).

As of December 28, 1999, the use of the Japanese version of ICH MedDRA (MedDRA/J) was authorized for reporting of adverse drug reactions and infectious diseases and its use was enforced on April 1, 2004 (Notification No. 0325001 of the Safety Division and Notification No. 0325032 of the Evaluation and Licensing Division, PMSB dated March 25, 2004).

Since October 27, 2003, electronic adverse drug reaction reports have been accepted (Notification No. 0828010 of the Safety Division dated August 28, 2003). The reports are required to be sent to the PMDA on April 1, 2006 (Partial Modification of the Pharmaceutical Affairs Law In accordance with the Special Corporation Rationalization Plan dated March 25, 2004).

3.17 Dissemination of Information

Marketers of drugs or medical devices, wholesalers, marketer or leasers of medical devices and overseas exceptional approval are asked collect and examine information on efficacy and safety and for the proper use of drugs and medical devices and supply such information to health professionals such as physicians and pharmacists.

3.18 Measures related to the Law Concerning Access to Information Held by Administrative Organizations

With the enactment of the Law Concerning Access to Information Held by Administrative Organizations on April 1, 2000, anyone has the right to request disclosure of documents held by national government organizations. This law covers disclosure of documents held by government organizations except those concerning non-disclosable information such as information on individuals, information on corporations, etc. This was

partially amended by Cabinet Order No. 371, December 21, 2005.

Based on this Law, the MHLW must disclose the contents of its reviews (records of meetings of the PAFSC, new drug approval information dossiers, etc.).

The criteria for disclosure and non-disclosure were published on March 28, 2001 (Notification No. 245 of the PMSB dated March 27, 2001). The above notification was abolished because of the issuing of new official documents associated with the amended Pharmaceutical Affairs Law, etc. and new procedures for processing work related to public disclosure of information held by the PFSB were specified (Notification No. 0330022 of the PFSB dated March 30, 2007.

These procedures clarify the actual decisions on whether or not disclosure is granted for documents held by the PFSB (not including those held by the Department of Food Safety). These documents are classified into five types: (1) evaluation and licensing-related documents, (2) safety-related documents, (3) compliance-related documents, (4) narcotics-related documents, (5) blood and blood products-related documents, and (6) other activity-related documents.

Documents for which the forms are designated (drug approval application forms, adverse drug reaction report forms, narcotics import license application forms, etc.) are clearly marked as ○ (disclosure), ● (non-disclosure) or Δ (partial disclosure). For approval application summaries for which no forms are designated, examples are given and the criteria for disclosure and non-disclosure are specified.

Approval application documentation from pharmaceutical companies is not accessible as a rule before approval but becomes accessible after approval. However, even after the approval is granted, where there is a risk that, by being made public, the rights, competitive standing, or other legitimate interests of the corporation, etc. are harmed, the information (such as that on the manufacturing method, specifications and test methods, impressions of the applicant, etc.) are not disclosed. Attached application data or Module 3 (or Part 3, quality-related documentation), Module 4 (or Part 4, nonclinical study reports) and Module 5 (or Part 5, clinical study reports) are not accessible.

Later, the criteria for disclosure of Adverse Drug Reaction Report Forms were revised by Notification No. 4 of the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ) dated January 6, 2004. Notification No. 0422004 of the PMDA dated April 22, 2005 specifies points to consider in the disclosure of data related to new drug approval reviews.

3.19 Patent System

The patent term is 20 years from the time of application as a rule. However, if the patent can not be implemented because of laws and regulations to ensure safety of drugs, etc. the patent term can be extended for a maximum of 5 years. The extension is for the period that the patented invention cannot be used, such as the period from the date of the start of clinical trials or date of patent registration, whichever is later, until one day prior to the date on which the patentee receives approval for the drug.

Patentees who want an extension of the patent term must submit an application to the Patent Office for extension of registration including the required items such as the requested extension period before the patent rights become invalid within 3 months from the date of receipt of drug approval. In cases where it is anticipated that it will not be possible to obtain approval as specified by government ordinance by the day before 6 months prior to the date on which the patent expires, a document showing necessary information including the patent number must be submitted. If an application for an extension is submitted, it can be considered that the patent term has been extended until rejection becomes final or the extension is registered (**Fig. 4.** Procedures for patent applications).

Japanese language website of the Patent Office:

http://www.jpo.go.jp/indexj.htm

English website:

http://www.jpo.go.jp/index.htm

3.20 Drug Abuse Control

Japan has become signatory to the following three conventions: the Single Convention on Narcotic Drugs of 1961, the Convention on Psychotropic Substances of 1971, and the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988, and has ratified all of these conventions. In addition, Japan has enacted five laws of its own: the Narcotics and Psychotropics Control Law, the Opium Law, the Cannabis Control Law, the Stimulants Control Law, and the Law Concerning Special Provisions for the Narcotics and Psychotropics Control Law, etc. and Other Matters for the Prevention of Activities Encouraging Illicit Conduct or Involving Controlled Substances through International Cooperation.

June 26, the final day of the International Narcotics Conference held in 1987, was designated as “International Drug Abuse Eradication Day.” At a special United Nations meeting on narcotics in 1998, the “Declaration on guidance to prevent drug abuse” was adopted.

The problem of drug abuse, including narcotics, stimulants and hemp, has spread worldwide at present and it is one of the most serious social problems affecting the

human race not only in terms of survival but also as a threat to safe and stable societies and nations. Japan is now facing the a serious situation of stimulant abuse with feelings of resistance and alarm concerning drug abuse waning among young people such as middle and high school students.

One aim of the Law for Partial Amendment of the Pharmaceutical Affairs Law (Law No. 69) announced on June 14, 2006 (enforcement expected within one year) was to strengthen control of illegal drugs because such drugs are being sold in a disguised form suggesting they are not intended for human consumption even though they can cause health damage due to abuse and risk leading to the use of other illegal drugs such as narcotics and stimulants.

Measures for the regulation of designated drugs (drugs with a high probability of such actions as excitation of the central nervous system that present a risk to public health and hygiene) have been added to the Pharmaceutical Affairs Law as countermeasures against illegal drugs. Basically, the manufacture, import and advertising of designated drugs for purposes other than healthcare is prohibited. On February 28, 2007, Guidelines on Monitoring of Import of Designated Drugs were issued (Notification No. 0228009 of the PFSB).

4. MARKETING APPROVALS

4.1 Drug Marketing Approvals

Drug marketing approval refers to governmental permission for a drug with the quality, efficacy and safety or a drug that is manufactured by a method in compliance with manufacturing control and quality control standards based on an appropriate quality and safety management system to be marketed, generally distributed, and used for healthcare in Japan. Whether or not a substance under application is appropriate for human health care is objectively determined in light of state of the art medical and pharmaceutical technology. Specifically, the Minister or prefectural governor reviews the name, ingredients, composition, dosage and administration, indications and ADRs, etc. of the product in an application submitted by a person with a marketing business license. A GMP compliance review is performed to assure that the plant manufacturing the product complies with the manufacturing control and quality control standards. Marketing approval is granted to products meeting these standards. This approval system is the essential basis for ensuring good quality, efficacy, and safety of drugs and related products, which is the principal objective of the Pharmaceutical Affairs Law.

4.2 Marketing Approval Reviews

The surveys and clinical trial

consultation services performed previously by the OPSR and the review work undertaken by the Evaluation Center are now undertaken by the independent administrative organization, PMDA established on April 1, 2004. Therefore, the PMDA covers the entire range of work from clinical trial consultations to reviews.

Application forms for approval to market drugs are usually submitted to the PMDA. When application forms for new drugs are received by the PMDA (SOGO-KIKO), a compliance review of the application data (certification from source data), GCP on-site inspection, and detailed review are undertaken by review teams of the PMDA and the team prepares a review report.

The approval review process consists of expert meetings of review team members and experts to discuss important problems. A general review conference attended by team members, experts and representatives of the applicant is held after the expert meeting.

The evaluation process followed by the PMDA is as follows (refer to the PMDA website: http://www.pmda.go.jp/):

(1) Interview (presentation, inquiries, and replies)

(2) Team review

(3) Inquiries and replies

(4) Review report (1)

(5) Expert meeting (includes at least three clinical specialists as experts)

(6) General review conference (main agenda items and names of participating experts made available 2 weeks prior to meeting; presentation)

(7) Follow-up expert meeting

(8) Review report (2)

(9) Report to the Evaluation and Licensing Division, PFSB

The PAFSC is then consulted for discussions by the related committees and the Pharmaceutical Affairs Committee as required on the basis of the review report. After the report of the PAFSC report is obtained and it is confirmed that the standards are met in a separate GMP compliance review, the Minister grants the new drug manufacturing/distribution approval (**Fig. 5**). Information concerning new drug approval" prepared from the review data is placed on the website of the PMDA so that accurate information concerning the quality, efficacy and safety obtained during the approval review process is supplied to medical institutions, etc.

In reviews of new drugs prepared from vaccine or blood, the specifications and test methods are examined by the National Institute of Health Sciences, or by the Infectious Disease Surveillance Center (IDSC) prior to approval.

When the active ingredients, dosage, administration route, and indications are the same as those of approved drugs, a

review by the PMDA is undertaken after reviews on drug equivalence and compliance, and approval is granted.

A basic notification concerning drug approval reviews was issued on April 8, 1999 and came into force for approval reviews of drugs from April 1, 2000. This basic notification was partially revised on March 31, 2005 and the application categories were more strictly defined.

On March 28, 2000, a notification was issued stating that the standard review period for applications submitted after April 1, 2000 would be reduced to one year. The general review conference is held within 6 months after application (excluding the time taking by the applicant to prepare replies, etc.).

With the agreement reached on the common technical document (CTD) guidelines of the International Conference on Harmonization (ICH), new guidelines for preparation of approval application data were issued (Notification No. 899 of the Evaluation and Licensing Division, PMSB dated June 21, 2001). Applications using the CTD became obligatory for new products in applications filed on or after July 1, 2003.

These guidelines consist of five parts: Module 1 (Regulatory information such as application forms and information concerning attached documentation), Module 2 (Data summary), Module 3 (Data on quality), Module 4 (Non-clinical study reports) and Module 5 (Clinical study reports). Modules 2 to 5 should be prepared on the basis of the CTD guidelines. Part 1 consists of documents requested by each regulatory authority. Detailed standards are shown in the Appendix.

Electronic specifications for the CTD (eCTD) have been prepared and have been applied to application data submitted electronically since April 1, 2005 (Notification No. 0527004 of the Evaluation and Licensing Division, PFSB dated May 27, 2004).

In addition to the standard processing period of 1 year taken by the MHLW, the applicant takes another 1 year as a rule to respond to inquiries, etc., which makes the maximum period from the application to approval 2 years. The applicant is requested by the MHLW to withdraw the application in case a longer time is required for responding to inquiries or conducting additional studies (Notification No. 0604001 of the Evaluation and Licensing Division, PFSB dated June 4, 2004).

Since additional expenses are required for reduction of the review period, a major increase in application fees for all new drugs was implemented on April 1, 2007.

4.3 Priority Review System and Designation of Drug Products for Priority Reviews

1) Priority Review System

Drug approval reviews are normally

processed in the order that the application forms are received, butfor drugs designated as orphan drugs and other drugs considered to be especially important from a medical standpoint such as new drugs to treat serious diseases, a decision must be made whether or not to specify an overall evaluation of (1) the seriousness of the targeted disease and (2) the clinical usefulness, as stipulated in Article 14-(7) of the Pharmaceutical Affairs Law. With this system, applications for the specified drugs are reviewed on a priority basis (Notification No. 0227016 of the Evaluation and Licensing Division, PFSB dated February 27, 2004)

(1) Priority review criteria

(A) Seriousness of indicated diseases

(i) Diseases with important effects on patient's survival (fatal diseases)

(ii) Progressive and irreversible diseases with marked effects on daily life

(iii) Others

(B) Overall assessment of therapeutic usefulness

(i) There is no existing method of treatment.

(ii) Therapeutic usefulness with respect to existing treatment

a) Standpoint of efficacy

b) Standpoint of safety

c) Reduction of physical and mental burden on the patient

(2) Designation of drug products for priority reviews

When drugs are designated for priority reviews, opinions of experts on such designations are compiled by the PMDA immediately after the application and reported to the MHLW. Based on this report, the Evaluation and Licensing Division decides whether or not to apply the priority review. The Evaluation and Licensing Division notifies this decision to the applicant and the PMDA. The Evaluation and Licensing Division reports this application to the next meeting of the review committee concerned of the PAFSC and obtains their approval. Products for priority review are given priority at each stage of the review process as much as possible. When products subject to priority review are approved as new drugs, this fact is made public.

2) Review of Products Designated for Priority Face-to-face Advice

When products have been designated for priority face-to-face advice at the development stage, it is possible to obtain priority face-to-face advice on indications and other items

concerning the designated product. Products are designated on the basis of an overall evaluation of the seriousness of the indicated disease and the clinical usefulness using the propriety review selection criteria. Applicants are requested to submit results of clinical studies up to late Phase II as a rule as data for estimating the clinical usefulness. Hearings and inquiries are undertaken for the applicant as required and the designation is decided after hearing the opinions of experts in the field. The results, including the reason, are notified to the applicant in writing. Orphan drugs are all handled as products for priority face-to-face advice and an application is not required.

4.4 Restricted Approval System

The drugs to which this system applies are those used in emergencies to prevent the spread of diseases that might have a major effect on the public health. It also applies to drugs for diseases for which the drug concerned is the only method of treatment and which are marketed overseas. Such products may be granted a restricted approval by the Minister without going through ordinary approval review procedures after hearing the opinion of the PAFSC.

4.5 Orphan Drugs

Policies to promote research and development on orphan drugs were adopted in 1993, and a notification was issued by the MHW concerning designation criteria and measures to promote research. The criteria for designation include less than 50,000 patients indicated for the drug concerned and excellent usefulness of the drug from the medical standpoint. The PAFSC gives its opinion on the designation.

Drugs designated as orphan drugs are entitled to certain priority measures such as financial aid, tax relief on research expenses, guidance and advice, priority review and extension of the reexamination period from the conventional 6 years to a maximum of 10 years for drugs and from 4 years to a maximum of 7 years for medical devices.

4.6 Drugs for Pediatric Use

Drugs used in pediatric clinics are often considered as “therapeutic orphans” throughout the world because they are difficult to develop and not very profitable. This also applies in Japan and very few drug products are indicated for pediatric use. Clinical trials on children are inadequate, products that can be used for children are not sufficient and information in package inserts (dosage, efficacy, safety, etc.) related to applications in children is also insufficient. Therefore, “off-label use” of drugs basically intended for adults, use of in-hospital products without adequately verified safety and use, etc. of drugs for

pediatric use obtained by individual import are common.

At present, laws and regulations aimed at drug development and direct promotion of information dissemination in the pediatric field such as those in the EU and United States do not exist in Japan. When clinical trials are planned for dose setting, etc. in children during approval applications or after approval of drugs intended for use in children to collect information on experience of use in pediatric populations, the reexamination period can be now extended for a set period not exceeding 10 years in consideration of special surveys and clinical studies during the reexamination period (Notification No. 1324 of the PMSB dated December 27, 2000).

In cases of requests by related academic societies, necessity in healthcare and requests made to study the addition of indications by the Research and Development Division of the Health Policy Bureau, notifications concerning application for partial changes in approved items such as indications required on the basis of clinical studies or clinical results have been issued (Notifications No. 4 of the Research and Development Division, Health Policy Bureau and No. 104 of the Evaluation and Licensing Division, PMSB dated February 1, 1999). This can also be applied to drugs intended for use in the pediatric field. In these notifications, it states that all or part of the clinical studies do not have to be performed again and when the indications related to off-label use are public knowledge in medicine or pharmacology, this can be applied to judgments on whether or not to approve indications.

The Study Group on Unapproved Drugs was founded in December 2004 to perform reliable clinical studies on drugs not approved in Japan for which efficacy was established and approvals granted in the West in order to assure prompt approvals in Japan. Periodic surveys and scientific evaluations of requests of academic societies and patients are undertaken, often involving drugs for pediatric use. In March 2006, the Study Group on Pediatric Drug Treatment was established to collect and evaluate evidence on the efficacy and safety of pediatric drug treatment, to conduct surveys on prescriptions for drugs for pediatric use and to provide information to health professionals for the environmental improvement to adequate pediatric drug treatment.

In ICH, E11: Clinical Investigation of Medicinal Products in the Pediatric Population, has reached Step 5, and in Japan, Guidance on Clinical studies on Drugs in Pediatric Populations has been issued (Notification No. 1334 of the Evaluation and Licensing Division, PMSB dated December 15, 2000). PMDA consultations include those on clinical development in pediatric populations and development of products for pediatric use.

4.7 Codevelopment

The objective of codevelopment is to reduce the risk of the development of new drugs and to promote more efficient development. Codevelopment regulations, including requirements for composition of the codevelopment group and requirements for those preparing the data, had been specified in the past, but codevelopment was deregulated by the basic guidelines for drug approval applications issued on April 8, 1999.

The main points of this deregulation included cancellation of the requirement that the group had to include members with previous experience in receiving a new drug approval. Among the requirements for those preparing the data, it was previously required what when the codevelopment group performed a clinical trial, the group members had to be joint sponsors of the trial, but currently other members in the group can use data in applications from clinical trials performed by any member of the group.

If clinical trials performed by other companies in the group meet certain requirements, data prepared by persons other than the applicant can be accepted as approval application data and reviews of applications submitted by several members of the codevelopment group can apply the same application data. Requirements for data submitted for approval applications have been simplified.

4.8 Transfer of Marketing Approvals

Marketing approvals can be transferred to legally authorized marketers through succession, merger, contracts, etc. provided that all data and related information are transferred from the original approval holders.

4.9 Approval Applications for Drugs Manufactured Overseas

Pharmaceutical manufacturers outside Japan can apply directly under their own name for marketing approval if they perform the studies regarding quality, efficacy and safety required for the drugs they intend to export to Japan and undertake the necessary procedures (**Fig. 6.** Procedure for manufacturing and distribution of drugs for overseas manufacturers in Japan).

In such cases, the overseas manufacturer appoints a marketer in Japan among those that have received a marketing business license of the type corresponding to approved product. The appointed marketer takes measures required to prevent the onset of health and hygiene-related hazards caused by the approved drug in Japan and can also undertake manufacturing and marketing in Japan.

4.10 Issuing of Certificates by MHLW

The notification on issuing export certificates for drugs and medical devices was partially revised and items related to

issuance of certificates for cosmetics and package inserts of drugs were deleted (Notification No. 170 of the PMSB dated June 6, 2001). Currently, the MHLW issues the following certificates upon request: business licenses for marketing and manufacturing of drugs, etc., marketing approvals for drugs, etc., attached documentation for new drug marketing applications, GLP compliance for drugs, notifications clinical trial protocols for investigational products, certification of pharmaceutical products, and statements of approval and licensing status of pharmaceutical products (**Table 2.** Divisions of the Pharmaceutical and Food Safety Bureau in Charge of Certification Work). Regulations related to the import of bovine spongiform encephalitis (BSE) from China were abolished by Notification No. 0926003 of the PFSB dated September 26, 2007. The Ministry would like to use formats specified by the WHO; however, it will use country-specific formats when necessary. Export certificates on drugs, quasi-drugs, etc, are issued using the specified format via the PMDA. Certificates for the items related to compliance of drug manufacturing plants with GMP can be obtained by applying directly to the Compliance and Narcotics Division, PFSB of the MHLW.

4.11 Issuing Certificates Based on the Who Certification System

Certificates of drugs for export have been revised in accordance with WHO guidelines. Certificates for drugs approved by the MHLW were formerly issued for each item but since January 1998, certificates including the approval and licensing status, GMP compliance and product information are issued using two forms, one for certification of pharmaceutical products and one for statements of approval and licensing status of pharmaceutical products based on the new WHO certification system.

5. JAPANESE PHARMACOPOEIA AND OTHER STANDARDS

5.1 Japanese Pharmacopoeia (JP)

The Japanese Pharmacopoeia (JP) was established and published to regulate the properties and qualities of drugs by the MHLW based on the provisions of Article 41, Paragraph 1 of the Pharmaceutical Affairs Law after hearing the opinion of the Pharmaceutical Affairs and Food Sanitation Council (PAFSC). The JP is a book of drug standards specified and published by the Minister.

Since it was first published in June 1886, the JP has been revised several times. The Pharmaceutical Affairs Law specifies that the JP must be subjected to a complete revision at least once every 10 years, and such revisions have actually appeared every 5 years since the 9th revision in April 1976. In addition, the JP has been

partially revised before the complete revision even 5 years since the 11th Edition.

The PAFSC held a meeting of its Subcommittee on the Japanese Pharmacopoeia to cope with recent progress in the medical and pharmaceutical sciences in November 2001. The basic compilation policies that include the characteristics and role of the JP, the actual measures taken for the 15th edition to achieve the basic policies, date of enforcement, and items related to the organization of the Committee on the Japanese Pharmacopoeia were formulated. Content regulations including clarification of significance and specifications of contents were examined and the JP basic content regulations were published in a report of the PAFSC entitled "Future approaches to the Japanese Pharmacopoeia."

Basic compilation policies for the 16th edition of the JP (Office communication dated August 3, 2006)

(1) Basic policies

1) Complete entries of all drugs important in healthcare
2) Improvement of quality by introduction of the latest scholarship and technology
3) Promotion of internationalization
(4) Prompt partial revisions as required and smooth application based on government policies.
5) Assurance of transparency in the revision process of the JP and widespread application of the JP.

(2) Characteristics and the role of the JP

The JP is a publication that contains the specifications required to assure the quality of drugs in Japan in accordance with the scientific and technological progress and medical demand at the time. It includes the specifications and test methods to assure the overall quality of drugs in general, and to clarify the role of standards to evaluate the quality of medically important drugs.

The JP is compiled by utilizing the knowledge and experience of many pharmaceutical professionals. It is a book of standards that can be utilized widely by people in the field and it also serves to publish and explain information on drug quality for the general public. The JP contributes to the smooth and efficient promotion of government policy and the maintenance and assurance of international coordination related to drug quality.

3) Date of enforcement

The first supplement of the 15th edition of the JP was announced in Notice No. 285 of the MHLW dated September 28, 2007 and was enforced by Notice No. 316 of the Ministry from October 1, 2007.

The second supplement of the

15th edition and the 16th edition of the JP are scheduled to be issued in March 2008 and March 2011, respectively.

(4) Selection of products for entry in the JP

Items selected for entry in the JP must be those important in healthcare that must be entered as soon as possible after marketing based on the necessity of the drug in medical practice, wide application and experience of use.

(5) Compilation Review Organization for the JP

The review organization was revised based on a report of the PAFSC issued in November 2001 and consists of 11 panels: Panels on general affairs, drug names, pharmaceutical excipients, physicochemical test methods, medicinal chemicals, biological products, biological test methods, antibiotics and crude drugs, as well as a subpanel on general affairs and a Pharmacopoeial Discussion Group (PD) related panel. Then a panel on water for pharmaceutical manufacturing and JP standard product panel were added. Three working groups were established under the panel on medicinal chemicals to promote deliberations related to drugs. Then part of the JP Review Organization was transferred to the JPMA after it was established in April 2004.

The technical research committees of the Osaka Pharmaceutical Manufacturers Association and Pharmaceutical Manufacturers Association of Tokyo, Tokyo Crude Drug Association, Japan Pharmaceutical Excipients Council, Chinese Crude Drug Council of Japan, Japan Antibiotics Research Association, Japan Flavor and Fragrance Materials Association, Japan Crude Drug Federation, Japan Pharmaceutical Manufacturers Association, Japanese Association of Hospital Pharmacists, Japan Pharmaceutical Association, Japan Association of Plant Oils, etc. cooperated in preparation of the draft version of the 15th edition of the JP.

5.2 Standards Based on Article 42 of the Pharmaceutical Affairs Law

For drugs that require special precautions with respect to public health and sanitation, several necessary standards have been established concerning the methods of manufacture, properties, quality, storage methods, etc. based on Article 42 of the Pharmaceutical Affairs Law. The following standards exist at present:

- Radiopharmaceutical Standards
- Minimum Requirements for Biological Products

- Minimum Requirements for Blood Grouping Antibodies
- Standards for Biological Materials
- Standards for *in vitro* Diagnostics designated by the Minister according to Article 42-(1) of the Pharmaceutical Affairs Law

5.3 Standards for Biological Materials

The Standards for Biological Materials were specified in Notice No. 210, 2003 of the MHLW for quality and safety assurance of raw materials and packaging materials manufactured from biological materials and used in the manufacturing process for drugs, quasi-drugs, cosmetics and medical devices based on the provisions of Article 42 (Standards of Drugs, etc.) of the Law. These standards including interim measures came into effect from July 30, 2003. They consist of General Notices, General Rules for Blood Products, General Rules for Human-derived Biological Products and General Rules for Animal-derived Biological Products. The Standards for Cell and Tissue-derived Drugs and Medical Devices were abolished on July 29, 2003. With the specification of the Standards for Biological Materials, the Minimum Requirements for Biological Products were partially revised by Notice No. 211, 2003 of the MHLW and the General Rules for Blood Products were abolished by the Minimum Requirements for Biological Products.

Notice 262 issued by the MHLW on July 5, 2004 states that the standards for raw materials of biological origin have been partially revised as indicated below. These revisions, including interim measures, came into effect on the day of notification.

- **Standards for raw materials of ruminant origin**

(1) The spine, skull, trigeminal ganglion and dorsal root ganglion of ruminants have been added to the list of materials prohibited for use as raw materials in drugs, medical devices, quasi-drugs and cosmetics (hereafter drugs, medical devices, etc.).

(2) In conjunction with the confirmation of a cow infected with BSE in the United States in December 2003, the United States was removed from the list of countries of origin of raw materials originating from cows and other ruminants that can be used as raw materials for drugs, medical devices, etc.

(3) Gelatin and collagen used in drugs, medical devices, etc., which are manufactured from raw materials derived from skin, have been removed from the list of regulated items from countries of origin with confirmed cases of BSE.

Based on Notice No. 310 of the MHLW dated September 28, 2007, Chile was removed from the list of countries of origin of raw materials originating from cows and other ruminants.

5.4 Quality Standards Based on Notifications

In addition to quality standards specified on the basis of laws and ordinances, the quality specifications have also been published as listed below based on notifications for administrative guidance.

- Japan Pharmaceutical Codex
- Japan Crude Drug Codex
- Insecticide Standards
- Standards for Raw Materials for *in vitro* Diagnostics
- Japan Pharmaceutical Excipient Standards

5.5 Government Batch Test

Government supervision and certification based on batch tests are specified for drugs that require advanced and sophisticated manufacturing technology or testing methods. Such drugs are tested in order to assure their quality in institutions designated by the MHLW, and the drugs cannot be sold or otherwise marketed unless they pass these tests.

At present, a part of biological products is subject to such testing.

The designated testing institution is the National Institute of Infectious Diseases.

6. PHARMACEUTICAL SUPERVISION

6.1 Pharmaceutical Supervision

Based on the provisions of the Pharmaceutical Affairs Law, the Minister of the MHLW, prefectural governors, or other may appoint "**pharmaceutical inspectors**" in connection with the rationalization of pharmaceutical manufacture, import, labeling, advertisements or distribution. This pharmaceutical inspection system covers falsely labeled drugs, drugs of poor quality, drugs that have not been approved or licensed, and false or exaggerated advertising. Pharmaceutical inspectors perform on-site inspections as needed, and when violations are discovered, the inspectors may issue various orders including administrative measures. The main measures are as follows:

- Revocation of approval, change orders in approved items
- Revocation of licenses, business suspension orders
- Temporary suspension of sales and disposal of drugs, etc.
- Recall orders
- Improvement orders in cases where the buildings and equipment, etc. do not comply with regulatory requirements

6.2 Product Recalls

On March 8, 2000, a notification clarifying the “recall” of drug products and

medical devices was issued.

The notification emphasizes the importance of “complete” recalls by the manufacturers/distributors, and specifies that the meaning of “recall” is to retrieve drug products from the market or to “repair” medical devices.

Also, the notification specifies the necessity of recalls in case the drug fails to demonstrate the desired therapeutic effects in general clinical practice, even though it is safe.

6.3 Prevention of Medical Accidents Caused by Drugs, etc.

A notification was issued to eliminate mistakes in the use of drugs, etc., in connection with the name, container, specifications, etc. in order to prevent medication accidents (Notification No. 935 of the PMSB dated September 19, 2000. More active participation of related companies was requested in Notifications No. 1127003 of the PFSB dated November 27, 2003 and No. 0602009 of the PFSB dated June 2, 2004. For the brand names of new drugs, guidance on the use of a flowchart to avoid use of similar names for newly approved drugs applied in the Japan Pharmaceutical Information Center (JAPIC) is given in an Office Communication dated October 17, 2005. General principles for brand names of generic drugs are given in Notification No. 0922001 of the Evaluation and Licensing Division, PFSB dated September 27, 2005.

New replacement approval applications for changes in brand names as a measure to prevent accidents are subject to accelerated reviews and the application fees were revised from April 2005. Entry of approved products in the NHI price lists has been increased from once a year to twice a year. An environment conducive to brand name changes to prevent medical accidents has been achieved.

Other policies to avoid medical accidents include requirements for differentiation of injections in routine use such as applying colors to syringes used in parenteral nutrition lines (Notification No. 888 of the PMSB dated August 31, 2000).

6.4 Safety Measures against Bovine Spongiform Encephalitis (BSE)

Bovine spongiform encephalitis (BSE) frequently occurred in England in the latter half of the 1980s and there were also cases reported in EU member countries. Pharmaceutical companies have been requested to undertake voluntary inspections and make adjustments in approval documentation (Notification No. 1226 of the PMSB dated December 12, 2000) in view of the need to ensure quality of and to take safety measures for pharmaceutical products manufactured using raw materials of bovine origin.

Companies have been requested to respond positively to an additional

notification (No. 1069 of the PMSB dated October 2, 2001) to secure high quality and safety of pharmaceutical products using raw materials of bovine origin because of the first report of BSE infection in Japan on September 21, 2001.

As a preventive measure in keeping with international trends to enhance safety measures for drugs and medical devices using bovine-derived raw materials, Notification No. 041400 of the PFSB dated April 14, 2003 concerning bovine-derived raw materials that require precautions related to the site of use and other factors, handling of blood products, handling of products derived from human urine and handling of approvals, was issued. Based on Notification No. 0522002 of the PFSB of 2003, “Canada” was added to countries in which BSE occurred in Attached Table 1 and “Canada” was removed from countries of low risk for BSE in Attached Table 2.

Following the confirmation of a cow infected with BSE in the United States in December 2003, the PFSB issued Notification No.0218004 dated February 18, 2004, entitled “Quality and safety assurance related to drugs, medical devices, etc., manufactured using bovine and other ruminant-derived products and bovine and other ruminant-derived spinal products from the United States” and Notification No. 0218001 of the Evaluation and Licensing Division, PFSB and Notification No. 0218003 of the Safety Division, PFSB dated February 18, 2004, entitled “Handling of approvals with respect to quality and safety assurance related to drugs, medical devices, etc., manufactured using bovine and other ruminant-derived products and bovine and other ruminant-derived spinal products from the United States”. Notification No. 0705001 of the PFSB dated July 5, 2004 entitled, “Handling of approval applications concerning quality and ensuring safety of drugs and medical devices manufactured using bovine and other ruminant-derived products and bovine and other ruminant-derived spinal products from the United States associated with the partial revision of the Standard for Biological Materials” was issued.

The Standards for Biological Materials were specified in Notice No. 210, 2003 of the MHLW and specifications for raw materials and packaging materials used in the manufacture of biological products or raw materials and packaging materials manufactured from biological materials and used in the manufacturing process for drugs, quasi-drugs, cosmetics and medical devices based on the Law were designated.

It has been considered necessary to adopt quality and safety assurance measures based on current scientific levels for drugs manufactured using raw materials of human or animal origin. Companies have been requested to undertake voluntary inspections and make adjustments in approval documentation.

Notice 262 issued by the MHLW in July

2004 partially revised the Standards for Biological Materials and Notification No. 0705001 of the PFSB dated July 5, 2004, entitled “Partial revision of the Standards for Biological Materials” was issued. Notification No. 0325003 of the Evaluation and Licensing Division, PFSB dated March 25, 2005 entitled “Handling of TSE data associated with enforcement of the partially revised Pharmaceutical Affairs Law” was also issued.

In an office communication of the Compliance and Narcotics Division, PFSB dated September 5, 2006 entitled “Self-checking of drugs, etc. using raw materials derived form cattle produced in the United States,” instructions are given to verify by self-check forms (self-check points) as an additional preventive measures since it was clear that products in some lots were manufactured using raw materials derived form cattle produced in the United States even after the deadline for changing the raw materials. The Evaluation and Licensing Division of PFSB issued Notification No. 0928001 dated September 28, 2007, entitled “Handling of Pharmaceutical Products Using Bovine-derived Materials to Comply with Partial Revision of the Standards for Biological Materials,” notifying the removal of Chile from the list of countries free from where biological materials can be imported for medical use and again requested the industry to self-inspect the compliance with the Standards for Biological Materials.

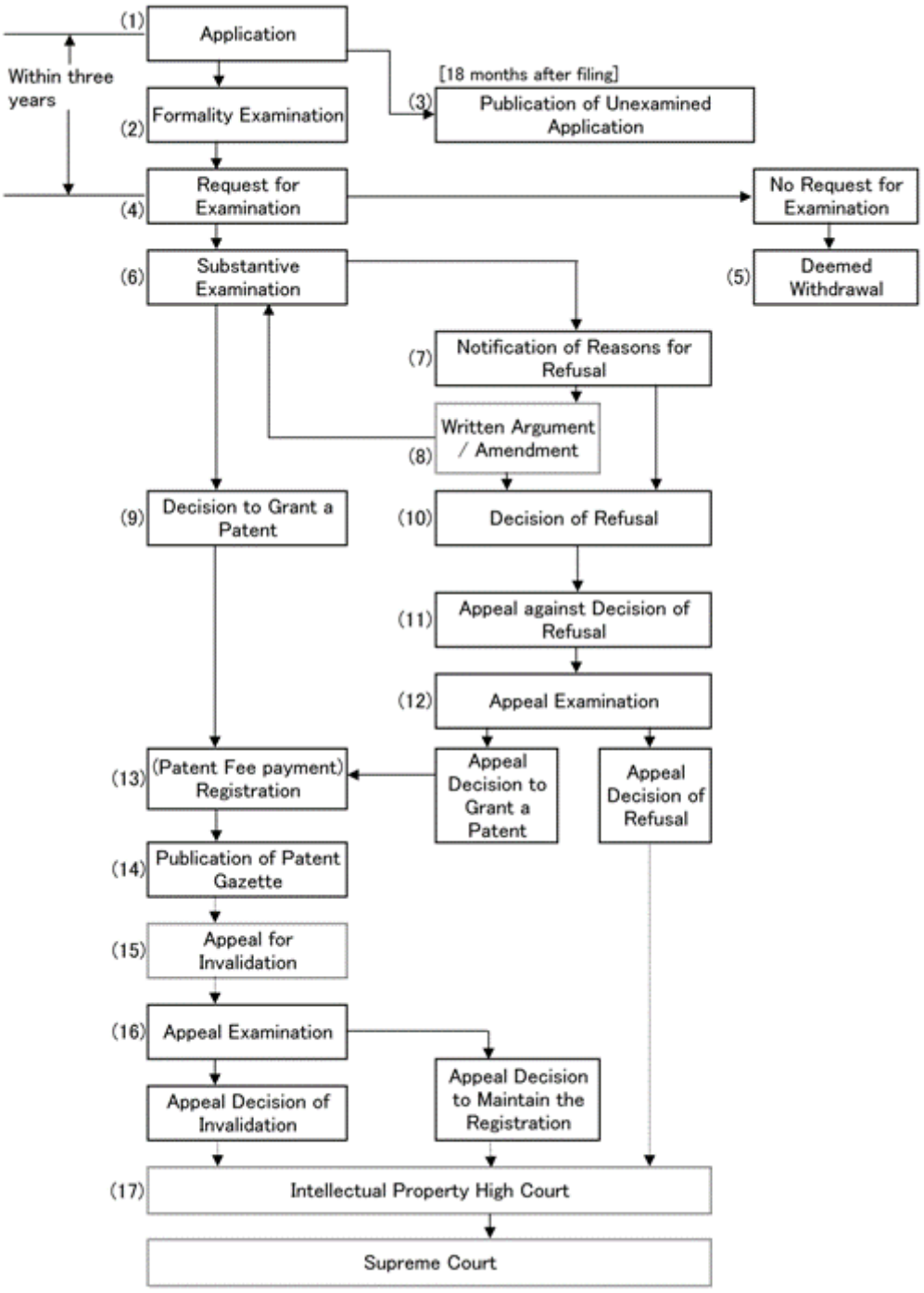


Fig. 4 Flowchart of Patent Application

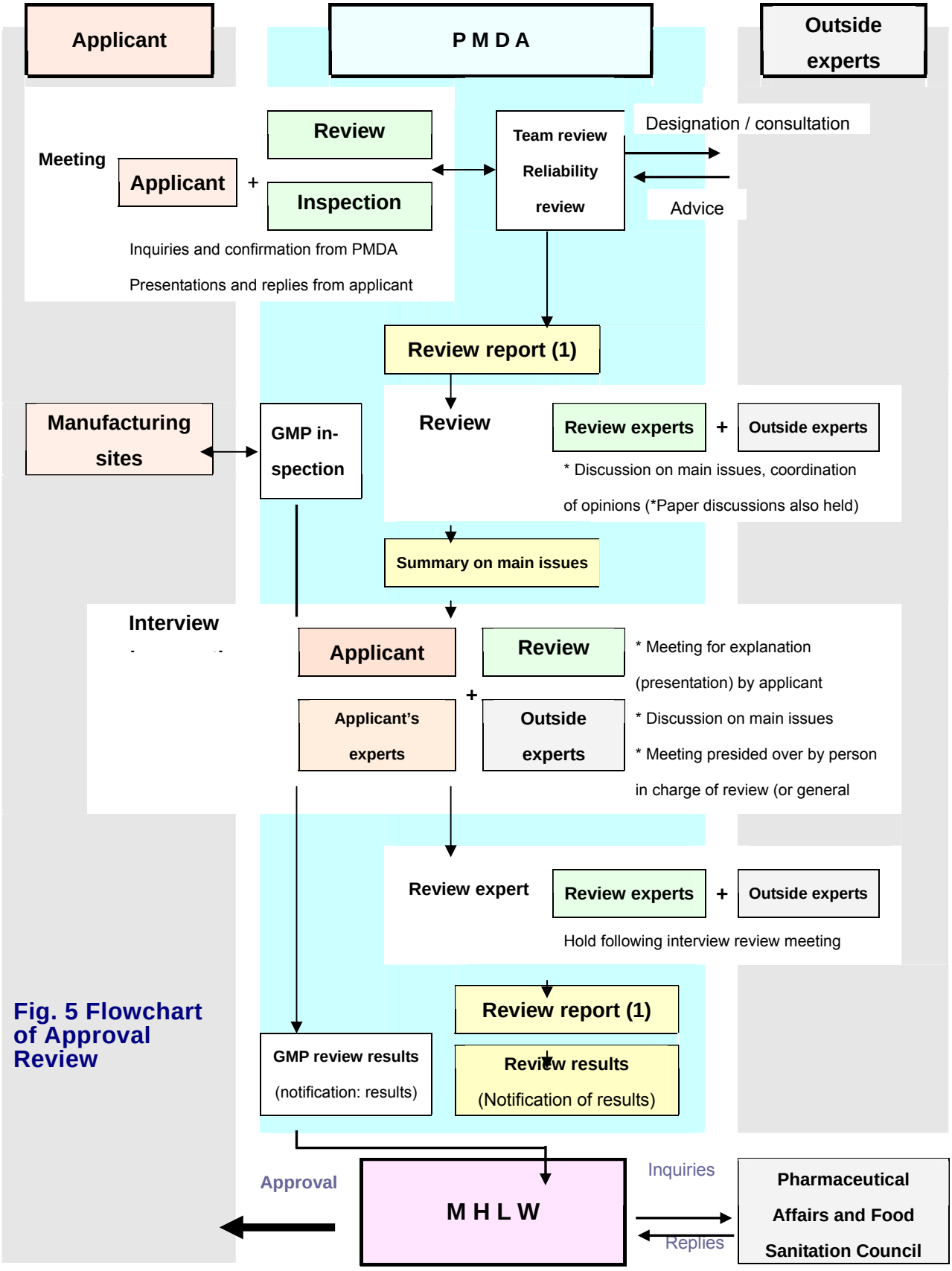


Fig. 5 Flowchart of Approval Review

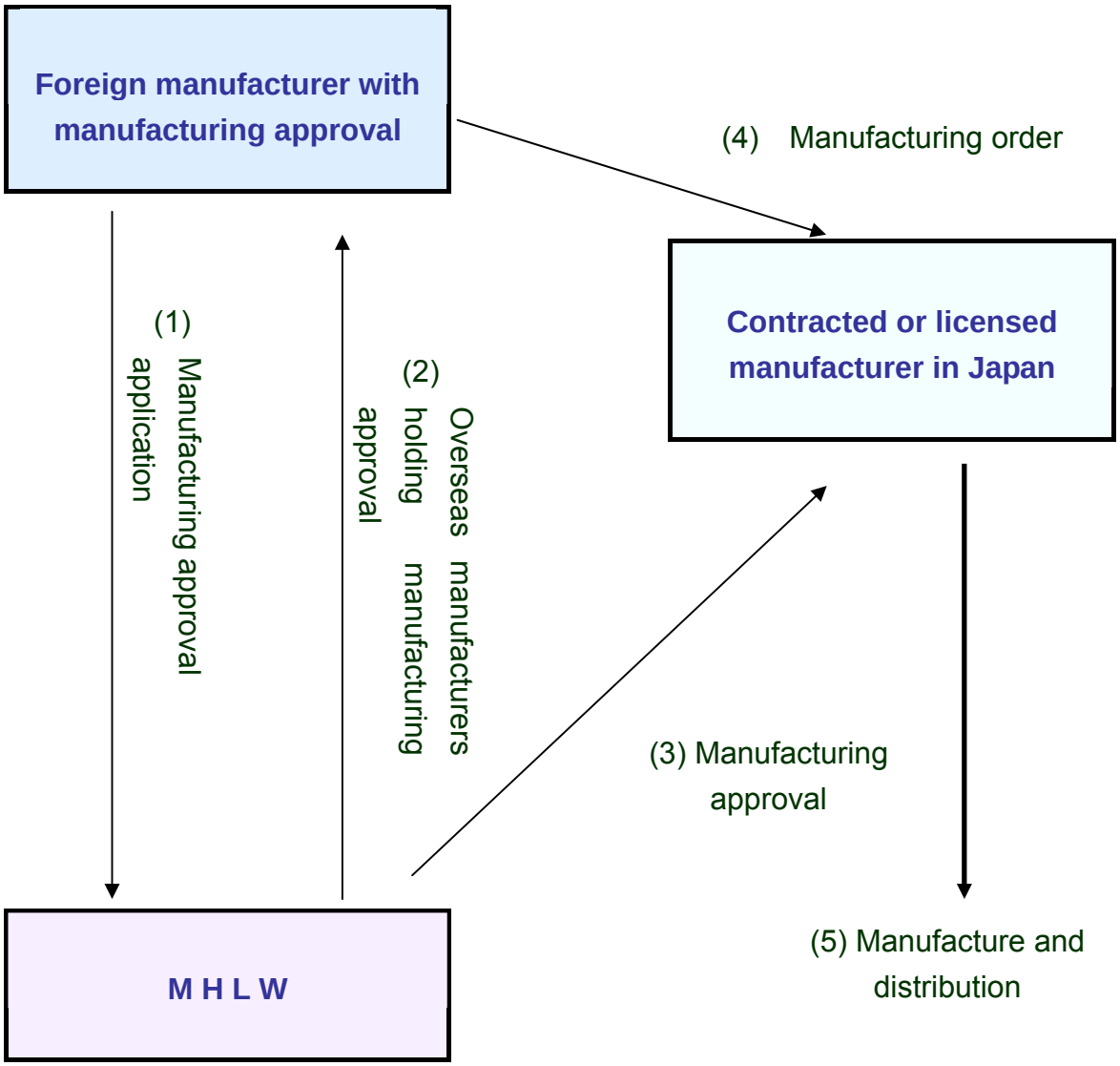


Fig. 6 Procedure for manufacturing and distribution of drugs for overseas manufacturers in Japan

Table. 1 List of Main Controlled Substances

Classification	Characteristics
Poisonous and deleterious substances	Poisonous and deleterious substances are designated by the MHLW as drugs which cause or might cause damage to the functions of humans or animals when injected and absorbed or applied externally to humans or animals because the effective dose is close to the lethal dose, cumulative effects are potent or the pharmacological effects are intense.
Prescription drugs	Prescription drugs are designated by the MHLW as drugs which may be sold or supplied only under the prescription of a physician, dentist or veterinarian.
Habit-forming drugs	Habit-forming drugs are drugs designated by the MHLW as habit-forming.
Drugs for designated diseases	Drugs for designated diseases are drugs intended for the treatment of cancer and other diseases designated by cabinet order, which might cause damage to patients unless used under the guidance of a physician or dentist.
Drugs prepared and sold at pharmacy	Drugs prepared and sold at pharmacies that do not contain any active ingredients designated by the Minister and are prepared by the pharmacist using equipment and devices in the pharmacy and directly sold or provided to consumers.
Narcotics	Narcotics are drugs designated by the MHLW as drugs which affect psychological function by their effects on the central nervous system, are habit forming and can cause severe damage when abused. The narcotics specified in the Narcotics and Psychotropics Control Law include morphine, codeine, pethidine and cocaine.
Psychotropics	Psychotropics are drugs designated by the MHLW, as drugs which affect psychological function by their effects on the central nervous system, are habit forming and cause less severe damage than narcotics or stimulants when abused. The psychotropics specified in the Narcotics and Psychotropics Control Law include hypnotics such as barbital, anxiolytics such as diazepam, and analgesics such as pentazocine.
Opium and powdered	Opium and powdered opium obtained by concentration and processing of the liquid extract from the opium poppy. Opium and powdered opium

opium	processed as drugs are not controlled by the Opium Law but regulated as narcotics under the narcotics and psychotropics classification.
Cannabis	Cannabis sativa L. and its products, excluding the stems of fully-grown cannabis plants and its products (excluding the resin) and cannabis seeds and their products.
Stimulants	Stimulants are drugs designated by the MHLW as drugs which are habit-forming, can cause severe damage when abused and have potent stimulant effects. The stimulants specified in the Stimulants Control Law include phenylaminopropanes (amphetamines), phenylmethylaminopropanes (methamphetamines), their salts and products containing them.
Clinical study drugs	Clinical study drugs are drugs used in either pre- or post-marketing clinical trials, namely investigational products or drugs or other compounds used as comparator drugs in such trials.
Investigational products for post-marketing clinical trials	Investigational products for post-marketing clinical trials are drugs or comparator drugs used in post-marketing clinical trials.
Biological products	Biological products are drugs, quasi-drugs, cosmetics, or medical devices using materials manufactured from humans or other organisms (excluding plants) as raw materials or packaging materials, which are designated by the Minister of Health, Labor and Welfare as requiring special precautions in terms of public health and hygiene.
Specified biological products	Specified biological products are biological products designated by the Minister of Health, Labor and Welfare as requiring measures to prevent the onset or spread of risk to public health and hygiene due to the biological product concerned after selling, leasing or giving.

Table. 2 Divisions of the Pharmaceutical and Food Safety Bureau in Charge of Certification Work

Division	Item to be Certified
Evaluation and Licensing Division	1. Items related to business licenses for manufacturing/distribution of drugs, etc. 2. Items related to manufacturing/distribution approvals for drugs, etc. 3. Items related to attached documentation for new drug manufacturing/distribution approval applications 4. Items related to compliance of drugs with GLP (Standards for Conduct of Nonclinical Studies on the Safety of Drugs) 5. Items related to clinical study protocol notifications for drugs 6. Items related to certification of pharmaceutical products 7. Items related to statements of approval and licensing status of pharmaceutical products
Compliance and Narcotics Division	- Items related to conformity of drug manufacturing plants with GMP
Safety Division	1. Items related to business licenses for manufacturing/distribution of drugs, etc.

CHAPTER 3

Drug Development

1. PROCESS FROM DEVELOPMENT TO APPROVAL AND LICENSE

New drugs are defined as drugs with ingredients, dosage, administration route, or indications, which are clearly different from those of drugs, which have already been approved for manufacture and marketing or those listed in the JP. Applications for approval to manufacture and market new drugs must be submitted to the Ministry of Health, Labor and Welfare with the results of non-clinical and clinical studies required to show the quality, efficacy and safety of the new drug attached to the approval application form (Article 14-3 of the Pharmaceutical Affairs Law [PAL]).

1.1 Development of New Drugs

It is important to prepare data for the review process during the course of drug development. Results to show quality, efficacy, and safety of new drugs must be obtained in non-clinical and clinical studies. The non-clinical studies include physicochemical studies and animal studies on pharmacology, pharmacokinetics, and toxicity. The clinical studies usually consist of Phase I, II and III studies (or human pharmacology, therapeutic exploratory, therapeutic confirmatory and therapeutic use categories). On starting each phase of the clinical studies, it is necessary to adequately confirm the safety of the drug product from the results of non-clinical studies or the results of previous clinical studies.

The Pharmaceutical Affairs Law specifies that the data submitted to obtain approvals must be obtained and compiled according to the standards specified in its Article 14, Paragraph 3. Related ordinances include the Ordinance on **Standards for Conduct of Clinical Trials** (MHW Ordinance No. 28 dated March 27, 1997, partially revised by MHLW Ordinance No. 106 dated June 12, 2003, MHLW Ordinance No. 172 dated December 21, 2004, and MHLW Ordinance No. 72 dated March 31, 2006) (**GCP**); the Ordinance on **Standards for Conduct of Nonclinical Studies on the Safety of Drugs** (MHW Ordinance No. 21, March 26, 1997, partial amendment: Ordinance No. 127 dated October 20, 2000) (**GLP**) and Standards for the Reliability of Application Data (Article 18-4-3, Enforcement Regulations, Pharmaceutical Affairs Law) which were enforced from April 1, 1997. Therefore, the acceptance of the data is conditioned

on adherence to the standards. It is important that studies to obtain data for approval reviews should be performed by standard methods whenever possible in order to assure proper evaluations of drugs. Reviews on compliance with these standards are performed by the Pharmaceuticals and Medical Devices Agency (PMDA, SOGO-KIKO) at the request of the MHLW.

1.2 Reviews and Guidance by the PMDA (SOGO-KIKO)

The PMDA (SOGO-KIKO) conducts reviews, guidance, and assistance from the development to the approval review stage of new drugs. This includes reviews of compliance with quality standards, reviews of clinical trial protocol notifications and guidance and assistance by means of consultations on non-clinical studies and clinical studies.

1) GLP Reviews

The PMDA undertakes reviews of compliance with GLP, which specifies standards for the conduct of safety studies, for safety-related non-clinical studies at the request of the MHLW. These reviews are performed on the basis of the GLP compliance review guidelines (Notification No. 23 of the PMDA dated April 1, 2004, Partial Revision No. 530 of the PMDA dated June 29, 2004, Revision No. 529 of the PMDA dated March 30, 2007) (see **3.1.4. GLP**).

2) Review of Clinical Study Protocol Notifications

The PMDA undertakes reviews of initial clinical study protocol notifications for new drugs with new active ingredients (the first clinical study on humans in Japan) from the standpoint of assurance of the safety of subjects in addition to the required guidance by the PMDA at the request of the Minister of Health, Labor and Welfare.

3) Interview advice

The PMDA has established a consultation system for clinical study protocols to improve and reinforce the quality of clinical studies. The consultations and review work have been united under the same teams in the Review Department. With the increasing demand for clinical trial consultations, improvements have been made in the quality of consultations with respect to preparation for and implementation of consultations, preparation of records, etc. as measures to meet the demands for those requesting consultations (Notifications 0307001 – 0307007 of the PMDA dated March 7, 2006, partial amendment Nos. 0330007 and 0330004 of the PMDA dated March 30, 2007). Prior consultation is also available to assure smooth interview advice. The interview advice (clinical

trial consultations and simple consultations) handled by the PMDA is as follows. (Charges: per consultation as of March 2008) (Details are available at the following site.) http://www.pmda.go.jp/english/index.html

• Interview advice (face-to-face interviews) (As of October 2006)

(1) Clinical trial consultations

- Consultations on compliance with drug reliability standards: ¥2,875,500
- Consultations on drug procedures: ¥139,800
- Consultations on drug bioequivalence studies: ¥556,000
- Consultations before start of Phase I clinical trials on drugs: ¥4,239,400
- Consultations on drug quality: ¥1,478,300
- Consultations on drug safety: ¥1,782,800
- Consultations before start of early Phase II clinical trials on drugs: ¥1,623,000
- Consultations before start of late Phase II clinical trials on drugs: ¥3,028,400
- Consultations on completion of Phase II clinical trials on drugs: ¥6,011,500
- Consultations before drug application: ¥6,011.400
- Consultations on protocol of reevaluation or reexamination clinical trial: ¥3,320,600
- Consultations on completion of reevaluation or reexamination clinical trial: ¥3,319,400
- Consultations on addition of drugs: ¥2,675,600
- Consultations before new non-prescription drug application: ¥445,100
- Consultations before clinical trials or applications for medical devices or in vitro diagnostics: ¥1,549,700

* Consultations on compliance with reliability standards for drugs and in vitro diagnostics: ¥650,300

(2) Simple consultations (As of April 2005)

- Simple consultation on generic prescription drugs: ¥21,200
- Simple consultation on non-prescription drugs: ¥21,000
- Simple consultation on quasi-drugs: ¥21,000
- Simple consultation on medical devices or in vitro diagnostics: ¥34,300

* Simple consultations on coordination of entries, etc. on new drugs: ¥21,000

* Simple consultation on GMP/QMS survey: ¥24,700

4) Compliance Reviews

Following revision of the Pharmaceutical Affairs Law in June 1996, the PMDA started reviews of compliance with quality standards, GLP, and GCP by verification and comparisons with raw data to determine if the attached data used in approval reviews of new drugs has been compiled correctly based on study results. Compliance reviews are applied after approval applications are filed. They consist of both paper reviews and on-site reviews.

- Paper reviews

With the establishment of the PMDA, paper reviews became based on “Guidelines for Paper Compliance Review for New Drug Approval Application Data (Notification No. 0131010 of the Evaluation and Licensing Division, PFSB dated January 31, 2006) and “Implementation Procedures for Paper Reviews” (Notification No. 0330001 of the PMDA dated March 30, 2007) when the applicant provides the PMDA with data as evidence for approval reviews. The review assures that the approval review data has been collected and compiled in accordance with the above criteria. Since August 2001, the PMDA has provided a checklist for self-compliance review by the applicant prior to approval applications.

- On-site reviews

In these reviews, the PMDA review staff examines the data at the sites where it was collected or compiled. The guidelines for on-site GCP compliance reviews have been revised. The procedures for conducting GCP on-site inspections related to documentation attached to approval applications for new drugs are shown in Notification No. 0131006 of the Evaluation and Licensing Division, PFSB dated January 31, 2006. The revised guidelines were applied from April 4, 2004.

The reviews are generally performed in the applicant’s offices and facilities and medical institutions performing the clinical study (four facilities, as a rule). In selection of the review facilities, consideration should be given to the number of subjects in the clinical trials and the dates of GCP reviews performed in the past. Appendix 4 shows the GCP on-site reviews conducted since April 1, 1997. The PMDA also provides a checklist as reference for self-inspections before on-site inspections of sponsors and medical institutions.

1.3 Approval Reviews

A detailed team review is performed by the review staff in the PMDA after the confirmation of reliability in the compliance review by the PMDA. For the main points concerning reviews, refer to “Points to Consider for Approval Application Data for New Drugs” (Notification No. 0330009 of the Evaluation and Licensing Division, PFSB dated March 31, 2005). The application is then discussed by the committees and Department on Drugs of the PAFSC on the basis on the most recent and advanced scientific knowledge. The final decision concerning approval is made by the Minister of Health, Labor, and Welfare (Refer to 4.2 Approval Reviews, Chapter 2). **Fig. 7** (Flowchart of New Drug Development and Approval) shows the general procedures followed in the approval reviews of new drugs.

With the enforcement of the revised Pharmaceutical Affairs Law in April 1997, efforts are being made to publish information on the deliberations of the PAFSC and other regulatory bodies. Materials being made public include the Review Report and New Drug Application Summary, as well as the proceedings of the reviewing Committees on New Drugs, Pharmaceutical Affairs Section, PAFSC. This publication is intended to assure transparency of the approval review process (refer to Section 5.3: Public Disclosure of Information).

2. DATA REQUIRED FOR APPROVAL APPLICATIONS

To reinforce the review system from April 2000 based on international conditions in drug development, the data, the data to be attached to approval applications for drugs is specified in the new basic notification “Approval Applications for Drugs” (Notification No. 481 of PMSB dated April 8, 1999). Detailed handling is specified in “Points to consider in drug approval applications” (Notification No. 666 of the Evaluation and Licensing Division, PMSB, MHLW dated April 8, 1999). These notifications were issued in consideration of the globalization of drug development from April 2000. With the revision of the Pharmaceutical Affairs Law in April 2005, two new notifications were issued on the handling of approval applications for manufacturing and distribution of drugs. (Notification No. 0331015 of the PFSB dated March 31, 2005 and Notification No. 0331009 of the Evaluation and Licensing Division, PFSB dated March 31, 2005). Notification No. 481 of PMSB was cancelled.

Subsequently, agreement was reached on the common technical document (CTD) by the ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for

Human Use) and a notification entitled “Handling data attached to drug approval applications” (Notification No. 663 of the PMSB, MHLW dated June 21, 2001), which is a partial revision of the previous notification mentioned above. On the same day, another notification “Guidelines for preparation of data attached to applications for approval to manufacture or import new drugs (Notification No. 899 of the Evaluation and Licensing Division, PMSB, dated June 21, 2001, partially revised: Notification No. 0701004 of the Evaluation and Licensing Division, PFSB, dated July 1, 2003 (partially revised on May 25, 2004 in Notification No. 0525003 of the Evaluation and Licensing Division, PFSB, Office Communication dated May 24, 2004), was issued to specify guidelines for preparation of data to be attached to approval applications based on the CTD. The data required for approval applications using CTD forms is shown below. The data in modalities 2 to 5 are prepared on the basis of the CTD guidelines shown in Attachments 1 and 3 to 5 of these guidelines.

For electronic specifications of CTD (e-CTD), “Electronic specifications of the common technical document” (Notification No. 06404001 of the PFSB dated June 4, 2003, partially revised on May 27, 2004 in Notifications No. 0527001 and No. 0527004 of the Evaluation and Licensing Division, PFSB. These specifications were enforced from April 1, 2005. Handling of submissions of electronic data and Q&A are shown in Office Communications dated March 31, 2005, April 27, 2005, October 5, 2006, and December 22, 2006.

1) Module 1: Regulatory information such as application forms and information on attached documentation

(1) Table of Contents
(2) Approval application (copy)
(3) Certificates [Declarations of those responsible for collection and compilation of data for approval applications, GLP and GCP related data, contracts for codevelopment (copies), etc.]
(4) Patent status
(5) Background of origin, discovery and development
(6) Data related to conditions of use in foreign countries, etc.
(7) List of related products
(8) Package insert (draft)
(9) Documents concerning non-proprietary name
(10) Data for review of designation as poisons, deleterious substances, etc.
(11) Draft of basic protocol for post-marketing surveillance
(12) List of attached documentation
(13) Others

2) Module 2: Data summaries or "Gaiyo"

(1) CTD Table of Contents
(2) CTD introduction
(3) Quality Overall Summary
(4) Non-clinical overview
(5) Clinical overview
(6) Non-clinical summary
<1> Pharmacology
<2> Pharmacokinetics
<3> Toxicity
(7) Clinical summary
<1> Summary of biopharmaceutics and associated analytical methods
<2> Summary of clinical pharmacology studies
<3> Summary of clinical efficacy
<4> Summary of clinical safety
<5> Synopses of individual studies

3) Module 3: Quality

(1) Table of Contents
(2) Body of data
(3) Literature references

4) Module 4: Non-clinical study reports

(1) Table of Contents
(2) Study reports
(3) Literature references

5) Module 5: Clinical study reports

(1) Table of Contents
(2) Tabular listing of all clinical studies
(3) Clinical study reports and related information (clinical overview, etc.)
(4) Literature references

(**Fig. 8**. Organization of ICH Common Technical Documents)

2.1 Data to be Attached to Approval Application of Drugs

2.1.1 Prescription Drugs

The data required for applications for prescription drugs shown in the attachments 1 and 2-(1) of the basic Notification No. 481 of the PMSB dated April 8, 1999.

On approval of the CTD by ICH, this notification was partially revised (Notification No. 663 of the PMSB and No. 899 of the Evaluation and Licensing Division, PMSB dated June 21, 2001, partial revision: July 1, 2003, Notification No. 0701004 of the PFSB, partial revision: May 25, 2004, Notification No. 052003 of the PFSB, Office Communication dated May 24, 2004), were also revised. With the revision of the Pharmaceutical Affairs Law in April 2005, the basic notification was revised (Notification No. 0331015

dated March 31, 2005). Attached tablets 1 and 2-(1) are shown in **Table 3** (Data to be Submitted with an Application for Approval to Manufacture/Distribute: a New Prescription Drug). Application data for drugs corresponding to (1) to (7), (8), (9) (9-2) and (9-4) are handled by the CTD format (Notification No. 0331009 of the Evaluation and Licensing Division, dated March 31, 2005).

2.1.2 Non-prescription Drugs

The range of data to be submitted with applications for non-prescription drugs is specified as shown in **Table 4** (Data to be Submitted with an Application for a Non-prescription Drug) (Notification No. 0331015 of the PFSB dated March 31, 2005. After complete enforcement of the CTD (from July 1, 2003), the present guidelines for preparation of data to be attached to approval applications can be applied to approval applications for non-prescription drugs as in the past. For the time being, data on the manufacturing method and specifications and test methods for non-prescription drugs with new active ingredients are prepared using the CTD for reference.

3. GUIDELINES CONCERNING DRUG APPROVAL APPLICATIONS

Guidelines outlining standard test methods and essential criteria for reference in the preparation of data for drug manufacturing and distribution approval applications have been published in order to assure efficient and appropriate research and development. These guidelines have been prepared on the basis of results of studies undertaken by groups of experts in the field concerned.

In recent years, various standards and guidelines have been established and implemented according to ICH harmonization and the reliability and amount of research data has increased. To meet demands for more efficient and less costly development of new drugs, international utilization of data is on the increase.

Japan has taken various measures in keeping with this change in the international environment, and data from nonclinical studies such as physicochemical studies, stability studies and animal studies performed in foreign countries are accepted, in principle, if the studies comply with the Japanese guidelines.

Two notifications were issued in relation to the acceptance of foreign clinical data: Handling of Data on Clinical trials on Drugs Performed in Foreign Countries (Notification No.739 of the PMSB dated August 8, 1998) and Ethnic Factors to be

Considered in the Acceptance of Foreign Clinical Trial Data (Notification No. 672 of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau dated August 11, 1998) and its Q and A (Office Communications dated February 25, 2004 and October 5, 2006). According to this guideline, when data from clinical studies performed in foreign countries are used for new drug application in Japan, the data is first checked to assure that it complies with legal requirements in Japan. Whether or not the drug is apt to be affected by ethnic factors (intrinsic or extrinsic factors) is then evaluated. When necessary, a bridging study is performed, and when it is concluded that the clinical study outcome in a foreign population can be extrapolated to the Japanese population, the foreign data can be accepted. Since the possibility of acceptance is actually left up to the authorities concerned, this topic is often part of the consultations on clinical studies undertaken by the PMDA.

It is necessary to promote international collaborative clinical trials to achieve more efficient and rapid development of new drugs to eliminate the drug lag in which the approval timing of new drugs is several years behind that in other countries. Therefore, basic concepts related to international collaborative clinical trials have been compiled (Notification No. 0928010 of the Evaluation and Licensing Division, PFSB dated September 28, 2007).

The data attached to applications for approval to manufacture and distribute drugs must be in Japanese, but as part of the deregulation process, it was specified in Notifications No. 256 of the PMSB and No, 265 of the Evaluation and Licensing Division, PMSB, both dated March 18, 1998, that documents in English in Modules 3, 4, and 5 need not be completely translated into Japanese as long as a Japanese summary is attached. In approval applications using the CTD format, a Japanese summary is not required for entries in the original in English.

In the future, international acceptance of data among the tripartite regions (Europe, Japan, and the United States) will be promoted further by advances made in harmonization of approval application data by ICH. Data from nonclinical and clinical studies performed in Japan should be used more widely in the West in the future.

3.1 Nonclinical Studies

1) Guidelines on Physicochemical Properties, Specifications, and Tests Methods

The contents of specifications and test methods in approval applications must include the required test items in reference to the specified test guidelines. For drugs with new active ingredients manufactured by chemical

synthesis, refer to “Setting of Specifications and Test Methods of New Drugs” (ICH Q6A) (Notification No. 568 of the Evaluation and Licensing Division, PMSB dated May 1, 2001)　For new biological products (biotechnological products/drug products derived from living organisms), refer to “Setting of Specifications and Test Methods of Biological Products (biotechnological products/drug products derived from living organisms)” (ICH Q6B) (Notification No. 571 of the Evaluation and Licensing Division, PMSB dated May 1, 2001).　These guidelines on specifications and test methods were prepared based on ICH agreements.

The following guidelines have been revised or established concerning physicochemical properties, specifications, and tests methods:

(1) Setting of Specifications and Test Methods of New Drugs (ICH Q6A) (Notification No. 568 of the Evaluation and Licensing Division, PMSB dated May 1, 2001
(2) Setting of Specifications and Test Methods of Biological Products (biotechnological products/drug products derived from living organisms) (ICH Q6B) (Notification No. 571 of the Evaluation and Licensing Division, PMSB dated May 1, 2001
(3) Text (Items) on Analytical Validation (ICH Q2A, currently Q2(R1)) (Notification No. 755 of the Pharmaceuticals and Cosmetics Division, PAB dated July 20, 1995)
(4) Text (Items) on Analytical Validation (ICH Q2B, currently Q2(R1)) (Notification No. 338 of the Pharmaceuticals and Cosmetics Division, PAB dated October 28, 1997)
(5) Guidelines on Impurities in Bulk Drugs with New Active Ingredients (ICH Q3A, currently Q3(R2)) (Notification No. 877 of the Pharmaceuticals and Cosmetics Division, PAB dated September 25, 1995)
(6) Guidelines on Impurities in Drug Preparations (ICH Q3B, currently Q3B(R2)) (Notification No. 539 of the Pharmaceuticals and Cosmetics Division, PAB, dated June 23, 1997)
(7) Guidelines on Residual Solvents in Drug Preparations (ICH Q3C, currently Q3C(R3)) (Notification No. 307 of the Evaluation and Licensing Division, PMSB dated March 30, 1998)
(8) Handling of Manufacturing (Import) Approval in Association with International Harmonization of Pharmacopoeia (Notification No. 574 of the Evaluation and

Licensing Division, PMSB dated May 1, 2001)

(9) Guidelines related to Formulation Development (ICH Q8) (Notification No. 0901001 of the Evaluation and Licensing Division, PFSB dated September 1, 2006)

The quality standards published in the Japanese Pharmacopoeia, Japan Pharmaceutical Codex, etc. serve as references for specifications and test methods including content specifications, identification, purity and assay.

For sustained-release drugs, refer to the Guidelines for Design and Evaluation of Sustained-release (Oral) Preparations (Notification No. 5 of the First Evaluation and Registration Division, PAB dated March 11, 1988) in addition to the above guidelines.

2) Guidelines for Stability Tests

Standard methods for long-term stability studies, stress stability studies and accelerated stability studies for bulk drugs and preparations are specified in Guidelines for Stability Tests Attached to Approval Applications to Manufacture or Import Drugs (Notification No. 165 of the PAB and No. 43 of the Pharmaceuticals and Cosmetics Division, PAB dated February 15, 1991). However, based on an ICH agreement, stability tests on drugs with new active ingredients and new combinations must be performed in accordance with the ICH Stability Test Guidelines (ICH Q1A, currently Q1A(R2)) (Notification No. 30 of the New Drugs Division, PAB dated April 21, 1994). The former guidelines for stability tests of prescription drugs with new active ingredients (Notification No. 565 of the Evaluation and Licensing Division, PMSB dated May 1, 2001) has been abolished and new stability guidelines based on ICH agreements have been established (Revision of Stability Test Guidelines (ICH Q1A(R2)), Notification No. 0603001 of the Evaluation and Licensing Division, PFSB dated June 6, 2003). Stability test guidelines were also established for approval applications in climatic zones III and IV outside the three ICH regions (EU, Japan and the US) (ICH Q1F) (Notification No. 0603007 of the Evaluation and Licensing Division, PFSB dated June 6, 2003) but they were abolished (Notification No. 0703001 of the Evaluation and Licensing Division, PFSB dated July 3, 2003) with the expansion of application of the ICHQ1A guidelines based on ICH agreement (Notification No. 0603001 of the Evaluation and Licensing Division, PMSB dated June 3, 2003). Photostability tests for drugs with new active ingredients and new combinations are performed on the

basis of Guidelines for Photostability Tests of New Bulk Drugs and New Preparations (ICH Q1B) (Notification No. 422 of the Pharmaceuticals and Cosmetics Division, PAB dated May 28, 1997). For drugs with new routes of administration, stability tests must be performed as specified in Guidelines for Handling Results of Stability Tests of Drugs with New Routes of Administration (ICH Q1C) (Notification No. 425 of the Pharmaceuticals and Cosmetics Division, PAB dated May 28, 1997), and for biological products, stability tests must be performed as specified in Guidelines for Handling Results of Stability Tests of Biological Products (biotechnological products/drug products derived from living organisms) (ICH Q5C) (Notification No. 6 of the Evaluation and Licensing Division, PMSB dated January 6, 1998).

Concepts concerning simplification of stability tests on a scientific basis have also been specified in Application of Bracketing and Matrixing Methods in Stability Tests on Drug Substances and Drug Products (ICH Q1D) (Notification No. 0731004 of the Evaluation and Licensing Division, PFSB dated July 31, 2002).

3) Guidelines for Toxicity Tests

Formerly, toxicity tests required for new drug applications were specified in the Guidelines for Toxicity Studies Required for Applications for Approval to Manufacture or Import Drugs (Part 1) (Notification No. 718 of the Evaluation and Registration Division, PAB dated February 15, 1984), but these guidelines were revised in September 1989 and November 1999 in order to bring Japanese requirements into greater harmony with those of other countries. The Guidelines for Toxicity Studies of Drugs (Notification No. 24 of the First Evaluation and Registration Division, PAB dated September 11, 1989) specifies the standard methods for safety tests conducted to support new drug manufacturing or import approval applications to help applicants properly evaluate the safety of drugs. Based on ICH agreements, the following guidelines have been revised or established, and the Guidelines for Toxicity Studies of Drugs (1989) have been replaced by these guidelines:

(1) Revisions of Guidelines for Single and Repeated Dose Toxicity Studies (ICH S4) (Notification No.88 of the Pharmaceuticals and Cosmetics Division, PAB dated August 10, 1993).

(2) Guidelines for Reproductive and Developmental Toxicity Studies (ICH S5A/S5B) (Notification No.316 of the Pharmaceuticals

and Cosmetics Division, PAB dated April 14, 1997 and (ICH S5B(M), currently S5(R2)) Notification No. 1834 of the Evaluation and Licensing Division, PMSB dated December 27, 2000).

(3) Guidance for Toxicokinetics (Evaluation of systemic exposure in toxicity tests) (ICH S3A) (Notification No.443 of the Pharmaceuticals and Cosmetics Division, PAB dated July 2, 1996).

(4) Guidance for Specific Items in Genotoxicity Studies on Drugs (ICH S2A) (Notification No.404 of the Pharmaceuticals and Cosmetics Division, PAB dated July 2, 1996).

(5) Guidance on Dose Selection for Carcinogenicity Tests of Drugs (ICH S1C) (Notification No. 544 of the Pharmaceuticals and Cosmetics Division, PAB dated August 6, 1996) and its supplement (ICH S1C(R), currently S1C(R1)) (Notification No. 551 of the Evaluation and Licensing Division, PMSB dated July 9, 1998).

(6) Guidance on Requirements for Carcinogenicity Tests of Drugs (ICH S1A) (Notification No.315 of the Pharmaceuticals and Cosmetics Division, PAB dated April 14, 1997).

(7) Timing of Preclinical Studies in Relation to Clinical Trials (ICH M3(M), currently M3(R1)) (Notification Nos. 1019 and 1831 of the Evaluation and Licensing Division of PMSB dated November 13, 1998 and December 27, 2000).

(8) Guidance on the Need for Carcinogenicity Studies of Pharmaceuticals (Notification Nos. 548 and 1831 of the Evaluation and Licensing Division, PMSB dated July 9, 1998 and December 27, 2000, respectively).

(9) Guidance on Carcinogenicity Tests of Pharmaceuticals (Notification No. 1607 of the Evaluation and Licensing Division, PMSB dated November 11, 1999).

(10) Guidance on Genotoxicity Tests of Pharmaceuticals (Notification No. 1604 of the Evaluation and Licensing Division, PMSB dated November 11, 1999)

(11) Genotoxicity Tests: Standard combination of genotoxicity tests of Pharmaceuticals (Notification No. 554 of the Evaluation and Licensing Division, PMSB dated July 9, 1998)

(12) Immunotoxicity Studies for Human Pharmaceuticals (ICH

S8) (Notification No. 0418001 of the Evaluation and Licensing Division, PMSB dated April 18, 2006)

Data on the following studies that should be conducted in accordance with the above guidelines are required for the review and evaluation of a new drug application by the Ministry (Table 3: Documentation that must be submitted with application for marketing approval of prescription drugs):

(1) Single dose toxicity studies
(2) Repeated dose toxicity studies
(3) Genotoxicity studies
(4) Carcinogenicity studies
(5) Reproductive and developmental toxicity studies
(6) Skin irritation studies
(7) Other toxicity studies

Drug dependence studies were specified separately from the toxicity guidelines in Scope of Application and Guidelines for Animal Studies and Clinical Observations on Drug Dependence (Notification No. 113 of the Narcotics Division, PAB dated March 14, 1975) and Guidelines for Animal Studies and Clinical Observations on Drug Dependence (Notification No. 383 of the Narcotics Division, PAB dated June 7, 1978).

For biological products, the guideline “Nonclinical safety evaluation of biotechnological drugs” (ICH S6) (Notification No. 326 of the Evaluation and Licensing Division, PMSB dated February 22, 2000) should be referred to.

4) Good Laboratory Practice (GLP)

For toxicity tests conducted to confirm the safety of drugs, the reliability of the data should be assured so that the results obtained are correctly analyzed and assessed. For this purpose, all toxicity tests conducted to support applications for new drug manufacturing and distribution approval and reexamination must be conducted in accordance with the Good Laboratory Practice Standards for Safety Studies on Drugs (GLP). (Safety pharmacology studies to be conducted on and after July 1, 2003 must comply with GLP.)

Following the introduction of the GLP requirements in the USA, the Japan Pharmaceutical Manufacturers Association started to prepare a draft of its voluntary GLP guidelines in 1976. In 1978, the MHW established the GLP Committee. The first GLP requirements in Japan were published in March 1982 and enforced in April 1983. They were partially revised and updated in October 1988.

Thereafter, the GLP Guidelines, which had formerly been in the form of a MHW bureau notification were legalized as the MHW Ordinance on Standards

for Implementation of Nonclinical Studies on Safety of Drugs (Ordinance No.21, March 26, 1997) (**GLP**) in order to assure greater reliability than previously of the nonclinical safety data. This new GLP was implemented from April 1, 1997.

Compared with the previous GLP, the MHW Ordinance GLP stipulates various responsibilities, including that of the sponsor when requesting outside facilities to perform nonclinical studies. The ordinance requires establishment and defines the responsibilities of Quality Assurance Units, the obligation of the management of testing facilities to prepare standard operating procedures (SOP) containing test methods and procedures, and the obligation of study directors to prepare study protocols and final reports.

This ordinance consists of seven chapters and 18 articles as outlines below:

Chapter 1 (Articles 1-4)

Purpose of this ordinance, definition of terms, responsibilities of sponsors

Chapter 2 (Article 5-8)

Responsibilities of management of testing facilities, study directors and Quality Assurance Units

Chapter 3 (Articles 9 and 10)

Structures, facilities and equipment of testing facilities

Chapter 4 (Articles 11 and 12)

Standard operating procedures in testing facilities (prepared by management) and animal care-takers

Chapter 5 (Articles 13 and 14)

Handling of investigational products and comparators

Chapter 6 (Articles 15 and 16)

Study protocols (prepared by study director) and proper conduct of studies.

Chapter 7 (Articles 17 and 18)

Final reports (prepared by study director) and retention of study data

Verification of the GLP ordinance compliance of study facilities performing nonclinical studies in compliance with the GLP ordinance (GLP-compliant studies) at the time of approval reviews is performed as a rule based on the results of paper and on-site reviews by the PMDA at the request of the MHLW and the MHLW decides on whether or not to accept the data concerned as approval review data.

GLP compliance reviews conducted by the PMDA are performed on the basis of the “GLP compliance guidelines” specified by the PMDA (Notification No. 151 dated June 6, 1994; No. 705 dated July 9, 2001; partially revised in Notification No. 1226 dated December 27, 2002; Notification

No. 529 dated March 30, 2007; partially revised on June 29, 2004 in Notification No. 530). GLP compliance conditions are evaluated in the following three categories by the GLP Evaluation Committee established by the PMDA based on the results of the GLP compliance review.

Class A: Compliance with GLP.

Class B: Some improvements possible but the effects of non-compliance on data reliability are considered tolerable; compliance with GLP if improvements are made.

Class C: Noncompliance with GLP.

When evaluated as Class A or B in the GLP compliance reviews, the results of the tests performed in the facility will be accepted, in principle, for use as review data for a period of 3 years or 2 years, respectively, from the day of notification of the evaluation results.

These GLP requirements also apply to data generated in other countries when they are used to support applications in Japan. The MHLW has GLP inspections of testing facilities in foreign countries conducted based on the GLP Inspection Guidelines (Notification No. 254 of the Evaluation and Licensing Division and No. 30 of the Safety Division, PAB dated March 27, 1997). These Guidelines were abolished by the Guidelines for Pharmaceutical GLP On-site Inspections by the MHLW (Notification No. 0805003 of the Evaluation and Licensing Division, PFSB dated August 5, 2005) and on-site GLP inspections performed by the MHLW are specified in the Guidelines for Pharmaceutical GLP On-site Reviews. Bilateral agreements have been concluded with several countries to mutually accept GLP inspection results and data.

So far, the agreements have been concluded with the following countries or regions: Switzerland and the EU.

5) Guidelines for General Pharmacological Studies

The data to be attached to approval applications for drugs following approval of the CTD by ICH is given in Notification No. 663 of the PMSB dated June 21, 2001. Data related to general pharmacology has been changed to data on clinical pharmacology, secondary/safety pharmacology, and other pharmacology. The safety pharmacology guideline (ICH S7A) (Notification No. 902 of the Evaluation and Licensing Division, PMSB dated June 21, 2001) based on ICH agreements will be enforced for safety pharmacology studies performed on or after July 1, 2003, and also safety pharmacology studies should be

conducted as a rule in accordance with the GLP Ordinance. Some secondary pharmacology studies are performed using the guidelines on general pharmacology studies as a reference. Other pharmacology studies including pharmacodynamic studies should be conducted by referring to the Methods of Studying Drug Interactions (Notification No. 813 of the Evaluation and Licensing Division, PMSB dated June 4, 2001).

Guidelines for General Pharmacology Studies required for Applications for Approval of Manufacture or Import New Drugs (Notification No. 4 of the New Drugs Division, PMSB dated January 29, 1991) were published. They give the basic concepts and basic test items for general pharmacology studies performed in research and development on new drugs. These guidelines specify the following: (1) an overall understanding of types and degrees of pharmacological actions together with pharmacological action related to efficacy and clarification of the pharmacological action profile of the investigational product must be provided; (2) adverse drug reactions that might occur during clinical application must be predicted and information on countermeasures when adverse reactions do occur provided; and (3) consideration must always be given to adverse actions clarified by toxicity studies among the effects on biofunctions.

6) Guidelines for Pharmacokinetic Studies

Pharmacokinetic data is useful in determining doses and other conditions for toxicity and pharmacological tests in animals. Moreover, the assessment and understanding of these data may provide very useful information for the assessment of efficacy and safety in humans. Guidelines on Non-clinical Pharmacokinetic Studies (Notification No. 496 of the Evaluation and Licensing Division, PMSB dated June 26, 2001) were announced requiring applicants to study the absorption, distribution, metabolism and excretion of test drugs in animal and *in vitro* study systems to clarify their pharmacokinetic profile. In these guidelines, the distribution studies are single dose studies as a rule, and the Guideline for Repeated Dose Tissue Distribution Studies (Notification No. 442 of the Pharmaceuticals and Cosmetics Division, PAB dated July 2, 1996) should be used for reference for repeated dose studies. In cases where consideration should be given to repeated doses and repeated dose studies are performed, reference should be made to “Guidance for repeated administration tissue distribution

studies" (Notification No. 442 of the Pharmaceuticals and Cosmetics Division, PAB dated July 2, 1996).

7) Guidelines for bioequivalence Studies

The following guidelines have also been issued concerning bioequivalence:

(1) Guidelines for bioequivalence testing of generic drugs (Notification No. 487 of the Evaluation and Licensing Division, PMSB dated December 22, 1997, Notification No. 786 of the Evaluation and Licensing Division, PMSB dated May 31, 2001)

(2) Partial revision of guidelines for bioequivalence testing of generic drugs (Notification No. 1124004 of the Evaluation and Licensing Division, PMSB dated November 24, 2006)

(3) Guidelines for bioequivalence testing of oral solid dosage forms with different content (Notification No. 64 of the Evaluation and Licensing Division, PMSB dated February 14, 2000, Notification No. 786 of the Evaluation and Licensing Division, PMSB dated May 31, 2001).

(4) Guidelines for bioequivalence testing of products with different dosage forms (Notification No. 783 of the Evaluation and Licensing Division, PMSB dated May 31, 2001)

(5) Guidelines for bioequivalence testing of oral solid dosage forms with formulation modifications (Notification No. 67 of the Evaluation and Licensing Division, PMSB dated February 14, 2000, Notification No. 786 of the Evaluation and Licensing Division, PMSB dated May 31, 2001).

(6) Guidelines for Bioequivalence Studies of Generic Products for Topical Dermatological Use (Notification No. 0707001 of the Evaluation and Licensing Division, PMSB dated July 7, 2003).

(7) Guidelines for bioequivalence testing of topical dermatological dosage forms with formulation modifications (Notification No. 1124001 of the Evaluation and Licensing Division, PMSB dated November 24, 2006).

3.2 Clinical Studies

1) Basic Requirements

The primary objectives of clinical studies are to evaluate therapeutic and prophylactic efficacy of investigational new drugs for target diseases or

symptoms as well as their risks and possible ADRs in humans, and ultimately to assess their clinical usefulness based on a comparison of their efficacy and safety. In performing clinical studies, investigators must give scientific and ethical consideration to the subjects' human rights to minimize their risk relative to the expected benefits.

Guidance concerning drug development strategies and evaluation processes has been issued in the three ICH regions. In 1998, General Considerations for Clinical Studies (Notification No. 380 of the Evaluation and Licensing Division, PMSB dated April 21, 1998) was prepared as one aspect of MHLW's efforts to promote international harmonization of approval review data for new drugs.

This notification consists of the objective of the guidelines, general principles (protection of clinical trial subjects and scientific approach in design and analysis) and development methods (points to consider for development plans and for individual clinical studies).

In order to protect the study subjects these Guidelines specify that, as a condition to start a clinical study, the safety of the drug must be shown from nonclinical studies or previous human studies. Throughout drug development, qualified clinicians and other experts should review and evaluate all newly obtained data from toxicity studies on animals and human studies to assess their implications for the safety of the subjects.

Clinical studies should be designed, conducted and analyzed in keeping with sound scientific principles in order to achieve their objectives, and they should be reported appropriately. The essence of rational drug development is to pose important questions and answer them with the results of carefully controlled clinical studies. The primary objectives of any study should be clear and explicitly stated.

Clinical studies can be classified by their objectives. The basic logic behind serially conducted studies of a drug is that the results of prior studies should influence the protocols of later studies (**Table 5.** Classification of Clinical Studies According to Objectives).

Following an ICH agreement to issue common GCP for scientific and ethical conduct of clinical studies in three regions, the MHLW **Ordinance on Standards for Implementation of Clinical Studies** on Drugs (**GCP**) (MHW Ordinance No. 28 dated March 27, 1997, partial revision by MHLW Ordinance No. 106 dated June 12, 2003, MHLW Ordinance No. 172 dated

December 21, 2004, and MHLW Ordinance No. 72 dated March 31, 2006) was issued with the aims of specifying the requirements for the planning, conduct, monitoring, auditing, records, analysis and reports of clinical studies performed to collect data to be submitted with applications for approval to manufacture and distribute drugs; to protect the human rights, safety and welfare of the study subjects; and to assure the scientific quality of the study and the reliability of its results.

The Evaluation and Licensing Division of the PMSB issued a notification (No. 889 dated July 24, 2000) on the topic of monitoring and audits to promote and establish GCP. The purpose of this document is to ensure medical institutions performing clinical trials accept the sponsor for monitoring and auditing at sites as a means to. The document emphasizes two points: time points of monitoring and/or auditing should be agreed on between the two parties and a designated area for monitoring and/or auditing activities (e.g., comparing information contained in the patient records with data entered on case report forms) must be provided to the sponsor by the medical institution. Electronic retention of some essential documents is approved based on MHLW Ordinance No. 36 on coordination of MHLW ordinances in accordance with coordination of laws and ordinances on the application of information technology for transfer of documents, etc. dated March 26, 2001. Details concerning investigator-initiated clinical trials are specified in MHLW Ordinance on Partial revision of the GCP Ordinance (MHLW Ordinance 106 of 2003).

2) Considerations for the Development Plan

2.1) Nonclinical studies

Important considerations for determining the nature of nonclinical studies and their timing with respect to clinical studies include:

(1) Duration and total exposure (dose) in individual patients.
(2) Characteristics of the drug.
(3) Disease or condition targeted for treatment.
(4) Use in special populations.
(5) Route of administration.

The actual timing of each nonclinical safety study is specified in Guidelines on Timing of Nonclinical Safety Studies for Clinical Trails on Drug Products (partial revision of Notifications of the Evaluation and Licensing Division, PMSB No. 1019 dated November 13, 1998 and No. 1831 dated December 27, 2000).

(i) Safety studies

For the first studies in humans, the dose used should be determined by

careful examination of the prerequisite nonclinical pharmacological and toxicological evaluations. Early nonclinical studies should provide sufficient information to support selection of the initial human dose and safe duration of exposure, to provide information about the physiological and toxicological effects of a new drug.

(ii) Pharmacological studies

The basis and direction of the clinical exploration and development rests on the nonclinical pharmacology profile, which includes the following information:

(1) Pharmacological basis of principal effects (mechanism of action).

(2) Dose-response or concentration-response relationships and duration of action.

(3) Study of the potential clinical routes of administration.

(4) Systemic general pharmacology, including pharmacological effects on major organ systems and physiological processes.

(5) Absorption, distribution, metabolism, and excretion

2.2) **Quality of investigational products**

Preparations used in clinical studies should be well characterized, with information on bioavailability wherever feasible. The preparation should be appropriate for the stage of drug development. Ideally, the preparation should be adequate to allow testing in a series of studies that examine a range of doses. This topic is covered in Manufacturing Control and Quality Control Standards for Investigational Products and Standards for the Buildings and Facilities of Manufacturing Plants for Investigational Products (Investigational Product GMP) (Notification No.480 of PAB dated March 31, 1997). Investigational products must be manufactured according to this Investigational Product GMP.

2.3) Phases of clinical development

Clinical studies have been conventionally classified by phase of development (I to IV). The ICH conference proposed a new classification system according to the objective of studies as described in the General Considerations for Clinical Studies (Notification No. 380 of the Evaluation and Licensing Division, PMSB dated April 21, 1998), and according to this system clinical studies are classified to the following four types.

(1) Human pharmacology studies

(2) Therapeutic exploratory studies

(3) Therapeutic confirmatory studies

(4) Therapeutic use studies

Objectives and types of studies in these four categories are listed in **Table 5** (Classification of Clinical Studies According to Objectives).

Studies must be designed and data analyzed or evaluated according to the above clinical guideline. **Fig. 9** (Correlation between Development Phases and Types of Study) illustrates the close but variable correlation between the two classification systems. The distribution of the circles, open circles and shaded circles, in the figure shows that the types of study do not automatically define the phases of development.

Clinical development is ideally a step-wise process in which information from small early studies is used to support and plan later larger, more definitive studies. To develop new drugs efficiently, it is essential to identify characteristics of the investigational product in the early stages of development and to plan appropriate development based on this profile.

(i) **Phase I** (typical study: clinical pharmacology)

Phase I entails the initial administration of an investigational new drug to humans. The most typical study is that on clinical pharmacology. Although clinical pharmacology studies are typically identified with Phase I, they may also be indicated at other points in the development sequence. Studies conducted in Phase 1 typically involve one or a combination of the following aspects:

(1) Estimation of initial safety and tolerability

(2) Characterization of pharmacokinetics

(3) Assessment of pharmacodynamics

(4) Early assessment of efficacy

As a reference, the basic concepts concerning the study items and conduct of all clinical pharmacokinetic studies for the purpose of drug development are given in Notification No. 796 of the Evaluation and Licensing Division, PMSB dated June 1, 2001 entitled “Clinical pharmacokinetic studies on drugs.”

(ii) **Phase II** (typical study: therapeutic exploratory)

Phase II is usually considered to be the phase in which studies with the primary objective of exploring therapeutic efficacy in patients is initiated. The most typical Phase II study is the therapeutic exploratory

study performed on a group of patients who are entered into the study according to clearly defined criteria and whose condition is monitored. An important goal for this phase is to determine the dose(s) and regimen for Phase III studies. Dose response designs should be used to assess and confirm the dose-response relation for the indication concerned. Additional objectives of Phase II clinical studies include evaluation of study endpoints, therapeutic regimens (including concomitant medication) or target populations for further study in Phase II or III.

(iii) **Phase III** (typical study: therapeutic confirmatory)

The primary objective of Phase III studies is to confirm the therapeutic effects. Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase I and II that a drug is safe and effective for use in the proposed indication and recipient population. These studies are intended to provide data to serve as an adequate basis for manufacturing approval.

"Arrangements for supplying and receiving of control drugs" were established as voluntary arrangements among member companies of the JPMA in July 1981 for the smooth supply and receipt of control drugs by the companies developing new drugs and the manufacturers/marketers of control drugs when pharmaceutical companies developing new drugs evaluate efficacy and safety of new drugs with approved drugs already on the market as controls. After four subsequent revisions, the most recent version appeared on November 1, 2005.

(iv) **Phase IV** (various types of study: therapeutic use)

The Phase IV studies are conducted after approval to confirm therapeutic efficacy and safety when used for the proposed indication and targeted population in general clinical practice. Studies include clinical experience surveillance to assess the incidence of adverse drug reactions, special survey to assess efficacy and safety in special populations, and post-marketing clinical trials to obtain additional information.

2.4) Studies concerning new indications, new dosage regimens, etc.

Development of additional indications, dose levels, dosage regimens, administration routes, etc. requires new protocols for both clinical and nonclinical studies. Human pharmacology may also be necessary for application.

2.5) Special considerations

Consideration should be given to special circumstances and populations when they are targeted as part of the development plan.

(i) **Studies of drug metabolites**

The main metabolites must be identified and detailed pharmacokinetic studies performed. The timing for studies to evaluate metabolism is decided in accordance with the characteristics of the drug concerned.

(ii) **Drug interactions**

If a potential for drug interaction is suggested by the metabolism profile, by the results of nonclinical studies or by information on similar drugs, studies on drug interaction are highly recommended. To explore interaction with the drugs that are frequently coadministered, it is usually important that drug interaction studies be performed in nonclinical and, if appropriate, in clinical studies.

(iii) Special populations

Some groups in the general population may require special study because they deserve unique risk/benefit considerations, or because they may need modification of use of a drug or schedule of a drug compared to general adult use.

Pharmacokinetic studies in patients with renal and hepatic dysfunction are important to assess the impact of the potentially altered drug metabolism or excretion. Other special populations are as follows:

(1) Elderly.

(2) Ethnic populations.

(3) Pregnant women.

(4) Nursing women.

(5) Children.

3) Considerations for Individual Clinical Studies

The following important principles should be followed in planning the objectives, design, conduct, analysis and reporting of a clinical study. Each item from the objectives to reporting should be defined in a written protocol before the study starts.

3.1) Objectives

The objective(s) of the study should be clearly stated. They may include exploratory or confirmatory characterization of the safety and/or efficacy and/or assessment of pharmacological, physiological or biochemical effects.

3.2) Design

The appropriate study design should be chosen to provide the desired information in consideration of the following points by referring to relevant clinical guidelines:

(1) Selection of subjects.

(2) Selection of control group.

(3) Number of subjects.

(4) Safety and efficacy variables.

(5) Methods to minimize bias (randomization, blinding, and compliance).

3.3) Conduct

The study should be conducted according to the principles described in the General Considerations for Clinical Studies or in accordance with other pertinent elements outlined in the GCP or other guidelines related to clinical studies. Adherence to the study protocol is essential.

3.4) Analysis

The study protocol should cite a specified analysis plan that is appropriate for the objectives and design of the study. Methods of analysis of the primary endpoints and surrogate endpoints should be included in the protocol. The results of the clinical study should be analyzed in accordance with the plan prospectively stated in the protocol.

3.5) Reporting

Clinical study reports should be appropriately prepared in accordance with the **Structure and Content of Clinical Study Reports** (Notification No.335 of the Pharmaceuticals and Cosmetics Division, PAB dated May 1, 1996).

4) Statistical Analysis of Clinical Study Results

In March 1992, the MHW (currently MHLW) published Guidelines for Statistical Analysis of Clinical Study Results (Notification No.20 of the New Drugs Division, PAB dated March 4, 1992) which list examples of misuse of statistical methods and indicate the methods which are considered most appropriate then to prevent errors and scientifically assess drug efficacy.

The ICH guidelines, Statistical Considerations in the Design of Clinical Trials (ICH E9) (Notification No. 288 of the Evaluation and Licensing Division, PMSB dated April 1, 1997), have been published to replace Notification No. 20 issued in 1992. The guidelines are intended to propose approaches when the sponsor designs, conducts, analyzes and assesses a clinical study of an investigational product as part of the overall clinical development. These guidelines should attract interest from individuals in many fields of science, and they state as a prerequisite that the actual responsibility for all statistical work related to a clinical study should be borne by statisticians with appropriate qualifications and experience. The participation of statisticians is intended to verify together with other clinical study experts that statistical principles have been appropriately applied in the study to

support drug development. Therefore, to implement the principles explicitly stated in these guidelines, the statisticians must combine adequate theoretical and practical education and experience. The principles stated in these guidelines are meant primarily to be applied in the latter half of development, mainly in therapeutic confirmatory studies.

In confirmatory studies, the primary variables are not limited to those related to efficacy but may include those concerning safety, pharmacodynamics and pharmacokinetics. In addition, some of the confirmatory knowledge is derived from data compiled for several studies, and under such conditions, some of the principles in the guidelines are applied. The studies in the initial phases of drug development mainly involve therapeutic exploratory studies, but statistical principles are also applied to these studies. Therefore, these guidelines should be applied to all phases of clinical development whenever feasible.

5) Guidelines for Clinical Evaluation

Data on the results of clinical studies must be analyzed precisely and objectively as they are the means of identifying the drug's expected efficacy and ADRs, when the drug is used, thereby playing an important role in the evaluation process by the regulatory authority. Guidelines on the methodology for clinical studies and the evaluation criteria have been published as "Guidelines for Clinical Evaluation." The results from ICH are also introduced into Japanese regulations as ICH guidelines.

As of March 2006, the following 29 guidelines for clinical evaluations by therapeutic category, common for clinical evaluation, and otherwise related to clinical evaluations have been published:

[1] Guidelines for clinical evaluation of drugs classified by therapeutic category

(1) Guidelines on Clinical Evaluation Methods of Oral Contraceptives (Notification No. 10 of the First Evaluation and Registration Division, PAB dated April 21, 1987).

(2) Guidelines for Clinical Evaluation Methods of Drugs to Improve Cerebral Circulation and/or Metabolism in Cerebrovascular Disorders (Notification No. 22 of the First Evaluation and Registration Division, PAB dated October 31, 1987).

(3) Guidelines on Clinical Evaluation Methods of Antihyperlipidemic Drugs (Notification No. 1 of the

First Evaluation and Registration Division, PAB dated January 5, 1988)

(4) Guidelines on Clinical Evaluation Methods of Antianxiety Drugs (Notification No. 7 of the First Evaluation and Registration Division, PAB dated March 16, 1988).

(5) Guidelines on Clinical Evaluation Methods of Hypnotics (Notification No. 18 of the First Evaluation and Registration Division, PAB dated July 18, 1988).

(6) Guidelines on Clinical Evaluation Methods of Drugs to Treat Heart Failure (Notification No. 84 of the First Evaluation and Registration Division, PAB dated October 19, 1988).

(7) Guidelines for Clinical Evaluation Methods of Antibacterial Drugs (Notification No. 743 of the New Drugs Division, PMSB dated August 25, 1998).

(8) Guidelines on Clinical Evaluation Methods of Drugs to Treat Osteoporosis (Notification No. 742 of the Evaluation and Licensing Division, PMSB dated April 15, 1999)

(9) Principles for Clinical Evaluation of New Antihypertensive Drugs* (ICH E12A, currently E12) (Notification No. 0128001 of the Evaluation and Licensing Division, PFSB dated January 28, 2002)

(10) Guidelines on Clinical Evaluation Methods of Antiarrhythmic Drugs (Notification No. 0325035 of the Evaluation and Licensing Division, PFSB dated March 25, 2004)

(11) Guidelines on Clinical Evaluation Methods of Antianginal Drugs (Notification No. 0512001 of the Evaluation and Licensing Division, PFSB dated May 12, 2004)

(12) Guidelines for Clinical Evaluation Methods of Antimalignant Tumor Drugs (Notification No. 1101001 of the Evaluation and Licensing Division, PFSB dated November 1, 2005).

(13) Guidelines for Clinical Evaluation Methods of Antirheumatoid Drugs (Notification No. 0217001 of the Evaluation and Licensing Division, PFSB dated February 17, 2006).

(14) Guidelines for Clinical Evaluation Methods of Drugs for Overactive Bladder or Incontinence (Notification No. 0628001 of the Evaluation and Licensing Division, PFSB dated June 28, 2006).

[2] Guidelines for clinical evaluation in

general

(15) Studies in Support of Special Populations: Geriatrics (ICH E7) (Notification No. 104 of the New Drugs Division, PAB dated December 2, 1993).

(16) Dose-Response Information to Support Drug Registration (ICH E4) (Notification No. 494 of the New Drugs Division, PAB dated July 25, 1994).

(17) Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions (ICH E1) (Notification No. 592 of the Pharmaceuticals and Cosmetics Division, PAB dated May 24, 1995)

(18) Structure and Content of Clinical Study Reports (ICH E3) (Notification No. 335 of the Pharmaceuticals and Cosmetics Division, PAB dated May 1, 1996)

(19) General Considerations for Clinical Trials (ICH E8) (Notification No. 380 of the Evaluation and Licensing Division, PMSB dated April 21, 1998).

(20) Ethnic Factors to be Considered in the Acceptance of Foreign Clinical Trial Data (ICH E5, currently E5(R1)) (Notification No. 672 of the Evaluation and Licensing Division, PMSB dated August 11, 1998)

(21) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (ICH M3 (R1)) (Notification No. 1019 of the Evaluation and Licensing Division, PMSB dated November 13, 1998).

(22) Statistical Principles for Clinical Trials (ICH E7) (Notification No. 1047 of the Evaluation and Licensing Division, PMSB dated November 30, 1998)

(23) Clinical Investigation of Medicinal Products in the Pediatric Population (ICH E11) (Notification No. 1334 of the Evaluating and Licensing Division, PMSB dated December 15, 1999)

(24) Choice of Control Group and Related Issues in Conducting Clinical Studies (ICH E10) (Notification No. 136 of the Evaluating and Licensing Division, PMSB dated February 27, 2001)

[3] Other guidelines

(25) Research on Evaluation Methods of Immunotherapeutic Agents for Malignant Tumors (1980).

(26) Research on Evaluation

Methods of Blood Preparations, Especially Plasma Fraction Preparations (1984).

(27) Research on Overall Evaluation Methods of Interferon Preparations (1984).

(28) Guidelines on Clinical Evaluation Methods of Anti-inflammatory Analgesic Drugs (1985).

(29) Guidelines on the Design and Evaluation of Sustained-release (Oral) Preparations (Notification No. 5 of the First Evaluation and Registration Division, PAB dated March 21, 1988).

6) Procedures for Conduct of Clinical Studies

Regarding the conduct of clinical studies to collect data to be submitted with approval applications for new drug manufacturing and distribution, the Pharmaceutical Affairs Law and the **GCP** (MHW Ordinance No. 28 dated March 27, 1997, partial revision by MHLW Ordinance No. 106 dated June 12, 2003, MHLW Ordinance No. 172 dated December 21, 2004, and MHLW Ordinance No. 72 dated March 31, 2006) require that the MHLW be notified of the study protocol beforehand and provide various requirements to be met by the sponsor when requesting medical institutions to perform clinical studies. Compared with the former GCP, the following points are conspicuous: a) the scope of the GCP has been extended to cover post-marketing clinical trials, b) the role and responsibilities of sponsors such as pharmaceutical companies have been clarified and strengthened, and c) medical institutions performing clinical studies are obliged to comply with the GCP. When sponsors request clinical studies they must have obtained adequate data concerning the safety, efficacy and quality from previous nonclinical studies and other human studies which support as much as possible the objectives of the study, and the subject population, route of administration, dosage and administration, the time of exposure, and observations and evaluation items to be applied in the proposed study, as well as support for the ethical and scientific suitability of the study. All procedures must be specified in writing. Sponsors must request the study sites to inform the subjects adequately about the contents of the clinical study and obtain their written informed consent to participate in the study. The sponsor must also take the necessary measures beforehand to provide compensation for any health impairment caused by the investigational product. The range of the GCP covers not only clinical studies on patients, but also Phase I studies on healthy volunteers, bioequivalence studies on humans, studies on added

indications for approved drugs and post-marketing clinical trials conducted after the drug goes on the market. In addition, investigator-initiated clinical trials are specified to be covered by the GCP by partial revision of the GCP Ordinance in 2003.

According to the new GCP, when a clinical study is requested, a contract for clinical trials can be concluded only when 30 days have passed from the initial notification of the study protocol is received by the PMDA (SOGO-KIKO) (at least 2 weeks for subsequent notifications). The sponsor must report to the authorities any severe adverse reactions or infections that occur during the study, and the authorities may undertake on-site inspections concerning GCP compliance in the sponsor's facilities and the medical institution performing the study when problems arise during the study. For drugs required in emergencies to prevent diseases that have a major effect on the life or health of the patient or to prevent other damage to the health, clinical study protocols may be submitted within 30 days after the start of the study (MHLW Ordinance No. 89 dated May 2003).

At the time of the clinical study protocol notification, a system by which the PMDA reviews the contents of the initial notification at the request of the MHLW is now specified by law, and a "clinical trial consultation system" in which the PMDA gives guidance and advice concerning study protocols has also been established (refer to 1.2-3: Interview Advice).

7) Safety Information on Adverse Reactions and Infections during the Study

Safety information obtained during the study must be reported promptly, as is specified in the ICH guidelines on Clinical Safety Data Management (Notification No.227 of the Pharmaceuticals and Cosmetics Division, PAB dated March 20, 1995).

In the revision of the Enforcement Regulations of the Pharmaceutical Affairs Law in April 1997 for which the ICH guidelines served as a reference, the obligation to report adverse reactions, etc. related to the investigational product, including those occurring in foreign countries, to the Minister was specified by law. These provisions are outlined below.

A: 7-Day reports (When either of the following events is suspected to be caused by an adverse reaction of the investigational product concerned or by an infection suspected of being caused by the investigational product concerned, and the event is not expected from the description in the

investigator's brochure of the investigational product concerned: the report must be made within 7 days.)

(a) Death
(b) Cases that might result in death

B: 15-Day reports (For the following events: the report must be made within 15 days.)

(a) Any of the following events suspected to be caused by an adverse reaction of the investigational product concerned or by an infection suspected of being caused by the investigational product concerned, which is not expected from the description in the investigator's brochure of the investigational product concerned.
- Events requiring admission to a hospital for treatment or prolongation of the period of hospitalization
- Disability
- Cases that might result in disability
- Other medically serious condition
- Congenital diseases or abnormalities in the next generation

(b) Predicted deaths or events that might result in death.
(c) Measures related to safety problems of the investigational product concerned, including discontinuation or manufacture and/or marketing in a foreign country.
(d) Research reports showing the possibility of causing cancer or other serious diseases due to adverse reactions, etc. of the investigational product concerned.

8) GCP

The first GCP, Standards for Conduct of Clinical Trials on Drugs, intended to assure that clinical studies are performed on the basis of ethical considerations and from the proper scientific standpoint were issued as Notification No 874 of the PAB dated October 2, 1989, and this GCP was applied in the form of administrative guidance from October 1, 1990. Thereafter, the MHW undertook various studies to improve the quality of clinical studies in Japan in accordance with changes in the international regulatory situation, and a new GCP was issued as an MHW ordinance (No.28, March 27, 1997) based on a report of the Central Pharmaceutical Affairs Council (March 13, 1997). This new GCP, which is legally binding, went into effect from April 1, 1997.

The old GCP consisted mainly of

provisions concerning pharmaceutical companies as the sponsors of clinical studies, but the new GCP clarifies and reinforces the role and responsibilities of sponsors, and also includes provisions concerning the medical institutions and investigators (physicians) performing the clinical studies.

Further, the GCP was revised to expand its scope to cover clinical trials conducted by the physician or medical institution for approval application in order to manage clinical trials similarly to the current clinical trial system. The revised GCP was enacted by the Ordinance for Partial Revision of the Standards for the Conduct of Clinical Trials on Drugs (Notification No. 106 issued by the MHLW on June 12, 2002) and enforced on April 1, 2005 by the Ordinance for Partial Revision of the Standards for the Conduct of Clinical Trials on Drugs (Notification No. 172 issued by the MHLW on December 21, 2004). The GCP was further revised to improve the quality and function of the investigational review committee (Ordinance for Partial Revision of the Standards for the Conduct of Clinical Trials on Drugs (Notification No. 72 issued by the MHLW on March 31, 2006).

On September 19, 2007, a report was compiled by the MHLW Council of Ideal Registration-directed Clinical Trial. Based on this report, the type and scope of documents necessary for the conduct of clinical trials are to be reevaluated and rationalized. The GCP regulations are to be revised accordingly.

This GCP consists of six chapters and 59 articles. It has three main parts: standards for the sponsoring of clinical studies and standards for the management of clinical studies which are related to sponsors, and standards for the conduct of clinical studies which concern the medical institutions performing the clinical studies. These parts are outlined below.

Chapter 1: General Provisions (Articles 1 to 3)

The general regulations consist of Article 1 (Outline), Article 2 (Definitions of Terms) and Article 3 (Standards for Review Data). The GCP specifies the following standards (Article 1).

1) Standards to be followed by prospective sponsors in the collection and preparation of data related to results of clinical trials on drugs to be attached to approval applications.
2) Standards to be followed by prospective sponsors of clinical trials, institutions or persons performing clinical trials and sponsors of clinical trials to

conduct or manage clinical trials which are both ethically and scientifically sound.

3) Standards to be followed by sponsors in the collection and preparations of data from post-marketing clinical trials for reexamination or reevaluation of drugs.

Among data to be submitted by persons submitting applications to receive approval in Article 3, data concerning the results of clinical studies specified in Chapter 2, Section 1 (Articles 4 to 15), Chapter 3, Section 1 (Articles 16 to 26) and Chapter 4 (Articles 27 to 55, excluding Article 29, Paragraph 1, Item 2 and Article 48, Paragraph 3); and data concerning the results of clinical studies performed by persons specified in Chapter 2, Section 2 (Articles 15-2 to 15-9), Chapter 3, Section 2 (Articles 26-2 to 26-12) and Chapter 4 (Articles 27 to 55, excluding Article 29, Paragraph 1, Item 1 and Article 48, Paragraph 2) must be submitted.

Chapter 2: Standards for **Sponsoring Clinical Trials** (Articles 4 to 15-9)

Provisions to be followed when clinical trials are sponsored or managed in medical institutions by persons who wish to sponsor clinical trials and provisions to be followed when clinical trials are prepared or managed by persons who wish to conduct clinical trials by themselves (investigator-initiated trials).

- Prospective sponsors（persons who wish to sponsor clinical trials）must prepare standard operating procedures so that all work related to **sponsoring**（or preparation）**and management** of the clinical trial such as preparation of the clinical trial protocol, selection of a medical institution(s) and investigator(s) to perform the trial, control of the investigational product, collection of information on adverse reactions and retention of records can always be performed properly.
- Studies on the quality, toxicity and pharmacological action, as well as other studies on the investigational product required for sponsoring（or preparation of）the clinical trial must be completed.
- The clinical trial protocol and an investigator's brochure based on information concerning the quality, efficacy and safety of the investigational product must be prepared.
- A contract must be concluded between the sponsor and clinical research organization when all or part of the clinical trial management is contracted out.
- When persons or participating

medical institutions who perform clinical trials on their own outsource part of the work related to preparation to conduct or management of clinical trials, a contract must be concluded with the party undertaking the work showing that the work was outsourced to a site management organization (SMO).

- A contract must be concluded with the medical institution(s) performing the clinical trial. Persons who wish to perform clinical trials on their own must obtain the approval of the director of the participating medial institution beforehand.
- Insurance coverage and other measures required for compensation in cases of trial-related injury must be undertaken beforehand.
- Persons who wish to sponsor clinical trials may with the prior approval of the other party submit beforehand documents to the director of the participating medical institutions, and conclude contracts for outsourcing work or contracts for clinical trials by electronic methods.

Chapter 3: Standards concerning **management of clinical trials** (Article 16 to 26-12)

Provisions to be followed by the sponsor or persons performing clinical trials on their own for the scientific and ethical conduct of clinical trials

- The specified items must be included on the labels of the investigational products.
- Manufacturing records, quality test records and other records related to the investigational product must be prepared.
- Investigational products manufactured in factories fulfilling the Investigational Product GMP requirements must be supplied to or used by the medical institutions that perform the clinical trial.
- The status of all patients with unknown serious adverse drug reactions in Japan and overseas, and patients with adverse drug reactions known or thought to be linked with deaths in Japan and overseas must be reported to medical institutions performing clinical trials every six months.
- Standard operating procedures (SOP) concerning monitoring must be prepared and monitoring must be performed on the basis of these SOP.
- Monitors must confirm that the trial is being performed properly and that reliability of the data is adequately maintained by visits to the medical institutions performing the trial and direct access to the source data, and they must submit a monitoring

report to the sponsor, the person who performs the trial, or the director of the medical institution involved.

- An audit plan and audit SOP must be prepared and the audit must be performed in accordance with these documents. The auditor must prepare an audit report and an audit certificate proving that the audit has been performed, and these documents must be submitted to the sponsor, the person who performs the trial, or the director of the medical institutions involved.
- When the trial is completed or discontinued, the results obtained must be compiled in a clinical trial report. When the person conducting the clinical trial learns that the study results collected from the trial concerned were not attached to the application form as application data, this fact and the reason for it must be notified in writing to the directors of the medical institutions performing the trial.
- Records related to the clinical trial must be retained for the specified period.

Chapter 4: Standards for conduct of clinical trials (Articles 27 to 55)

Provisions to be followed by the medical institutions performing clinical trials scientifically and ethically

1) Provisions concerning the Institutional Review Boards (IRB) (Articles 27 to 34)

- An Institutional Review Board (IRB), which should meet the requirements specified in Article 28, must be established by the director of the medical institution performing the trial to review and discuss the proper conduct of clinical trials and other matters related to the trials.
- The IRB must review the ethical and scientific appropriateness of the clinical trial subject to review on the basis of the documents specified in Article 32, and state its opinion.
- The medical institution is not allowed to conduct a clinical trial when the opinion of the IRB is that it is not appropriate to conduct the trial.
- When an IRB can not be established in the medical institution conducting the trial, It is possible to select other institutional review boards both in and outside of medical institutions performing clinical trials at the discretion of the director of medical institutions performing clinical trials.
- The IRB can publish information related to institutional review boards to improve transparency

and assure the quality of reviews.

2) Provisions related to medical institutions performing clinical trials (Articles 35 to 41)

- Medical institutions performing clinical trials must have the facilities and personnel to undertake adequate clinical observations and laboratory testing, and they must be able to take the measures required when emergencies arise among the trial subjects.
- The director of the medical institution performing the trial must prepare SOP for work related to the trial, and take the necessary measures so that the clinical trial is conducted properly and smoothly in compliance with the trial protocol and the SOP.
- The director of the medical institution performing the trial must cooperate with monitoring or audits by the sponsor or the person conducting the clinical trial and review by the IRB.
- The head of a medical institution must appoint a person or persons to carry out trial-related clerical work.

3) Provisions related to investigators (Articles 42 to 49)

- The investigator must have sufficient clinical experience to be able to conduct the trial properly.
- The investigator must select the trial subjects in accordance with the objectives of the trial from the ethical and scientific standpoints. The necessary measures so that appropriate treatment can be given to subjects when adverse events occur must be taken beforehand.
- The investigator must prepare the proper case report forms as specified in the protocol, etc. and sign or seal them.
- When deaths suspected of being caused by adverse reactions of the investigational product or other serious adverse events occur, the investigator must immediately report this to the director of the medical institution performing the trial and inform the sponsor or the person supplied with the investigational product when the trial is investigator-initiated.

4) Provisions concerning informed consent of subjects (Articles 50 to 55)

- When a prospective subject is asked to participate in a clinical trial, the investigator must appropriately explain the

contents of the clinical trial and other matters beforehand to the subject using "written information" containing required items, and obtain the written consent of the subject.

- The investigator making the explanation and the prospective subject must date and sign or seal the consent form to make the consent effective.

Chapter 5: Standards concerning **reexamination data** (Article 56)

GCP standards also apply to the collection and preparation of data concerning the results of post-marketing clinical trials to be submitted for reexaminations or reevaluations, but taking account of the nature of post-marketing clinical trials, certain provisions for clinical trials for new drug application are applied to those for reexamination and the required changes in reading shall be made accordingly in this article.

Chapter 6: Standards concerning **sponsoring of clinical trials** (Article 57 to 59)

These GCP standards also contain provisions concerning the acts of prospective sponsors of clinical trials or persons conducting the clinical trials (Article 57), institutions requested to perform clinical trials (Article 58) and clinical trial sponsors (Article 59). However, since the scope of application differs from that of the standards related to approval review data, certain provisions for clinical trials for new drug application are applied for those for reexamination and the required changes in reading shall be made accordingly in this article.

Clinical trials performed to obtain data for approval applications must be conducted, results collected and data prepared in accordance with the GCP. In addition to clinical trials sponsored by companies, it is also possible for investigator-initiated clinical trials to be performed for the preparation of approval application data in compliance with the GCP. With the legalization of the GCP standards, data from clinical trials subject to the GCP will not be accepted as approval application data unless the trial was conducted and the data collected and prepared in accordance with the GCP.

Application data from clinical trials submitted to the MHLW must first undergo a GCP compliance review to assure that it meets GCP standards. This review consists of a paper inspection and on-site inspection at the medical institution(s) performing the trial,

etc. The review is intended to confirm the reliability of the data as application data. These GCP compliance reviews are performed by the PMDA at the request of the MHLW for data collected and prepared in Japan. The approval review is then undertaken by the MHLW in accordance with the results of PMDA review.

The on-site inspections are performed at both the sponsor's facilities and the medical institution(s) performing the trial. Inspections of the sponsor's facilities examine the organization, structure and management of the GCP-related division, GCP compliance of clinical trials and confirmation of the items included in the trial results. Inspections in the medical institutions review the outline of the facilities and organization, the structure and operation of the IRB, GCP compliance of the clinical trial and items in the case report forms.

9) Investigational Product GMP

In Article 17, Supply of the Investigational Product, in the GCP ordinance, it specifies that the sponsor shall supply to the medical institution performing the study investigational product manufactured in factories applying appropriate manufacturing control and quality control methods and with the buildings and facilities required to assure the quality of the investigational product. Requirements for manufacturing investigational products in order to assure the reliability of clinical studies by guaranteeing the quality of investigational products and to protect subjects from poor quality investigational products have been issued into the form of Notification No. 480 of the PAB dated March 31, 1997 entitled "Standards for Manufacturing Control and Quality Control of Investigational Products and Standards for Buildings and Facilities of Plants Manufacturing Investigational Products." The Investigational Product GMP requires the appointment of an investigational product supervisor with sufficient education, training, knowledge and experience in the manufacturing control and quality control of investigational products, with managers responsible for investigational product manufacturing control and quality control under this supervisor in each factory, and also specifies the responsibilities of each of these staff members. The preparation of investigational product manufacturing standards specifying the ingredients and quantities, specifications, test methods and manufacturing methods for each investigational product, the preparation of investigational product manufacturing control standards and

investigational product manufacturing hygiene control standards for each factory, and other provisions concerning validation, complaints, recall, self-inspections, education and training, and contracted manufacture are also specified.

The Investigational Product GMP also specify requirements for each type of facility manufacturing investigational products other than bulk products, investigational bulk products, investigational sterile preparations, investigational sterile bulk product, investigational biological products and investigational blood products.

The requirements for manufacturing control and quality control methods for drug substances are specified the Guidelines on GMP for Drug Substances (ICH Q7A, currently Q7) (Notification No. 1200 dated November 2, 2001) which includes 20 requirements for drug substances, including quality management, buildings and facilities and validation, as approved at ICH5 held in San Diego in November 2000.

4. REQUIREMENTS FOR DRUG MANUFACTURING AND MARKETING APPROVALS AND MANUFACTURING BUSINESS LICENSES

Proper control at the stage of drug manufacture is essential so that drugs can be supplied to patients with good quality. This means that the manufacturers and the buildings and facilities in the manufacturing plants must be appropriate so that drugs based on the approvals can be produced. The manufacturing process as a whole must be controlled on the basis of scientific principles, and it is also necessary to assure the quality of drugs manufactured by taking measures to prevent errors during processing.

Since a recommendation to introduce GMP was issued by the World Health Assembly (WHA), the general meeting of the World Health Organization (WHO) in July 1969, various countries have passed laws concerning control procedures essential for the manufacture of drugs. In Japan, these are established for GMP by Regulations for Buildings and Facilities of Pharmacies, etc. with respect to hardware, and by Manufacturing Control and Quality Control for Drugs and Medical Devices with respect to software. This is because the system of approval and item licensing under the Pharmaceutical Affairs Law has been replaced by a different legal framework. However under the revision to and enforcement of the Pharmaceutical Affairs Law of April 1, 2005, there has been issued a new MHLW Ordinance relating to Standards for Manufacturing Control and Quality Control for Drugs and Medical Devices (MHLW Ordinance No. 179, December 24, 2004), thereby integrating GMP hardware rendered necessary by the

characteristics of drugs with GMP software. Specifically, Article 9 establishes basic standards for the buildings and facilities of manufacturing plants where GMP is applicable, and Article 23 establishes standards for the buildings and facilities of manufacturing plants for sterile drugs.

With respect to the former Regulations for Buildings and Facilities of Pharmacies, etc., they are revised according to the MHLW Ordinance partially revising Regulations for Buildings and Facilities of Pharmacies, etc. (MHLW Ordinance No. 180, December 24, 2004, partial amendment: MHLW Ordinance No. 73 dated April 1, 2005). Under the revision to and enforcement of the Pharmaceutical Affairs Law of April 1, 2005, GMP has become a requirement for manufacturing and marketing approval (Article 14-2, Paragraph 4 of the Law) and regulations for buildings and facilities have become requirements for licensing as manufacturers (Article 13-4, Paragraph 1 of the Law).

When it is not found that the methods of manufacturing control or quality control at a manufacturing plant conform to the standards, the Minister of Health, Labor and Welfare can not grant a manufacturing and marketing license. And when the buildings and facilities of a manufacturing plant do not conform to the standards, the Minister of Health Labor and Welfare or prefectural governor can choose not to grant a license.

The requirements for manufacturing control and quality control methods for drug substance should be referred to the Guidelines on GMP for Drug Substance (ICH Q7A, currently Q7) (Notification No. 1200 dated November 2, 2001) which concretely specifies 20 requirements concerning manufacturing and control of drug substance, including quality control, buildings and facility, validation, as agreed in the ICH5 held in San Diego, California, USA in November 2000.

The following sections outline the GMP regulations:

1) Required Documentation

According to the Regulations for Manufacturing Control and Quality Control of Drugs, all of the operations in the plants must be divided into operations for manufacturing control and those for quality control, and various types of documentation are required, including standard operating procedures for standardization of all work conditions (drug product standards, manufacturing control standards, manufacturing hygiene control standards and quality control standards), documentation required for actual operation procedures based on these standards (manufacturing instructions and test and self-inspection protocols), records of the results of all of these operating procedures (records related to

manufacture, records of manufacturing hygiene control, and records of tests and self-inspections), and records of storage and distribution. Additional documents should be compiled if they are considered necessary for proper manufacturing control and quality control. These documents must be retained for designated time periods from the date of preparation.

When damage to the health of patients or other users of biological products (biotechnological technology-derived and of biological origin) occurs, records must be retained for the period required to clarify the cause of this damage.

2) Personnel Organization

All operations in manufacturing plants are subject to manufacturing control and quality control based on standard operating procedures as described previously, and the managers in each division used to bear responsibility for these operating procedures, but this now lies with the quality control unit. The final responsibility for deciding whether or not drugs should be shipped and that for solving problems related to overall manufacturing control and quality control in the plant lies with the drug manufacturing control manager designated in each plant under the Pharmaceutical Affairs Law.

Article 4 of the control regulations specifies that the plant must be organized so that there is a quality control unit independent of the manufacturing unit. Appropriate personnel with the ability to supervise the work so that it is performed correctly and smoothly must be appointed in accordance with the organization of the plant, and the scale and types of work involved. The duties of the product security pharmacist are clearly specified in the provisions of the Pharmaceutical Affairs Law. Article 3 of the control regulations specifies supervision of the manufacturing control manager and the quality control manager as one of the duties of product security pharmacist.

3) Manufacturing Control

The manufacturer, etc. must assure that the duties set forth below are carried out appropriately by the manufacturing department in compliance with standard operating procedures.

- To prepare and preserve manufacturing instructions.
- To manufacture products based on the manufacturing instructions.
- To prepare and preserve records related to product manufacture for each lot.

- To check packaging materials for products for each lot, and to prepare and preserve records related to the results thereof.
- To appropriately store and circulate products by lot and packaging materials by control unit, and to prepare and preserve records thereof.
- To check the cleaning of buildings and facilities, and to prepare and preserve records relating to the results thereof.
- To inspect and maintain buildings and facilities on a regular schedule, and to prepare and preserve records thereof. Further, to carry out appropriate calibration of measuring instruments, and to prepare and preserve records relating to the results thereof.
- To check that manufacturing control has been appropriately conducted on the basis of records relating to manufacturing, storage and distribution, as well as to sanitation control, and to notify the quality department in writing of the results thereof.

* Manufacturer, etc.: the manufacturer or overseas manufacturer

4) Quality Control

The manufacturer, etc. must assure that the duties set forth below are carried out systematically and appropriately by the quality department in compliance with standard operating procedures.

- To collect samples required for the testing and inspection of products, etc. for each lot, and of packaging materials for each control unit, and to prepare and preserve records thereof.
- To conduct testing and inspection of the samples collected for each lot or for each control unit, and to prepare and preserve records thereof.
- To store samples of products consisting of an amount two or more times greater than the amount required for testing and inspection for each lot under appropriate storage conditions for a period of one year longer than the expiration period or the shelf-life from the date of manufacture for the product concerned.
- To inspect and maintain on a regular schedule the facilities and implements relating to testing and inspection, and to prepare and preserve records thereof. Further to carry out appropriate calibration of measuring instruments relating to testing and inspection, and to prepare and preserve records related to the results thereof.
- To evaluate the test results of the samples collected, and to notify the manufacturing department in writing of the results thereof.

- Further, manufacturers, etc. makes use of the tests and inspections performed in the import source country, they must assure that the quality department carries out the duties set forth below:
- To confirm at on a regular schedule that that the product, etc. is manufactured in accordance with appropriate manufacturing procedures.
- To confirm on a regular schedule that the manufacturing plant of an overseas manufacturer conforms to the standards relating to manufacturing control and quality control in that country, and to prepare and preserve records thereof.
- To confirm the records of tests and inspections carried out by the foreign manufacturer, and to prepare and preserve records thereof.

5) Documents Concerning Procedures for Validation, etc.

The manufacturer must prepare written procedures for validation change control, deviation control, complaints, recalls, self-inspections, training and education for each plant so that these procedures can be performed appropriately.

6) Validation

The manufacturer, etc. must ensure that the following obligations are fulfilled by a person designated beforehand in compliance with the standard operating procedures.

- The validation plan and results must be reported in writing to the quality control unit.
- The document prepared based on the validation must be retained for 3 years from the date of preparation (when the drugs concerned are cell or tissue-derived drugs, the period until the expiration date plus 10 years).

The manufacturer, etc. must take appropriate measures when improvements are required in manufacturing control or quality control based on the results of the validation. Records of the measures taken must be prepared and retained.

7) Change Control

When manufacturers, etc. implement changes with respect to manufacturing procedures, etc. that might affect the quality of the product, they must assure that a previously designated person carries out the duties set forth below, in compliance the standard operating procedures:

- To evaluate the effect on product quality due to the changes, and to obtain the consent of the quality department for implementation of changes

based on the results of the evaluation.

- When implementing the changes, to take measures for amendment of the relevant documentation, education and training of personnel, and any other requisite measures.

8) Deviation Control

When a deviation from the manufacturing procedures occurs, the manufacturer, etc. must assure that a previously designated person carries out the duties set forth below, in compliance with the standard operating procedures:

- To record the details of the deviation.
- In cases where a major deviation has occurred, to evaluate the effect on product quality, to take requisite measures, to prepare and preserve the records, and to notify and obtain confirmation from the quality department.

9) Information Related to Quality and Handling Quality Defects

When the manufacturer, etc. acquires information relating to the quality, etc. of a drug, he must, except in cases in which it is clear that the items relating to the quality information are not attributable to the manufacturing plant concerned, assure that a previously designated person carries out the duties set forth below, in compliance with the standard operating procedures,

- To elucidate the causes of items relating to the quality information concerned, and in cases in which improvements related to manufacturing control or quality control are required, to take the requisite measures.
- To prepare and preserve a record specifying the nature of the quality information concerned, the results of the elucidation of causes, and the measures for improvement, and to promptly and in writing notify and obtain confirmation from the quality assurance department.
- In cases in which the manufacturer, etc. has identified a quality defect or the risk thereof, to assure that the manufacturing control manager notifies quality department in writing on the basis of the standard operating procedures.

10) Product Recalls

When manufacturers decide to recall drugs for reasons related to quality, etc., they must assure that a previously designated person carries out the duties set forth below in compliance with the standard operating procedures.

- To classify the recalled products and dispose of them appropriately after retention for a certain period.
- To prepare and retain recall records including the contents of the recall, results of clarification of the cause and measures taken for improvement and notify the quality department and manufacturing control manager in writing thereof.

11) Self-inspections

The manufacturer, etc. must have the following obligations fulfilled by a person designated beforehand in compliance with the standard operating procedures.

- To undertake their own self-inspections of the manufacturing control and quality control in the plant concerned periodically.
- To report the results of these self-inspections in writing to the manufacturing control manger.
- To prepare and retain records of the results of self inspections.
- The manufacturer must take appropriate measures when improvement is required in manufacturing control or quality control based on the results of the self-inspection. Records of the measures taken must be prepared and retained.

12) Education and Training

The manufacturer must have the following obligations fulfilled by a person designated beforehand in compliance with the standard operating procedures.

- To systematically educate and train the workers in terms of manufacturing control and quality control.
- To report the status of implementation of education and training in writing to the manufacturing control manager.
- To prepared and retain records of the conduct of education and training.

Further, in cases in which the manufacturer, etc. manufactures products sterile products, it must be assured that a previously designated person carries out the duties set forth below:

- To provide personnel engaged in manufacture or testing and inspection with education and training in hygiene control, microbiology, and other matters requisite for the manufacture of sterile products.
- To provide personnel engaged in work in clean areas or sterile areas with the education and training related to measures

requisite for the prevention of contamination by microorganisms.

The manufacturer, etc. must have the above work performed by persons designated beforehand and must have the following work performed based on written procedures when biological products are manufactured.

- The manufacturer shall provide education and training on microbiology, medicine and veterinary medicine for employees engaged in manufacture or testing of biological products.
- The manufacturer shall provide education and training on the measures required to prevent contamination by microorganisms for employees engaged in work in sterile areas or in areas handling pathogenic microorganisms.

13) Management of Documents and Records

The manufacturer, etc. must assure that, with respect to the documents and records specified under 1) through 12) above, a previously designated person carries out the duties set forth below in compliance with the standard operating procedures:

- In cases in which documents are prepared or revised, to carry out approval, distribution, retention, etc.
- In cases in which standard operating procedures are prepared or revised, to date them and retain a revision history.
- To retain documents and records for a period of 5 years from the date of preparation (or for standard operating procedures from the date at which they are no longer used) (provided, however, that in cases in which the shelf-life of the product relevant to the records, etc. concerned plus 1 year is longer than 5 years, and with the exception of records related to education and training, for the shelf-life plus 1 year).

The manufacturer, etc. must, when biological products are manufactured, assure that, notwithstanding the above, the documents and records specified from 1) to 12) are retained for periods from the date of their preparation as set forth below (records related to education and training, a period of 5 years). However, in the case of biological products that have been designated by the Minister of Health, Labor and Welfare, the manufacturer, etc. must assure that that a previously designated person store them for the period designated by the Minister.

- With respect to biological products or cell or tissue products, for a period of 5 years (except in cases where the shelf-life of the product concerned plus 1 year is longer than 5 years, for a period equal to the shelf-life plus 1 year).
- In the case of specified biological products or biological products manufactured using human blood as the raw material, for a period equal to the shelf-life plus 30 years.
- In the case of biological products or cell or tissue products (except as set forth above), a period equal to the shelf-life plus 10 years).

4.1 GMP Compliance Reviews

When an application is submitted for a new drug manufacturing and marketing approval, the plant must be inspected for the authorities to determine if it actually complies with the GMP standards.

Evaluation Rank Criteria

A: (Compliance): Manufacturing is performed properly.

B: (Slightly defective): There is little effect on drug quality but improvement necessary for complete compliance with control regulations.

C: (Moderately defective): Effect on drug quality can not be ruled out and improvement necessary for compliance with control regulations.

D: (Seriously defective): Clear violation of control regulations

First, a review is conducted for each product using the following criteria for GMP compliance as to each article in the control regulations and building and facility regulations. Next, a review is undertaken for each product using the following criteria on the basis of the results of the review of GMP compliance for each article in the control regulations and building and facility regulations:

- Compliance: Cases of A only.
- General compliance: Cases of A and B or B only.
- Improvement required: Cases of C evaluated for half or less of all items and no D, unless categorized "Compliance" or "General compliance."
- Non-compliance: Cases not corresponding to any of the above.

When GMP compliance by product is determined as "General compliance" or "Improvement required," an order for improvement(s) for the item(s) rated as B is issued in writing.

In such cases, the applicant must submit a concrete plan of improvements. When improvements are completed, a report on

the improvement must be submitted. When the improvements have been confirmed, the rating of the corresponding item is changed to "Compliance."

The results of reviews or assessments at each of the above stages are compiled, and a report of the GMP compliance review is prepared for the plant in the application concerned. When the initial GMP compliance review results of a product correspond to "General compliance" or "Improvement required," the subsequent course is entered in the GMP compliance review report.

4.2 Mutual Recognition of GMP

Japan has concluded mutual agreements for GMP approvals with countries with equivalent levels of GMP. These agreements are meant to assure the quality of drugs imported into Japan through mutual acceptance of GMP inspection results and exchange of information on drugs distributed in the two countries. These mutual agreements have been concluded with Germany, Sweden, Switzerland and Australia. Mutual recognition of drug GMP with the EU countries had been limited to Germany and Sweden, but the agreement has been expanded to include the 15 EU countries (Belgium, Denmark, Germany, Greece, Spain, France, Ireland, Italy, Luxembourg, Netherlands, Austria, Portugal, Finland, Sweden and the United Kingdom) as well as 10 new EU countries (Poland, Hungary, Czech Republic, Slovenia, Slovakia, Estonia, Latvia, Lithuania, Cyprus and Malta) for 25 countries in total since May 29, 2003 (Notification No. 0528001 of the Compliance and Narcotics Division, PFSB dated May 28, 2004, Notification No. 0528004 of PFSB dated May 28, 2004, and Notification No. 0428001 of PFSB dated April 28, 2004).

4.3 Regulations for Imported Drug Management and Quality Control

Since it is very important to assure the quality of imported drugs in the same way as drugs manufactured in Japan, items related to manufacturing control and quality control when importers and markets import drugs were specified in Import Control and Quality Control of Drugs and Quasi-drugs were specified (MHW Ordinance No.62, June 2, 1999) and enacted on August 1, 1999, but since the import business license has been including in the manufacturing/distribution business license, this was abolished on March 31, 2005. Instead, from April 1, 2005, import certificate needs to be submitted for custom clearance prior to the import of products when the manufacturer/distributor or manufacturer import drugs for business.

These regulations included matters to be agreed upon with the manufacturer in the exporting country by the importer in accordance with the agreement. The

importer must confirm that the drug to be imported is manufactured under appropriate manufacturing control and quality control, and must import, store and distribute drugs and conduct testing in accordance with standards, etc.

When a mutual agreement for GMP approvals has been concluded between the exporting country and Japan, part of the quality control work may be omitted if the following two conditions are met. One is that it is confirmed by the government organization in the exporting country, that the plant where the imported drug was manufactured complies with the GMP in the country. The other is that the records of tests performed by the manufacturer of the drug are provided to the importer in Japan.

5. OTHERS

5.1 Biotechnological Products

In December 1986, Guidelines for Manufacturing Drugs by Recombinant DNA Technology were published by the MHW (Notification No. 1051 of the PAB dated December 11, 1986. The guidelines were intended to assure the quality of drugs manufactured using recombinant DNA technology and guarantee safety during the manufacturing process by specifying four levels of safety for recombinants (living cells) i.e. GILSP (Good Industrial Large Scale Practice), Category 1, Category 2, and Category 3, at the manufacturing stage based on the degree of safety. These guidelines also specify the establishment of an institutional biosafety committee, the appointment of a biological safety officer (BSO), and supervision by a product security pharmacist. Manufacturers may submit approval applications for manufacturing plans to the Minister of the MHLW, but this procedure has also been revised Notification No. 769 of the PAB dated August 18, 1995. On February 19, 2004, the Law for Securing Multiplicity of Living Organisms under the Use Control of Genetically-engineered Living Organisms (Law No. 97 dated June 18, 2003) came into effect and the Guidelines for Manufacturing Drugs by Recombinant DNA Technology (Notification No. 1051) was abolished.

A notification entitled "Handling Clinical Trial Protocol Notifications, Manufacturing Approvals and License Applications for Drugs Manufactured by Recombinant DNA Technology" was originally issued as Notification No. 62 of the First Evaluation and Regulation Division, PAB dated December 11, 1986 and later revised as Notification No. 12 of the First Evaluation and Regulation Division, PAB dated May 21, 1987. Another notification, Preparation of Data Required for Approval Applications for Drugs Manufactured by Recombinant DNA Technology was issued as Notification No. 243 of the Evaluation and Regulation Division, PAB dated March 30, 1984.

Preparation of Data Required for Approvals Applications for Drugs Manufactured by Cell Culture Technology was issued as Notification No. 10 of the First Evaluation and Regulation Division, PAB dated June 6, 1988.

In addition, the following ICH guidelines were issued: Guideline on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH S6) (Notification No. 326 of the Evaluation and Licensing Division, PMSB dated February 22, 2000), Guideline on Viral Safety Evaluation of Human or Animal Cell-Derived Pharmaceuticals (ICH Q5A, currently Q5A(R1)) (Notification No. 329 of the Evaluation and Licensing Division, PMSB dated February 22, 2000), and Guideline on the Origin, Control, and Analysis of the Properties of Biological Products (Drugs Applying Biotechnology/Drugs Originating from Living Organisms) (ICH Q5D) (Notification No. 873 of the Evaluation and Licensing Division, PMSB dated July 14, 2000).

Another notification issued concerning biological products is Guidelines to Assure the Quality and Safety of Drugs for Gene Therapy (Notification No. 1062 of PAB dated November 15, 1995, partially revised in Notification No. 0329004 of PMSB dated March 29, 2002).

5.2 Drugs Using Materials of Human or Animal Origin as Ingredients (Biological Products)

It is necessary to take measures to assure quality and safety based on current scientific levels for drugs manufactured using materials of human or animal origin as raw materials. Therefore, the Biotechnology Committee of the Council on Drugs and Food Sanitation established “Basic concepts for the handling and use of drugs and devices utilizing cells or tissues” (December 1, 2000) and “Guidelines for assurance of quality and safety of drugs and devices processed from cells and tissues of human origin” (December 1, 2000) (Notification No. 1314 of the PMSB dated December 26, 2000). In addition, various notifications have been issued, manufacturers have been requested to undertake self-inspection and coordinate application documents, and safety measures have been specified. For ingredients of bovine origin in particular, notifications have been issued as required in accordance with worldwide risk conditions and measures to assure quality and safety have been strengthened [refer to Chapter2, 6.4 “Safety measures for bovine spongiform encephalopathy (BSE)]. Biological products and specified biological products were newly defined in the revised Pharmaceutical Affairs Law dated July 31, 2002 and measures to assure safety when there is a risk of infection have been designated.

5.3 Public Disclosure of Information on New Drug Development

A notification concerning publication of information on new drug approvals was issued (No. 1651 of the Evaluation and Licensing Division, PMSB dated November 11, 1999), and New Drug Approval Information Packages containing summary reviews prepared by the MHLW and nonclinical and clinical data submitted by the applicant have been published. From July 1, 2003, applications using the CTD will become obligatory and the methods of submitting data have been changed as specified in "Disclosure of Information concerning Approval Reviews of New Drugs" (Notification No. 0529003 of the Evaluation and Licensing Division, PMDA dated May 29, 2002). Basic procedures for submission and disclosure have also been specified (Notification No. 0422001 of the Evaluating and Licensing Division, PFSB dated April 22, 2005, Notification No. 042204 of the PMDA dated April 22, 2005, and Notification No. 1126005 of the Licensing and Evaluation Division of PFSB dated November 26, 2007).

"Collaborative policies on disclosure of clinical trial information via clinical trial registration records and databases" was issued on January 6, 2005 as a joint communiqué by four organizations: International Federation of Pharmaceutical Manufacturers Associations (IFPMA), Pharmaceutical Research and Manufacturers of America (PhRMA), European Federation of Pharmaceutical Industry Associations (EFPIA) and Japan Pharmaceutical Manufacturers Association (JPMA). These policies declared that registration for all clinical trials except exploratory studies must be disclosed and information on the results of all studies (except exploratory studies) on drugs approved or marketed in at least one foreign country must be disclosed.

Based on these policies, the Ministry of Education, Culture, Sports, Science and Technology in Japan initiated the UMIN Clinical Trial Registration System (UMIN-CTR; http://www.umin.ac.jp/ctr/index.htm) and the MHLW publishes information on clinical trials via "Clinical trial information" (http://www.clinicaltrials.jp/user/cte_main_e.jsp), a database for registration and disclosure of clinical trial information through cooperation with the Japan Pharmaceutical Information Center and JPMA.

Using these systems, pharmaceutical companies disclose information on clinical trials with adequate consideration given to privacy of individual subjects, intellectual property rights and contractual rights in order to improve the transparency of clinical trials.

5.4 ICH (International Conference on Harmonization of Technical Requirements for Registration of

Pharmaceuticals for Human Use)

In order to supply excellent drugs developed all over the world to patients, it is essential to avoid unnecessary repetition of tests on quality, efficacy and safety, and achieve international acceptance of such test data. Achieving this goal will not only make approval reviews faster and more efficient but also promote R&D, and urgent measures are required to realize this objective.

Therefore, the three main (tripartite) regions, Japan, the United States and the EU, have organized the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) with the harmonization of quality, efficacy and safety as the main topic, based on the cooperation of the tripartite pharmaceutical regulatory authorities and industry groups. ICH policies are drafted by a steering committee consisting of members from six groups, namely regulatory authorities and pharmaceutical industry organizations in the EU, Japan and the United States. Members include the Food and Drug Administration (FDA), Pharmaceutical Research and Manufacturers of America (PhRMA), the European Medicines Agency (EMEA), European Federation of Pharmaceutical Industries' Associations (EFPIA), Ministry of Health, Labor, and Welfare (MHLW) and the Japan Pharmaceutical Manufacturers Association (JPMA). The World Health Organization (WHO), Canada and the European Free Trade Association (EFTA) attend the steering committee meetings as observers. The International Federation of Pharmaceutical Manufacturers Associations (IFPMA) serves as secretariat of the ICH. At present, ICH has taken up about 50 topics, and established expert working groups consisting of specialists representing the six groups and government officials on each topic.

The ICH meeting where its results are announced and discussed has been held six times in the past.

ICH-1: Brussels, Belgium in November 1991.

ICH-2: Orlando, Florida, United States in October 1993

ICH-3: Yokohama, Japan in November 1995.

ICH-4: Brussels, Belgium in July 1997

ICH-5: San Diego, California, United States in November 2000

ICH-6: Osaka, Japan in November 2003.

Over 60 guidelines have been approved through ICH activities. The guideline on common technical documents aimed at standardization of approval application forms, which was thought to be impossible to achieve when the ICH was founded, reached final approval at ICH-5. The harmonization, the initial goal of ICH, is now almost completed. The eCTD (electronic CTD) has been incorporated

into the Japanese regulations.

The most important agreements reached by ICH to date have concerned standardization of pharmaceutical-related terminology. MedDRA was prepared for standardization of pharmaceutical-related terminology in the three regions. Definitions of adverse events affecting humans (undesirable events occurring after drug administration, including adverse reactions) have been defined in each region beforehand. It has been agreed that the company that receives the first approval in the world for a drug product with a new active ingredient collects safety information on the new active ingredient locally and overseas and prepares periodic safety update reports (PSUR).

In the future, new problems will be discussed, such as new guidelines for products applied in cutting-edge advanced technology including drugs for gene therapy and harmonization initiatives in non-ICH regions.

Harmonization by the ICH progresses in five steps known as the ICH process.

Step 1: Selection of topics to be studied. Establishment of expert working groups, and preparation of draft guidelines

Step 2: Approval of draft ICH guidelines by the steering committee. Collection of opinions on draft guidelines in each country

Step 3: Revision of guidelines based on the collected opinions

Step 4: Establishment of ICH guidelines by the steering committee

Step 5: Adoption of these guidelines in the domestic regulatory

As of May 2007, over 60 guidelines have been approved (Step 4 or 5) based on ICH activities.

QUALITY

Q1A: Stability Testing (Drugs with New Active Ingredients)

Q1AR: Stability Testing of New Drug Substances and Products (Partly Revised)

Q1A(R2): Stability Testing of New Drug Substances and Products (Partly Revised)

Q1B: Stability Testing: Photostability Testing of New Drug Substances and Products

Q1C: Stability Testing for New Dosage Forms

Q1D: Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products

Q1E: Stability Testing: Evaluation of Stability Data

Q2(R1): Text on Validation of Analytical Procedures: Test items and test procedures

Q3A(R2): Impurities: in New Drug Substances: Bulk drugs (Guidelines and Partial Amendment)

Q3B(R2): Impurities in New Drug Products (Guidance and Partial Amendment)

Q3C(R3): Impurities: Guidelines for Residual Solvents (Guidance and Partial Amendment)

Q5A(R1): Quality of Biotechnological Products: Viral safety Evaluation

Q5B: Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of R-DNA Derived Protein Products

Q5C: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products

Q5D: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products

Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process

Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products (Chemical Substances)

Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

Q8: Pharmaceutical Development

Q9: Quality Risk Management

NON-CLINICAL

S1A: Guidelines on the Need for Carcinogenicity Studies of Pharmaceuticals

S1B: Testing for Carcinogenicity of Pharmaceuticals

S1C(R1): Dose Selection for Carcinogenicity Studies of Pharmaceuticals (Guidance and Addendum)

S2A:Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals

S2B: Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals

S3A: Note for Guidance on Toxicokinetics: the Assessment of Systemic Exposure in Toxicity Studies

S3B: Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies

S4: Duration of Chronic Toxicity Testing in Animals (Rodent and Non-Rodent Toxicity Testing) (Guidance and Partial Amendment)

S5(R2): Detection of Toxicity to Reproduction for Medicinal Products (Guidelines and Partial Amendment)

S6: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

S7A: Safety Pharmacology Studies for Human Pharmaceuticals

S7B: Nonclinical Evaluation of Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals (Revision: Step 2)

S8: Immunotoxicity Studies for Human Pharmaceuticals

EFFICACY

E1: Recommendations on the Numbers of Patients and Duration of Exposure for the Safety Evaluation of Drugs Intended for the Long-term Treatment of Non-life-threatening Conditions

E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting

E2BM: Clinical Safety Data Management: Report Forms

E2C(R1): Clinical Safety Data Management: Periodic Safety Update Reports

E2D: Post-approval Safety Management: Definitions and Standards for Expedited Reporting

E2E: Pharmacovigilance Planning (PvP)

E3: Clinical Study Reports: Structure and Content

E4: Dose-Response Information to Support Drug Registration

E5(R1): Ethnic Factors in the Acceptability of Foreign Clinical Data (Guidance and Q&A)

E6(R1): GCP (Good Clinical Practice): Consolidated Guidelines and Its Implementation

E7: Guidelines on Clinical Trials in Special Populations: Geriatrics

E8: General Considerations for Clinical Trials

E9: Statistical Principles for Clinical Trials

E10: Choice of Control Group and Related Issues in Clinical Trials

E11: Clinical Investigation of Medicinal Products in the Pediatric Population

E12: Principles for Clinical Evaluation of New Antihypertensive Drugs

E14: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs

Multidisciplinary Topics

M1: Medical Terminology

M2: Electronic Standards for Transmission of Regulatory Information

M2 (eCTD): Electronic Common Technical Document Specification

M3(R1): Maintenance of the ICH Guideline on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

M4: Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use

M4Q: Quality

M4S: Safety

M4E: Efficacy

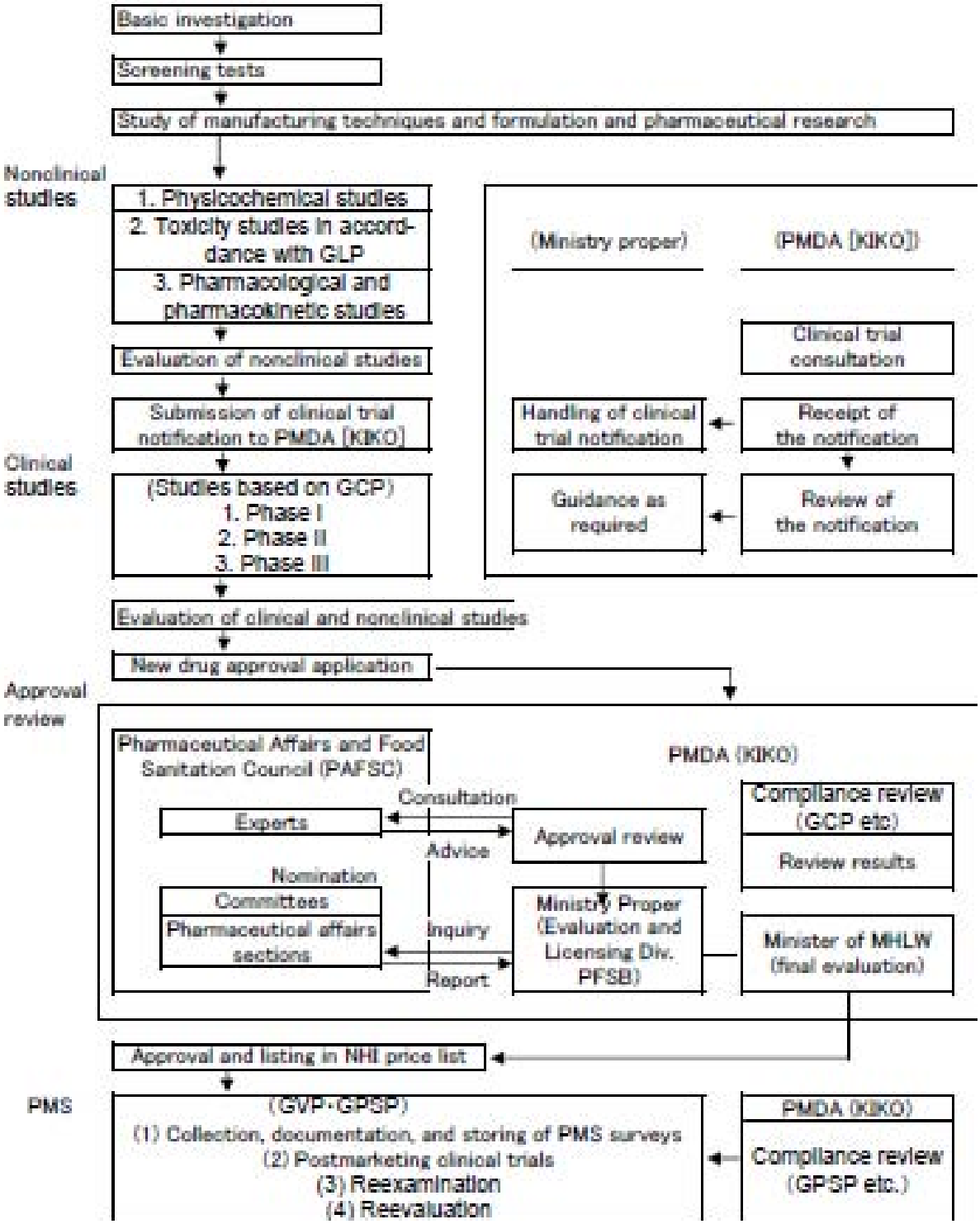


Fig. 7 Flowchart of New Drug Development and Approval

Table 3 Data to be Submitted with an Application for Approval to Manufacture/Distribute: a New Prescription Drug (Attached Table 2-1 in PFSB Notification No. 0331015 dated March 31, 2005)

Data and drugs		1. New drug	2. New combination	3. New route	4. New indication	5. New formulation	6.New dosage	7 Additional formulation	8. Similar composition	9. Other
a	1. Origin	○	○	○	○	○	○	○	○	×
	2. Foreign country	○	○	○	○	○	○	○	○	×
	3. Comparison	○	○	○	○	○	○	○	○	×
b	1. Structure	○	×	×	×	×	×	×	×	×
	2. Manufacture	○	○	○	×	○	×	○	○	♦
	3. Specifications	○	○	○	×	○	×	○	○	○
c	1. Long-term	○	○	○	×	○	×	♦	○	×
	2. Severe	○	○	○	×	○	×	♦	○	×
	3. Accelerated	○	○	○	×	○	×	○	○	○
d	1. Efficacy	○	○	○	○	×	○	×	♦	×
	2. Safety	○	♦	♦	×	×	×	×	♦	×
	3. Other	♦	♦	♦	×	×	×	×	×	×
e	1. Absorption	○	○	○	♦	○	○	×	×	×
	2. Distribution	○	○	○	♦	○	○	×	×	×
	3. Metabolism	○	○	○	♦	○	○	×	×	×
	4. Excretion	○	○	○	♦	○	○	×	×	×
	5. Bioequivalence	×	×	×	×	×	×	○	×	○
	6. Other	♦	♦	♦	♦	♦	♦	×	×	×
f	1. Single dose	○	○	○	×	×	×	×	○	×
	2. Repeated dose	○	○	○	×	×	×	×	♦	×
	3. Genotoxicity	○	×	×	×	×	×	×	×	×
	4. Carcinogenicity	♦	×	♦	×	×	×	×	×	×
	5. Reproductive toxicity	○	×	○	×	×	×	×	×	×
	6. Local irritation	♦	♦	♦	×	×	×	×	♦	×
	7. Other	♦	×	♦	×	×	×	×	×	×
g	Clinical	○	○	○	○	○	○	×	○	×

○: Date required ×: Data not required ♦: Data required depending on individual cases

a. Origin or background of discovery, conditions of use in foreign countries	1. Origin or background of discovery 2. Conditions of use in foreign countries 3. Special characteristics, comparisons with other drugs, etc.
b. Manufacturing methods, standards and test methods	1. Chemical structure and physicochemical properties, etc. 2. Manufacturing methods 3. Standards and test methods
c. Stability	1. Long-term storage tests 2. Tests under severe conditions 3. Accelerated tests
d. Pharmacological action	1. Tests to support efficacy 2. Secondary pharmacology, Safety pharmacology 3. Other pharmacology
e. Absorption, distribution, metabolism, and excretion	1. Absorption 2. Distribution 3. Metabolism 4. Excretion 5. Bioequivalence 6. Other pharmacokinetics
f. Acute, subacute, and chronic toxicity, teratogenicity, and other types of toxicity	1. Single dose toxicity 2. Repeated dose toxicity 3. Genotoxicity 4. Carcinogenicity 5. Reproductive toxicity 6. Local irritation 7. Other toxicity
g. Clinical studies	Clinical trial results

Table 4 Data to be Submitted with an Application for a Non-prescription Drug (Attached Table 2-2 in PFSB Notification No. 0331015 dated March 31, 2005)

Data and drugs		1. New ingredients	2. New ingredients for non-prescription drug	3. New combi- nation	4. Other
a	1. Origin	○	○	○	×
	2. Foreign country	○	○	○	×
	3. Comparison	○	○	○	○
b	1. Structure	○	×	×	×
	2. Manufacturing methods	○	×	×	×
	3. Specifications	○	○	○	○
c	1. Long-term	○	♦	♦	♦
	2. Severe	○	×	×	×
	3. Accelerated	○	♦	♦	♦
d	1. Efficacy	○	×	×	×
	2. Safety	○	×	×	×
	3. Other	♦	×	×	×
e	1. Absorption	○	♦	♦	♦
	2. Distribution	○	×	×	×
	3. Metabolism	○	×	×	×
	4. Excretion	○	×	×	×
	5. Bioequivalence	×	×	×	×
	6. Other	♦	×	×	×
d	1. Single dose	○	♦	♦	♦
	2. Repeated dose	○	♦	♦	♦
	3. Genotoxicity	○	×	×	×
	4. Carcinogenicity	♦	×	×	×
	5. Reproductive toxicity	○	×	×	×
	6. Local irritation	♦	♦	♦	×
	7. Other	♦	♦	×	×
g	Clinical	○	○	○	×

○: Date required ×: Data not required ♦: Data required depending on individual cases

(1) Drugs with new active ingred-ients	(2) Drugs with active ingredients other than new active ingredients, but which include ingredients which have never been used as active ingredients in any approved non-pre-sciption drug (“new ingredients of non-pre-scription drugs”)	(3) (3) Drugs with a combination of active ingredients which have not been used as active ingredients in approved non-prescription drugs, as specified in the following categories (except for drugs which are the subject of approval applications): (a) Drugs with new combined ingredients which have never been approved as active ingredients in the same therapeutic category (except for new combination ingredients that have mild pharmacological action(s) and do not alter intended therapeutic action) (b) Drugs with a combination of active ingredients with indications and/or dosage and administration different from those of already approved non-prescription drugs in the same therapeutic category (c) Drugs with active ingredients different in formulation from those of already approved non-prescription drugs in the same therapeutic category	(4) Other drugs (a) The drugs with a combination of ingredients which have mild pharmacological action(s) and do not alter intended therapeutic action or which are the subject of approval applications after completion of the evaluation of safety during the use of drugs (1), (2), and (3) in this table (“new non-prescription drugs”) which contain an ingredient different(s) from already approved non-prescription drugs in the “new active ingredient(s),” “new ingredient(s) of non-prescription drugs,” “a combination of active ingredients that differs in pharmacological action(s),” or “apparently different formulation” from that already approved as non-prescription drug(s) in the same therapeutic class (b) Drugs that do not fall in categories (a) above as well as (1), (2), or (3)

a. Origin or background of discovery, conditions of use in foreign countries	1. Origin or background of discovery 2. Conditions of use in foreign countries 3. Special characteristics, comparisons with other drugs, etc.	
b. Manufacturing methods, standards and test methods	1. Chemical structure and physicochemical properties, etc. 2. Manufacturing methods 3. Standards and test methods	
c. Stability	1. Long-term storage tests 2. Tests under severe conditions 3. Accelerated tests	
d. Pharmacological action	1. Tests to support efficacy 2. Secondary pharmacology, Safety pharmacology 3. Other pharmacology	
e. Absorption, distribution, metabolism, and excretion	1. Absorption 2. Distribution 3. Metabolism	4. Excretion 5. Bioequivalence 6. Other ADME
f. Acute, subacute, and chronic toxicity, teratogenicity, and other type of toxicity	1. Single dose toxicity 2. Repeated dose toxicity 3. Genotoxicity 4. Carcinogenicity	5. Reproductive toxicity 6. Local irritation 7. Other
g. Clinical studies	Clinical trial results	

Table 5 Classification of Clinical Studies According to Objectives

Type of study	Objective of study	Study examples
Human pharmacology	• Assess tolerance • Define/describe PK[1)] and PD[2)] • Explore drug metabolism and drug interactions • Estimate activity	• Dose-tolerance studies • Single and multiple dose PK and/or PD studies • Drug interaction studies • ADME studies
Therapeutic exploratory	• Explore use for the targeted indication • Dose-response exploration studies • Provide basis for confirmatory study design, endpoints, methodologies	• Earliest studies of relatively short duration in well-defined narrow patient populations, using surrogate or pharmacological endpoints or clinical measures
Therapeutic confirmatory	• Demonstrate/confirm efficacy • Establish safety profile • Provide an adequate basis for assessing the benefit/risk relationship to support licensing	• Adequate, and well controlled studies to establish efficacy • Clinical safety studies • Large simple studies
Therapeutic use	• Refine understanding of benefit/risk relationship in general or special populations and/or environments • Identify less common adverse reactions • Refine dosing recommendation	• Comparative effectiveness studies • Studies of mortality/morbidity outcomes • Large simple studies • Pharmacoeconomic studies

1) Pharmacokinetics
2) Pharmacodynamics

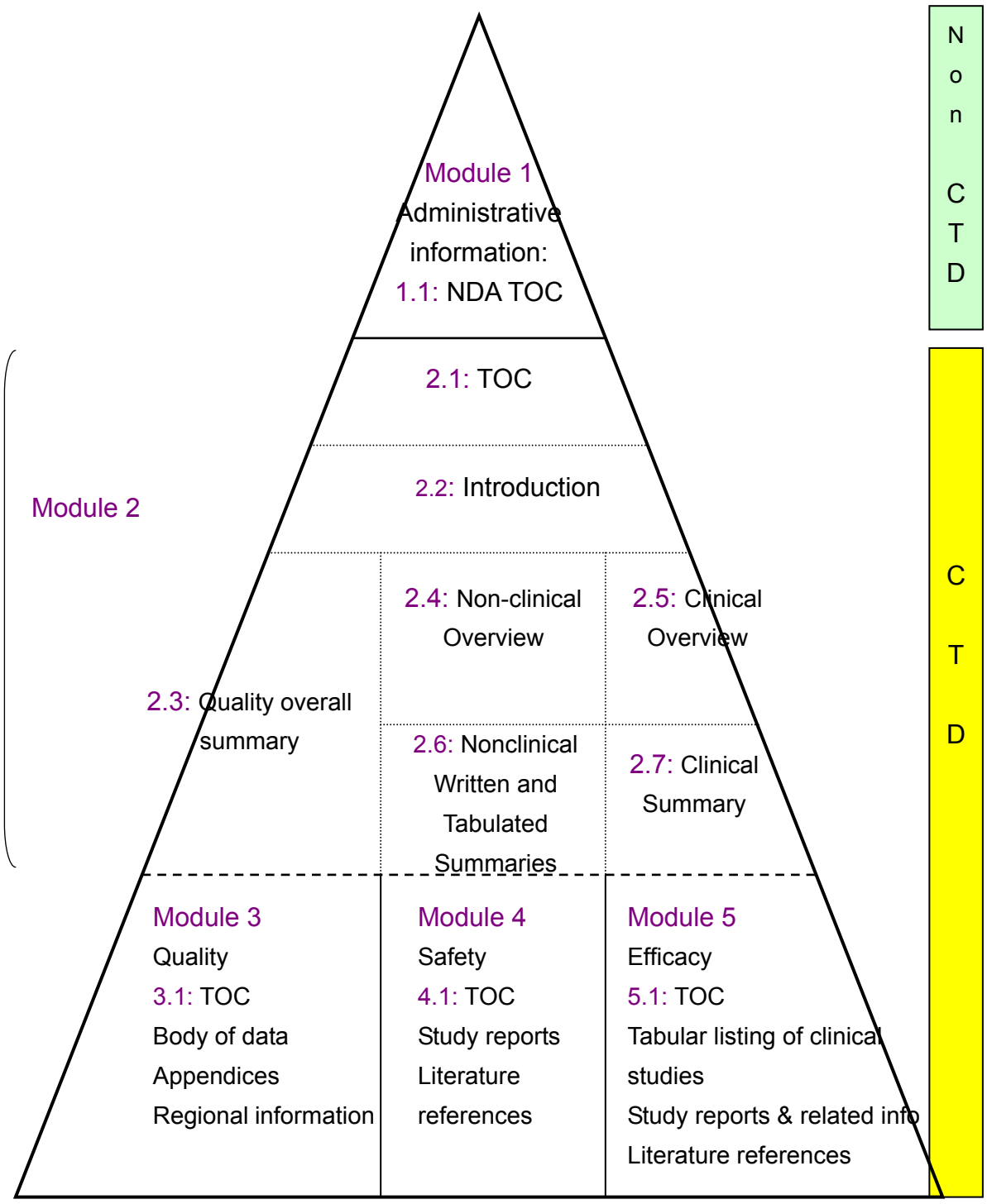


Fig. 8 Organization of ICH Common Technical Documents

The Common Technical Document is organized into five modules. Module 1 is region specific. Modules 2, 3, 4, and 5 are intended to be common for all regions. Conformance with this guidance should ensure that these four modules are provided in a format acceptable to the regulatory authorities.

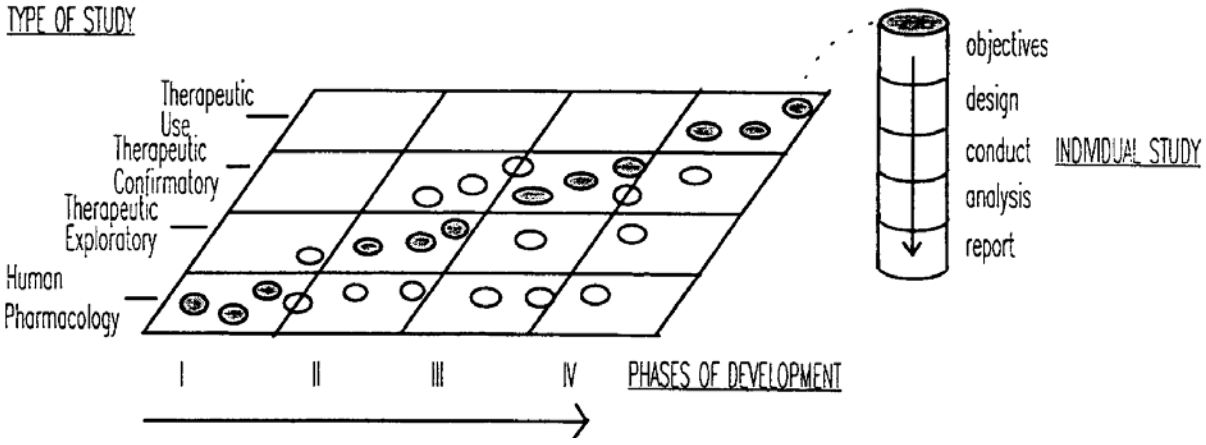


Fig. 9 Correlation between Development Phases and Types of Study

This matrix graph illustrates the relationship between the phases of development and types of study by objective that may be conducted during each clinical development of a new medicinal product. The shaded circles show the types of study most usually conducted in a certain phase of development, the open circles show certain types of study that may be conducted in that phase of development but are less usual. Each circle represents an individual study. To illustrate the development of a single study, one circle is joined by a dotted line to an inset column that depicts the elements and sequence of an individual study.

CHAPTER 4

Post-marketing Surveillance of Drugs

Post-marketing surveillance (PMS) to assure the efficacy and safety of drugs after they go on the market consists of three systems: the ADR reporting system, the reexamination system, and the reevaluation system (**Fig. 10.** Pharmaceutical Post-marketing Surveillance System).

Good Post-marketing Surveillance Practice (**GPMSP**) came into effect from April 1993 to assure proper implementation of PMS and also to assure the reliability of such PMS data. Thereafter, major revisions were made in the Pharmaceutical Affairs Law and its Enforcement Regulations in 1996 to 1997 to further strengthen post-marketing safety measures, and the GPMSP, which had formerly been considered as an administrative notification, became law and came into effect on April 1, 1997 (MHW Ordinance No. 10 date March 10, 1997). The Drug GPMSP was partially revised by MHW Ordinance No. 151 dated December 27, 2000, and "Early Post-marketing Surveillance" for new drugs was newly established. Post-marketing surveillance related to reexaminations has also been revised (to be enforced from October 1, 2001).

The GPMSP is applied as standards requiring compliance by manufacturers or importers when performing post-marketing surveillance or studies, and also as compliance criteria for preparation of data.

To assure the safety of drugs after marketing, the periodic safety update report (PSUR) system was introduced by Notification No. 32 of the Safety Division, Pharmaceutical and Medical Safety Bureau dated March 27, 1997 and the Guidelines on Methods for Surveillance of Results of Use of Prescription Drugs (Notification No. 34 of the Safety Division, Pharmaceutical and Medical Safety Bureau dated March 27, 1997) were specified. However, because of an increase in post-marketing ADRs not observed in the clinical trial stage of drug development and implementation of safety measures, regulations on safety measured for drugs (Notification No. 25 of the Safety Division, Pharmaceutical and Medical Safety Bureau) and entries in case report forms for ADRs and infections were specified in March 11, 1998. Furthermore, a new guideline, Implementation of Early Post-marketing Surveillance for Prescription Drugs (Notification No. 0324001, the Safety Division, PFSB dated March 24, 2006) to further strengthen the safety monitoring of medical products (Figure 12. Post-marketing Collection and Reporting of Pharmaceutical Safety

Information).

The system of reporting adverse reactions and infections and periodic safety reporting also became law.

In the revised Pharmaceutical Affairs Law enforced on April 1, 2004, there is a separation between the part that deals with the collection, preparation and consideration of information for appropriate use of post-marketing safety measures of the MHLW Ordinance on GPMSP related to the implementation of safety assurance measures, and the part that deals with tests and surveillance conducted to collect and prepare materials for reexamination and reevaluation. The former has been specified in the MHLW Ordinance on GVP (MHLW Ordinance Related to Standards for Post-Marketing Safety Management of Drugs, Medical Devices, Cosmetics and Medical Devices, Ministerial Ordinance No. 135 dated September 22, 2004), and the latter in the MHLW Ordinance on GPSP (MHLW Ordinance Related to Standards for Conducting Post-Marketing Surveys and Studies on Drugs; Ministerial Ordinance No. 171 issued by MHLW on December 20, 2004). The MHLW Ordinance on GPMSP was abolished.

The use of MedDRA is recommended to standardize international regulatory-related medical terminology use at all regulatory levels before and after marketing for regulatory communication in registration, records, and safety monitoring of drugs. Efforts are being made to achieve international coordination of terminology related to pharmaceutical regulations (adverse reactions, signs and symptoms, diagnosis, indications, laboratory tests, surgical and conservative interventions and patient characteristics). Since the end of March 2000, it has been possible to use MedDRA for clinical trial data, reexamination and reevaluation data and package inserts. It is used in data input, retrieval, evaluation, and presentation at both the pre- and post-marketing regulatory stages for drugs. From October 27, 2003, it became obligatory to use MedDRA in individual case safety reports. MedDRA is maintained by the Maintenance and Support Organization (MSSO) and two new versions are generally published each year.

1. GPSP

GPSP (good post-marketing study practice) specifies items that are to be strictly complied with in order to achieve appropriate post-marketing surveillance and studies conducted by marketers, and to assure the reliability of data submitted when applying for reexamination or re-evaluation.

The GPSP consists of 12 articles, which are summarized below.

(1) Purpose (Article 1)

These standards set forth the items that must be strictly complied with by marketers of drugs in conducting post-marketing surveillance and

studies.

This GPSP applies to prescription drugs, with in-vitro diagnostics and drugs for patch tests excluded. For post-marketing clinical studies forming part of post-marketing surveillance, GCP is also applicable, in addition to GPSP.

(2) Definitions of Terms (Article 2)

The terms “post-marketing surveys, etc.,” “drug use-results survey,” “specified drug use survey,” and “post-marketing clinical study” which are used in these standards, are defined as follows:

[1] Post-marketing surveys, etc. refers to drug use-results surveys or post-marketing clinical studies that the marketer of drugs conducts in order to collect, screen, confirm or verify information relating to the quality, efficacy and safety of drugs.

[2] Among post-marketing surveys, drug use-results survey refers to a survey by the marketer to screen or confirm information related to the incidence of each disease due to adverse drug reactions, together with the quality, efficacy and safety of drugs, without specifying the condition of the patients that use the drugs.

[3] Among drug use result surveys, specified drug-use survey refers to a survey by the marketer to screen or confirm information relating to the incidence of each disease due to adverse drug reactions, together with the quality, efficacy and safety of drugs, in specified populations of patients, such as pediatric patients, elderly patients, pregnant women, patients with renal and/or hepatic disorders, and patients using the drug for long periods.

[4] Among post-marketing surveys, post-marketing clinical study refers to a clinical study performed to verify assumptions arrived at as a result of studies undertaken with regard to results of clinical studies or drug-use surveys, or studies conducted in accordance with approved dosage and administration, and indications to collect information on quality, efficacy and safety unobtainable in routine medical practice.

(3) Standard Operating Procedures for Post-marketing Surveillance (Article 3)

The following standard operating procedures for post-marketing surveillance shall be prepared and retained by the marketer for the proper and smooth conduct of post-marketing surveillance. The date must be

entered in the SOP manual when SOP are prepared or revised.

[1] Procedures related to drug use-results surveys

[2] Procedures related to post-marketing clinical studies

[3] Standards related to in-house inspections

[4] Procedures related to education and training of personnel involved in post-marketing surveys, etc.

[5] Procedures related to the outsourcing of duties in post-marketing surveys, etc.

[6] Procedures related to the preservation of records involving duties in post-marketing surveys, etc.

[7] Any other procedures necessary for appropriate and smooth implementation of post-marketing surveys, etc.

(4) Supervisor of Post-marketing Surveys, etc. (Article 4)

[1] A supervisor of the marketer must be appointed to coordinate the duties involved in post-marketing surveys, etc. (supervisor of post-marketing surveys, etc.).

[2] The supervisor of post-marketing surveys, etc. must not be a member of a department involved in marketing.

[3] Duties to be performed by the supervisor of post-marketing surveys, etc.:

- To prepare and preserve a basic protocol for post-marketing surveys, etc. for each drug individually.
- To set forth in writing protocols for the implementation of drug use-results surveys, protocol for post-marketing clinical studies, and any other matters necessary for conducting post-marketing surveys, etc.
- To revise the basic protocol for post-marketing surveys, etc. as required.
- In cases in which a basic protocol for post-marketing surveys, etc. is prepared or revised, to date and preserve it.
- When it is considered necessary for the conduct of post-marketing surveys, etc., to provide written opinions to the marketer, and to preserve these documents or copies thereof.

[4] The marketer must respect the opinions provided by the supervisor of post-marketing surveys, etc.

[5] The marketer must not make any statements that would interfere with the supervisor of post-marketing surveys, etc. in the performance of his or her duties.

(5) Post-Marketing Surveys, etc. (Article 5)

[1] The marketer's supervisor of post-marketing surveys, etc. must assure that the duties for implementation of post-marketing surveys, etc. are performed as set forth below:

- To prepare plans, proposals and surveys for implementation of post-marketing surveys, etc.
- To confirm that post-marketing surveys, etc. are conducted appropriately and satisfactorily in accordance with the standard operating procedures for duties for post-marketing surveys, etc. and the basic protocol on post-marketing surveys, etc.
- To provide notification in writing of the results of post-marketing surveys, etc.

[2] The marketer must arrange that, for both drug use-results surveys and post-marketing clinical trials, records are prepared and preserved in order that the supervisor of post-marketing surveys, etc. understands the conditions under which the surveys or tests were conducted.

(6) Drug Use-Results Surveys (Article 6)

[1] The marketer must instruct the supervisor or other designated person to conduct drug use-results surveys according to the post-marketing surveillance SOP and basic post-marketing survey protocol.

[2] Contracts in writing must be concluded with the medical institutions competent in conducting the drug use-results survey and preserved.

[3] Contract may be handled by electronically.

[4] In protocols for drug use-results surveys, the purpose of the survey, scheduled number of cases, controls, survey method, survey period, items surveyed, analytical method and other necessary matters must be established.

(7) Post-Marketing Clinical Studies (Article 7)

[1] Post-marketing studies must be performed by the post-marketing surveillance supervisor or other person designated by the marketer based on the post-marketing surveillance SOP or basic post-marketing survey protocol.

[2] The studies must be conducted in compliance with GCP

(8) In-House Inspections (Article 8)

[1] In-house inspections are to be conducted on a regular schedule. Items that have been audited based on GCP do not require in-house inspections.

In cases in which a person other than the supervisor of post-marketing surveys, etc. conducts an in-house inspection, the supervisor of post-marketing surveys, etc. is to be notified in writing of the results of the inspection.
Records of the results of the in-house inspection are prepared and preserved.

[2] Post-marketing surveillance supervisors must report in writing the results of the self-inspections to the marketer.

[3] When it is found that improvements must be made in the work based on the results of the self-inspection, the necessary measures must be taken, and records of these measures must be prepared and retained.

(9) Education and Training (Article 9)

The supervisor of post-marketing surveys, etc. or a person designated by the marketer, etc. must assure that the duties set forth below are conducted.

[1] Planned education and training related to post-marketing surveillance must be performed by the post-marketing surveillance supervisors or other persons designated by the marketer for persons employed in post-marketing surveillance work.

[2] In cases in which education and training are performed by a person other than the supervisor of post-marketing surveys, etc., the supervisor of post-marketing surveys, etc., is notified in writing of the conditions of its implementation.

[3] Records of education and training are prepared and preserved.

(10) Delegation of Duties of Post-marketing Surveys, etc, (Article 10)

Some of the duties of post-marketing surveys, etc may be delegated to persons who are capable of properly and effectively carrying out these activities.

(11) Preservation of Records in Connection with Post-marketing Surveys, etc. (Article 11)

Records of reexamination and reevaluation data must be retained for 5 years from the date that reexamination or reevaluation is completed. Other records must be preserved for 5 years from the date they are no longer in actual use or date of the final entry.

(12)Standards for **Compliance of Reexamination and Reevaluation Data** in Connection with Post-marketing Surveillance (Article 12)

In addition to provisions of the GCP MHLW Ordinance, the provisions of Article 3 through Article

8, Article 10, and Article 11 of this GPSP MHLW apply *mutatis mutandis* to the collection and preparation of data for reexamination and reevaluation applications in connection with post-marketing surveys, etc.

2. DATA COMPLIANCE SURVEYS AND COMPLIANCE SURVEYS OF MARRKETERS BASED ON GPSP

GPSP compliance surveys for reexamination and reevaluation application data and surveys to assess GPSP compliance status of marketers, including verification of reliability of the collection and preparation of data submitted to the Minister of the MHLW to report adverse drug reactions and infections, are implemented in accordance with the Guideline for Implementation of GPSP On-site Surveys (Notification No. 0330003 of the Evaluation and Licensing Division, PFSB dated March 30, 2005) established by the MHLW.

In compliance surveys related to reexaminations, the survey is performed by a survey group consisting of employees of the PMDA as a rule when an application for a GPSP on-site survey is received by the PMDA. Compliance surveys related to reevaluations are performed by a survey group consisting of employees of the PMDA under instructions from the MHLW.

Compliance status surveys are conducted by a survey team consisting of personnel from the Pharmaceutical and Food Safety Bureau of the MHLW or prefectural governments as a rule.

On the basis of survey reports prepared by each survey team, data compliance surveys are conducted by the PMDA and marketers' compliance surveys by the MHLW, and a determination of "compliance" or "non-compliance" is made and necessary measures are undertaken.

Paper reviews on compliance of reexamination and reevaluation data are performed by the PMDA in accordance with the provisions of Guidelines on Compliance Paper Reviews on Approval Application Data for New Drugs (Notification No. 0131010 of the PFSB dated January 31, 2006).

3. GVP

Good Vigilance Practice (GVP) establishes standards for post-marketing safety management related to the collection, preparation, and study of proper use information on drugs, etc., and to the implementation of measures for safety assurance.

This standard consists of 16 articles. A summary is provided below.

(1) Purpose (Article 1)

This Ministerial Ordinance establishes the standards established by the MHLW

Ordinance related to post-marketing safety management set forth in Article 12-2, Paragraph 2 of the Pharmaceutical Affairs Law.

(2) Definitions of Terms (Article 2)

[1] Safety management information refers to material relating to the quality, efficacy or safety of drugs etc., and any other information required for the proper use of drugs, etc.

[2] Quality assurance activities refers to any activity related to post-marketing quality control concerned with requisite measures based on the collection and study of safety management information, or on the results.

[3] Early post-marketing surveillance refers to any safety assurance activities that are performed within a period of 6 months following commencement of marketing by the marketer of a drug in order to promote proper use of the drug in medical treatment, and to quickly identify the occurrence of serious adverse drug reactions, etc. It is specified as a condition of approval.

[4] Person in charge of drug information and person in charge of medical device information refer to persons whose main duties consist of collecting and providing safety assurance information through visits to health care professionals in order to contribute to the proper use of drugs or medical devices.

Articles 3 to 12 are specified for the first type of marketer (marketers of prescription drugs and highly controlled medical devices).

(3) Duties of General Marketing Compliance Officer (Article 3)

The general marketing compliance officer must undertake the following duties.

[1] To supervise the safety management supervisor.

[2] To respect the opinions of the safety management supervisor.

[3] To assure close coordination with the safety management supervisor, quality assurance supervisor, and other persons responsible for duties involving manufacturing and distribution of prescription drugs or highly controlled medical devices.

(4) Organizations and Personnel Involved in Safety Assurance (Article 4)

[1] A department (safety management department) meeting the following requirements must be established

to handle all duties related to safety assurance.

- This department is under the supervision of the general manufacturing/distribution supervisor
- This department must employ adequately qualified and competent personnel who are able to undertake safety assurance activities properly and smoothly.
- This department should be independent of all divisions responsible for marketing drugs and other departments that would hinder proper and smooth safety assurance activities.

[2] A safety management supervisor meeting the following requirements must be appointed.

- The safety management supervisor is the supervisor of the safety management department.
- This supervisor must have been engaged for at least 3 years in safety assurance work or related work.
- This supervisor must have the ability to properly and smoothly undertake safety assurance activities.
- This supervisor must not belong to any division responsible for marketing drugs, etc.

[3] When all or part of the safety assurance activities are undertaken by persons other than the safety management supervisor, a supervisor of the work concerned (safety management implementation supervisor) must be appointed.

(5) **Standard Operating Procedures for Post-marketing Surveillance** (Article 5)

[1] The following standard operating procedures for post-marketing safety management must be prepared.

- Procedures for collection of safety management information
- Procedures for drafting of safety assurance measures based on examination of safety management information and the results thereof
- Procedures for implementation of safety assurance measures
- Procedures for reporting from safety management supervisors to general marketing compliance officer
- Procedures for early

post-marketing surveillance

- Procedures for in-house inspections
- Procedures for education and training
- Procedures for retention of records
- Procedures for contacts with quality assurance supervisors and other supervisors engaged in work related to marketing of prescription drugs and highly controlled medical devices
- Other procedures necessary for properly and smoothly implementing safety assurance measures of post-marketing surveillance

[2] The duties and management system for persons employed for work related to post-marketing safety management must be specified in writing.

[3] Items required for appropriate and smooth implementation of safety assurance activities must be specified in writing.

[4] When the procedures in (1) or the documents in (2) and (3) are prepared or revised, they must be dated and retained.

[5] The general marketing compliance officer shall make available the procedures in (1), the documents in (2) and (3) and other documents required for safety assurance work in the office performing the work and also must make available copies of procedures and other related documents in other offices performing safety assurance work.

(6) Duties of the safety management supervisor (Article 6)

- Overall supervision of safety assurance work
- Confirmation that safety assurance work is being performed appropriately and smoothly and preparation and retention of records of such confirmation
- Offering of opinions in writing to general marketing compliance supervisor when safety assurance work is required and retention of copies of such opinions

(7) Collection of safety management information (Article 7)

[1] The following safety management information shall be collected by the safety management supervisor and safety management implementation supervisor and records shall be prepared thereof.

- Information from health professionals
- Information on reports presented at scientific meetings, reports from the

literature and other research reports

- Information from the Ministry of Health, Labor and Welfare, other government institutions, prefectural governments and organizations
- Information from foreign governments and overseas organizations
- Information from other pharmaceutical manufacturers/distributors
- Other safety management information

[2] The safety management implementation supervisor shall report the records in (1) in writing to the safety management supervisor.

[3] The safety management supervisor shall preserve the records in (1) and reports in (2).

(8) Drafting of safety assurance measures based on examination of safety management information and the results thereof Article 8)

[1] The safety management supervisor shall perform the following duties.

- Examine the collected safety management information without delay and record the results thereof.
- Supply all safety information that the quality assurance supervisor must be familiar with in writing without delay to the quality assurance supervisor.
- When it is confirmed necessary from an examination of safety management information, measures shall be drafted to discard, recall or suspend distribution of the product, revise package inserts, supply information to health professionals by persons in charge of drug or medical device information, reports to the Minister of Health, Labor and Welfare and other safety assurance measures.
- Drafts of safety assurance measures shall be reported in writing to the general marketing compliance officer and copies shall be retained.

[2] When the safety management supervisor has the safety management implementation supervisor examine safety management information, he or she shall issue instructions in writing and retain a copy. Records of the examination performed by the safety

management implementation supervisor shall be prepared and reported in writing. The safety management supervisor shall retain these results.

(9) Implementation of safety assurance measures (Article 9)

[1] The general marketing compliance officer must undertake the following duties.

- Appropriately evaluate drafts of safety assurance measures, decide the safety assurance measures to be taken and prepare and retain records thereof.
- When safety management supervisors undertake safety assurance measures, instructions shall be issued in writing and retained
- When safety management implementation supervisors undertake safety assurance measures, instructions shall be issued in writing and the safety management implementation supervisor shall retain copies. The safety management implementation supervisor shall prepare records and make reports in writing. Copies shall be given to the safety management supervisor.

[2] The following duties must be undertaken by the safety management supervisor.

- Safety assurance measures shall be undertaken based on instructions from the general marketing compliance officer and records thereof shall be prepared and retained.
- When safety assurance measures are undertaken by safety management implementation supervisors, instructions shall be issued in writing and copies shall be retained. Records shall be prepared, reported in writing and retained.
- The results of implementation of safety assurance measures shall be reported in writing to the general marketing compliance officer, and a copy shall be retained.
- Copies of reports from the safety management implementation supervisor shall be retained.

[3] Evaluation of drafts of safety assurance measures for which post-marketing safety management standard operating procedures have been specified beforehand, deciding on safety assurance measures to be taken,

and preparation and retention of records can be undertaken by the safety management supervisor in place of the general manufacturing/distribution supervisor.

(10) Early post-marketing surveillance (Article 10)

[1] A protocol (early post-marketing surveillance protocol) containing the following items must be prepared each time early post-marketing surveillance is performed.

- Objective of the early post-marketing surveillance
- Method of early post-marketing surveillance
- Period of early post-marketing surveillance
- Other necessary items

[2] When the early post-marketing surveillance protocol is prepared or revised, the early post-marketing surveillance protocol must be dated and retained.

[3] The general marketing compliance officer shall make available early post-marketing surveillance protocol in the office performing the work and also must make available copies in other offices performing surveillance work.

[4] The safety management supervisor shall confirm that early post-marketing surveillance is being performed appropriately and smoothly and records of such confirmation shall be prepared and retained. He or she shall also revise the early post-marketing surveillance protocol as required.

[5] When early post-marketing surveillance is performed by the safety management implementation supervisor, the safety management implementation supervisor shall prepare records and report in writing to the safety management supervisor, and the safety management supervisor shall retain such reports.

(11) In-house inspections (Article 11)

[1] In-house inspections of duties related to post-marketing safety management shall be performed on a regular schedule by a person appointed beforehand.

[2] When the person appointed beforehand in (1) is the safety management supervisor, the safety management supervisor shall prepare and retain records of in-house inspections.

[3] When the person appointed beforehand in (1) is a person other than the safety management

supervisor, that person shall prepare records of in-house inspections and report in writing to the safety management supervisor. The safety management supervisor shall retain these reports.

[4] The safety management supervisor shall report the results of the in-house inspection in writing to the general marketing compliance officer and shall retain a copy of the report.

[5] The general marketing compliance officer shall examine the necessity of improvements in post-marketing safety management based on the results of in-house inspections and when improvements are necessary, the general manufacturing/distribution supervisor shall undertake the specified measures and prepare records thereof. The safety management supervisor shall retain these records.

(12) Education and training (Article 12)

[1] The general marketing compliance officer shall prepare and retain education and training protocols for employees engaged in duties related to post-marketing safety management

[2] Education and training shall be performed as planned by a person appointed beforehand.

[3] When the person appointed beforehand in (2) is the safety management supervisor, the safety management supervisor shall prepare and retain records of education and training.

[4] When the person appointed beforehand in (2) is a person other than the safety management supervisor, that person shall prepare records of education and training and report in writing to the safety management supervisor. The safety management supervisor shall retain these reports.

[5] The safety management supervisor shall report the results of the education and training in writing to the general marketing compliance officer and shall retain a copy of the report.

(13) Standards for post-marketing safety management of type 2 marketers (marketers of drugs other than prescription drugs and controlled medical devices) (Articles 13 and 14)

The standards for type 1 marketers shall apply *mutatis mutandis* with the exception of the following.

[1] Establishment of a safety management division is not specified.

[2] No qualifications for safety

management supervisors are specified.

[3] Appointment of a safety management implementation supervisor is not specified.

(14) Standards for post-marketing safety management of type 3 marketers (Marketers of quasi-drugs, cosmetics and ordinary medical devices) (Articles 15)

The standards for type 1 marketers shall apply *mutatis mutandis* with the exception of the following.

[1] (1) to (3) in Article 13 above.

[2] Standard operating procedures for post-marketing safety management are not specified.

[3] Collection of safety information in (7) for quasi-drugs and cosmetics is limited to research reports and other safety management information.

[4] In-house inspections and education and training are not specified.

(15) Retention of records related to safety assurance (Article 16)

[1] The period of retention of 5 years from the date when the records are no longer utilized. However, the period shall be 10 years for biological products, 30 years for specified biological products, and 15 years for designated controlled medical devices and highly controlled medical devices. Records related to in-house inspections and education and training shall be kept for 5 years from the date of preparation

[2] Records specified by Ministerial Ordinance can be retained by persons designated by the marketer based on the standard operating procedures for post-marketing safety management.

4. ADVERSE DRUG REACTIONS AND INFECTIONS REPORTING SYSTEM

Programs for collecting and reporting safety information on drugs such as adverse drug reactions include an adverse drug reaction reporting system undertaken by pharmaceutical companies, the drug safety information reporting system undertaken by medical personnel, and the WHO International Drug Monitoring Program whereby drug safety information is exchanged among various countries (**Fig. 11.** Collection and Reporting of Pharmaceutical Safety Information).

4.1 Drug Safety Information Reporting System by Medical Personnel

This is a MHLW reporting system that directly collects safety information from

health professionals. The reporting facilities of this monitoring system had been designated in accordance with the type of product involved, such as prescription medicines, over-the-counter drugs, and medical devices. Because of the need for collection of further information required for post-marketing product safety strategies, the limitation on reporting facilities was eliminated in July 1997. This system has been expanded and revised to include all medical institutions and pharmacies, and the reporting format has been simplified in order to further increase the number of reports from physicians, dentists, and pharmacists. Furthermore, the need of reporty as the duty of medical personnel was specified in the Pharmaceutical Affairs Law in July 2003.

* The Pharmaceuticla Affairs Law revised on June 14, 2006 (Law No. 69 to be enforced in 2009) also requests the registered distributor to report safety information.

The information subject to reporting includes adverse reactions associated with the use of prescription medicines, over-the-counter drugs, medical devices, etc., including any adverse events, with the exception of mild, well-known adverse events, even though a causal relationship with the drug concerned is unclear.

When drugs and related products require especially intensive investigation and collection of information, the MHLW selects medical institutions and, if necessary, performs "special product monitoring surveys" in collaboration with them.

4.2 Adverse Drug Reaction and Infectious Disease Reporting System by Pharmaceutical Companies

This system, based on the Pharmaceutical Affairs Law (Article 77-(4)-2-1), requires the reporting of adverse drug reactions and infections by pharmaceutical companies to the PMDA for information processing. In light of the recent problems such as the development of AIDS associated with the use of HIV-contaminated, unheated blood products, provisions were established for "adverse drug reaction reporting" in the revised Pharmaceutical Affairs Law, which came into effect in April 1997, in order to define the legal basis for improving the previously somewhat ambiguous adverse drug reaction reporting system. These new provisions now also mandate reporting of the "occurrence of infections attributed to the use of the drug concerned."

Revisions in the Enforcement Regulations of the Pharmaceutical Affairs Law, which became effective at the same time, based on items agreed to at the International Conference on Harmonization (ICH), also have defined the scope of "serious cases" subject to reporting. In addition, regulatory information such as measures adopted in overseas to discontinue marketing of a drug due to

safety concerns must now be reported.

The collection and examination of Japanese and overseas drug safety information, as well as the adoption of specific measures based on this information, must be carried out in accordance with the standard operating procedures for post-marketing safety management (GVP).

The provisions in Article 253 of the Enforcement Regulations for reporting adverse drug reactions specify reporting within 15 days and within 30 days. The cases requiring reporting within 15 days were increased in Notification No. 0317006 of the Pharmaceutical and Food Safety Bureau dated March 17, 2005. This change was intended to assure focused supervision of serious cases caused by adverse reactions of drugs with little post-marketing clinical experience and to coordinate reporting criteria for adverse drug reactions with international standards. A summary of these provisions is presented below.

(1) Reporting Within 15 Days

The following must be reported within 15 days from the time they are first known:

a) The cases described below include suspected adverse reactions to the drug concerned reported both in Japan and overseas. These also include cases where the occurrence of an adverse reaction, its incidence, and/or the conditions of onset was unexpected based on the precautions in the package insert of the drug concerned (previously unknown serious cases).

(1) Death

(2) Disability

(3) Any events possibly leading to death or disability

(4) Any case that requires hospitalization for treatment or prolongs the duration of hospitalization.

(5) Any other serious cases involving items (1) through (4) above

(6) Any congenital disease or anomaly in the offspring of a treated patient.

b) Any case involving items (1) through (6) above resulting from any unknown or known infections due to use of the drug concerned, including cases both in Japan and overseas.

c) Any implementation of measures by regulatory authorities in foreign countries such as suspension of marketing of the drug.

d) Known deaths

e) Changes in onset trends of known serious adverse drug reactions that would result in or

increase public health hazards.

f) Serious cases considered to be caused by adverse reactions of drugs with new active ingredients within 2 years from the date of approval (known or unknown).

g) Serious cases discovered in early post-marketing surveillance among adverse reactions of drugs other than drugs with new active ingredients for which early post-marketing surveillance is an approval condition (known or unknown).

(2) **Reporting Within 30 Days**

The following must be reported within 30 days from the time they are first known:

a) Any cases involving items (2) through (6) in subsection (a) of the previous section attributed to a known adverse reaction of the drug concerned occurring in Japan (known serious cases).

b) Research reports about the drug concerned, which demonstrate that it does not have an approved indication.

(3) Periodic reports of unknown non-serious adverse reactions of drugs

The degree of seriousness of cases of adverse drug reactions was conventionally classified into three grades: serious, moderate and mild, but the classification has been changed to the two-stage serious and non-serious system used internationally. Cases suspected of being caused by adverse drug reactions that are unknown and non-serious must be reported periodically.

To further expedite assessments of adverse drug reactions by pharmaceutical companies, and to promote reporting of these adverse reactions in a more timely and proper manner, specific criteria for assessment of cases subject to reporting have been established by the Standards for Classification of Serious Adverse Drug Reactions (Notification No. 80 of the Safety Division, PAB dated June 29, 1992).

This seriousness classification of adverse drug reactions includes the following nine categories: liver, kidneys, blood, hypersensitivity, respiratory tract, gastrointestinal tract, cardiovascular system, neuropsychiatry, and metabolic and electrolyte abnormalities.

The scope of “seriousness” was defined by ICH conference in April 1997.

From October 27, 2003, three submission methods have been specified for E2B/M2: (1) via the Internet, (2) mainly FD (disk) reports together with paper reports, and (3) mainly paper reports with FD reports attached.

From January 2006, access to all cases of adverse drug reactions reported by companies has been possible on the homepage of the PMDA.

4.3 WHO International Drug Monitoring Program

The World Health Organization (WHO) first implemented an international drug-monitoring program in 1968. Adverse drug reaction data is collected from all participating member states, and a summary of the results of evaluation of this information is sent back to each country. Japan became a member of this program in 1972. Information about adverse drug reactions that occur in Japan has been reported to WHO, and likewise, WHO has provided any necessary information to Japan. There is also information exchange with countries including the United States, Great Britain, and Germany.

4.4 Evaluation and Communication of Safety Information and Adoption of Specific Measures

Drug safety information reported to the MHLW or other ogranizations is evaluated by consulting with experts at the meeting of the PMDA. Results are approved by the PAFSC's Committee on Safety of Drugs. Any necessary administrative measures are then taken on the basis of the results of these evaluations. These administrative measures include the following:

- Suspension of manufacturing and/or distribution of a drug, and/or recall of products
- Revocation of approval.
- Partial changes in approved indications, dosage and administration, etc.
- Orders for emergency safety information circulation
- Revision of the precautions.
- Changes in the designation or regulatory classification to poisons, narcotics, prescription drugs, etc.
- Guidance for pharmaceutical companies regarding implementation of reviews and research

Any important actions taken, requiring notification to health professionals, are handled as revisions to the "precautions" section. This is the most frequent type of administrative action taken.

The basic means of communicating this information is through the distribution of revised versions of package inserts containing revised precautions. In addition, a written "notification of a revision in the precautions" is distributed whenever a revision is made. When safety issues are of paramount concern and urgent communication of this information is necessary to prevent further harm to public health, a written notification entitled "Urgent Safety Information" (**"Dear Dr." letter**)

written in a specific manner is distributed. Communication of drug safety information to health professionals is accomplished using the above documents.

5. PERIODIC INFECTION REPORTS FOR BIOLOGICAL PRODUCTS

With the revision of the Pharmaceutical Affairs Law in July 2002, drugs manufactured from materials derived from humans or other living organisms (excluding plants) that require caution in terms of public health and hygiene are biological products specified by the MHLW. From July 30, 2003, the system of periodic infection reports was introduced by which manufacturers of such biological products must evaluate their products based on findings obtained from the latest reports on infections caused by raw materials of the products and report the results every 6 months to the Minister (Article 68-8 of the Pharmaceutical Affairs Law).

6. REEXAMINATION SYSTEM (ARTICLE 14-4 OF THE PHARMACEUTICAL AFFAIRS LAW)

The reexamination system is aimed at reconfirmation of the clinical usefulness of drugs by performing GPSP or GVP as one aspect of PMS, through collecting information on the efficacy and safety of the drug during a specified period of time after approval. This system was commenced in April 1980. Based on the revision of October 1993, the reexamination period for orphan drugs was extended to a maximum of 10 years.

There are limitations on the quantity and quality of data submitted for review at the time of approval of a new drug. Examples of such limitations include relatively small numbers of subjects in clinical studies performed prior to approval, relatively short use data of the drug, and lack of experience using the drug under diverse conditions such as concomitant medication, complications, and age. There are limitations on confirmation of all of these aspects before approval.

It is, therefore, obligatory for manufacturing/marketing companies to perform postmarketing surveillance of their drugs after approval in order to determine if any problems have arisen with efficacy when the drug is used in actual practice, or to see if the level of efficacy has not been changed by factors such as dosage, duration of administration, complications or concomitant medication. In terms of safety, any marked increase in the incidence of ADRs and changes in the incidence of ADRs due to factors such as dosage, duration of administration, complications, or concomitant medication should be detected and assessed.

When the revised Pharmaceutical Affairs Law was enforced from April 1997,

the surveillance and studies required for reexamination applications must be performed in compliance with the GPMSP, GCP or GLP depending on their objective. It is also obligatory to prepare application data in accordance with these standards. Based on the revision of the Law in April 2005, the GPMSP has been abolished and replaced with the GPSP and GVP.

6.1 Designation for Reexamination of Drugs

The drugs subject to reexamination include products designated by the MHLW at the time of marketing approval as drugs with, for example, active ingredients, quantities of ingredients, dosage and administration, and/or indications that are distinctly different from drugs that have already been approved (Article 14-4 of the Law).

The timing when these drugs should be reexamined is designated by the MHLW at the time of their approval as new drugs. The times that reexaminations should generally be conducted for specific products are given below.

(1) Reexamination 10 years after the date of approval:

- Orphan drugs

(2) Reexamination 8 years after the date of approval:

- Drugs containing new active ingredients

(3) Reexamination 6 years after the date of approval:

- New prescription combination drugs
- Drugs with new routes of administration

(4) Reexamination from 4 to within 6 years after the date of approval:

- Drugs with new indications
- Drugs with new dosages

The reexamination period for drugs with new active ingredients was extended from 6 years to 8 years based on Notification No. 0401001 of the PFSB dated April 1, 2007.

When pharmacoepidemiological surveys or clinical studies for setting pediatric doses performed, the study period can be prolonged before completion of the reexamination period as required (maximum reexamination period: 10 years).

6.2 Periodic Safety Reports (Article 63 of the Enforcement Regulations of the Law)

Collected post-marketing safety data, primarily in the form of drug use-results surveys, had been reported once a year during the period of reexamination to the MHLW (so-called "annual report system"). On the basis of agreements at the ICH concerning periodic safety update report (PSUR) system, however, a new "periodic safety report system" was enacted into law at the time of revision to the Pharmaceutical Affairs Law in April 1997.

As the base date for the reporting period

of these reports, the concept of the international birth date in the PSUR system was introduced. Based on this concept, the date designated by the MHLW at the time of approval is established as the base date. The frequency of reports is every 6 months during the first 2 years from this base date. Thereafter, reports are to be submitted once each year during the remaining period of reexamination. The drugs for which these reports are applicable include prescription medicines designated for reexamination (medical devices are subject to annual reporting as previously). In the event that a drug is marketed in a foreign country, reports must specify any adverse drug reactions that appeared in that country and information about any regulatory measures adopted. In addition, when PSUR prepared by foreign companies should be appended to the Japanese Periodic Safety Report together with the information obtained in drug use-results survey in the section "Future safety measures planned on the basis of surveillance results" in the Periodic Safety Report, and submitted, or the contents of the PSUR should be compiled and incorporated into the Japanese Periodic Safety Report and submitted. Either method is acceptable. A summary of the report items to be submitted includes the following:

- Period of the survey
- Number of cases surveyed
- Quantity of product shipped
- Status of implementation of drug use-results survey
- Summary of the surveillance results and analysis of the data
- Incidence of adverse drug reactions classified by type
- A list of cases in which adverse drug reactions occurred
- Measures adopted to ensure proper product use such as revisions of the precautions
- Package inserts
- Future safety measures planned on the basis of surveillance results

6.3 Data Required for Reexamination Applications and Reexamination Procedures

Post-marketing surveillance to acquire data required for reexamination applications, including drug use-results surveys, specified drug-use surveys, and post-marketing clinical trials, must be implemented in accordance with the GPSP. The data must also be collected and prepared in accordance with these standards (post-marketing clinical trials must be conducted also in compliance with the GCP).

Applications for reexamination must be completed within 3 months from the time of the designated base date. The data submitted and organization of this data should generally be as described below, with a focus on data from specified

drug-use surveys and post-marketing clinical trials of the drug concerned in the application. In addition, for any other research data acquired after drug approval related to indications, and/or safety of the drug concerned, a Periodic Safety Report submitted near the date of the reexamination application should be attached.

(1) Summary of Data for Reexamination Applications

The data should include a summary of the drug specified in the application; specific details up to the time of reexamination application including the changes in quantity and value of product shipped and the estimated number of patients who used the drug, the status of approval and sales overseas; summary of post-marketing surveillance; information about safety and efficacy; and references.

(2) Data Attached to Reexamination Applications

This data should include summary of drug use-results surveys; specified drug-use survey reports; post-marketing clinical trial reports; data from patients who have developed adverse drug reactions or infections; data from research reports; reports of specific measures adopted in Japan and overseas; and reports of serious adverse drug reactions.

(3) Compliance Survey Data

This includes data from GPSP compliance reviews as well as data from GCP and/or GLP compliance reviews as required.

(4) Reference Data

This includes, for example, case report forms used in drug use-results surveys, package inserts at the time of reexamination application, summaries of replies, review reports, a summary of the data at the time of product approval application (for Evaluation Committees), copies of approval forms, and a copy of periodic safety report submitted closest to the reexamination application.

Reexamination is based on submission of the above application data. **Fig. 13** (Reexamination system) is a flow diagram of this reexamination process. After the application is received, the PMDA evaluates compliance with standards such as GPSP and conducts surveys on quality, efficacy, and safety. The application is next reviewed by the Department on Drugs of the PAFSC. Then, the MHLW issues an official report of the results of the examination. The results of these examinations are classified into one of the three approval categories shown below, and any required specific measures are

adopted. Article 14 Paragraph 2 of the Pharmaceutical Affairs Law specifies three reasons for refusal of approval. These include cases where (1) the indications of the drug stated in the application have not been demonstrated; (2) the drug exhibits prominent harmful effects that outweigh any target indications, thus rendering the product not useful; and (3) the drug is judged to be markedly inappropriate with respect to public health and hygiene because of its characteristics or quality.

* Designated Classifications

[I] Approval refused (manufacturing and marketing suspended, approval revoked)

[II] Changes in approval (modifications in approved items as directed)

[III] Approved (as per application for reexamination)

7. REEVALUATION SYSTEM (ARTICLE 14-5 OF THE PAL)

The reevaluation of drugs is a system whereby the efficacy and safety of a drug, which has already been approved, is reconsidered on the basis of the current status of medical and pharmaceutical sciences. This system was initiated in December 1971 on the basis of administrative guidance. From January 1985, reevaluations were based on the Pharmaceutical Affairs Law, and the new reevaluation system came into effect from May 1988.

New Reevaluation System:

This new reevaluation system aimed at reevaluations of the efficacy and safety of all prescription drugs was started in May 1988. These reevaluations are at first performed by means of a review by the PAFSC. When the Council's decision requires further literature surveys by the manufacturers, they are required to perform such surveys according to the provisions of the Pharmaceutical Affairs Law (**Fig 14**。Reevaluation system).

The new reevaluations were designated from February 1990.

The MHLW has implemented various measures related to generic drugs. In the final report of the Council on the Pharmaceutical Sector in the 21st Century issued on May 28, 1993, it was suggested that manufacturing control and quality control must be thoroughly implemented for all products including original drugs. For this purpose the dissolution test was proposed as a routine verification method and in February 1997 the first ingredients were designated for "quality reevaluation" aimed at assuring the quality of drugs. Dissolution test conditions and specifications were set for original drugs that had no specified dissolution test. This

step was intended to assure the quality of generic drugs by confirming their equivalence to the original products.

Thereafter, a notification entitled "Guidelines for **bioequivalence studies** on generic drugs" was issued on December 22, 1997 and partially revised on May 31, 2001 (Notification No. 786 of the Evaluation and Licensing Division, PFSB) and on November 24, 2006 (Notification No. 1124004 of the Evaluation and Licensing Division, PFSB) to guarantee the therapeutic equivalence of generic drugs to the original drugs.

For the quality reevaluation, designation of the products was completed in 2006 and reevaluation of all products was completed in fiscal 2007. Results of the evaluation are expected to be publicly disclosed when become available.

For product items with dissolution tests established after completion of quality reevaluation, "public dissolution tests" were included in the third section of the Japanese Pharmaceutical Codex, which was newly published on March 23, 1999.

On May 31, 1999, the Japanese edition of the Orange Book was published as a collection of information on prescription drugs related to the results of quality reevaluations and their progress, and distributed to related institutions in each prefecture. To date (September 2007), the Orange Book has been issued 28 times.

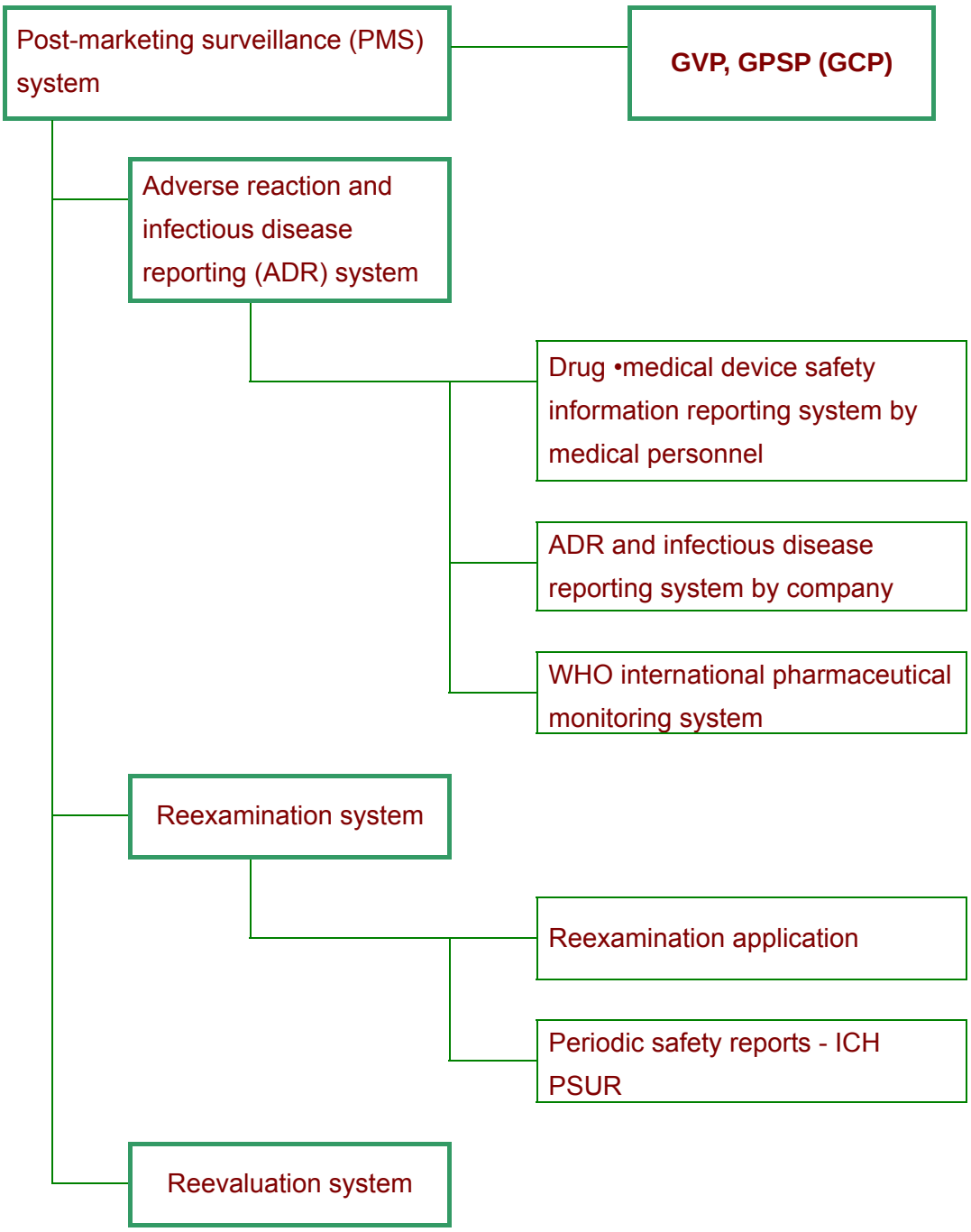


Fig. 10 Pharmaceutical Post-marketing Surveillance System

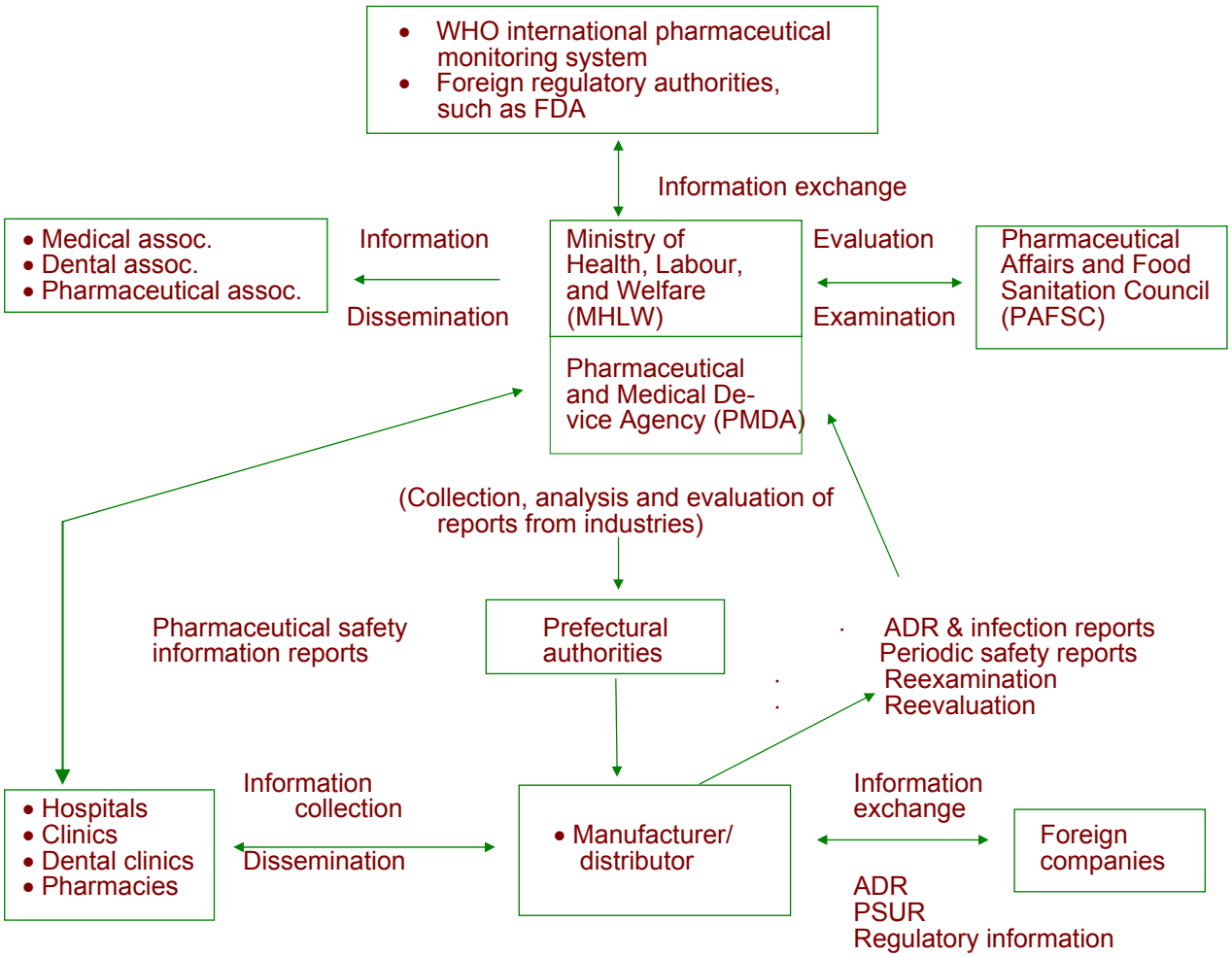


Fig. 11 Collection and Reporting of Pharmaceutical Safety Information

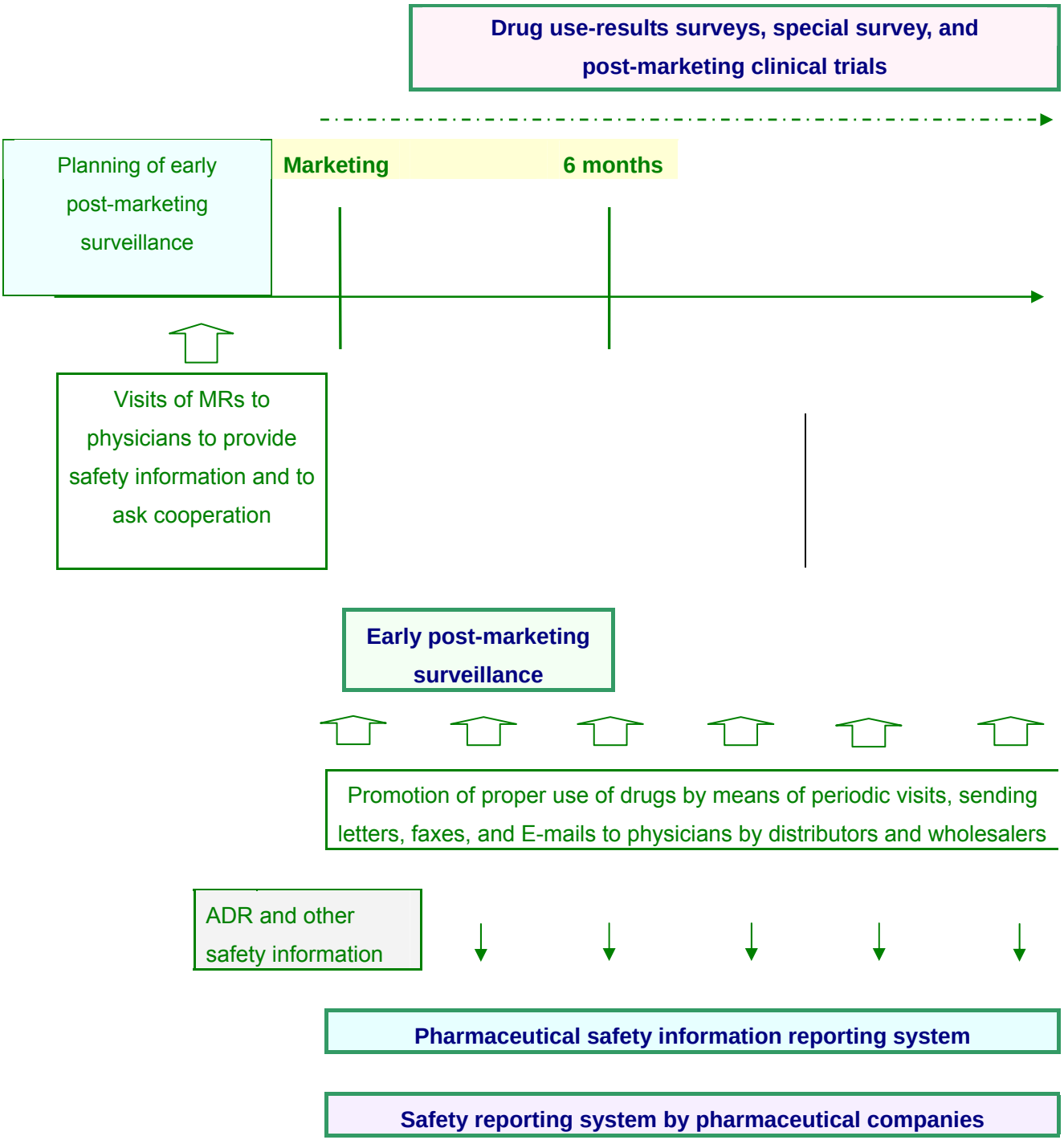


Fig. 12 Post-marketing Collection and Reporting of Pharmaceutical Safety Information

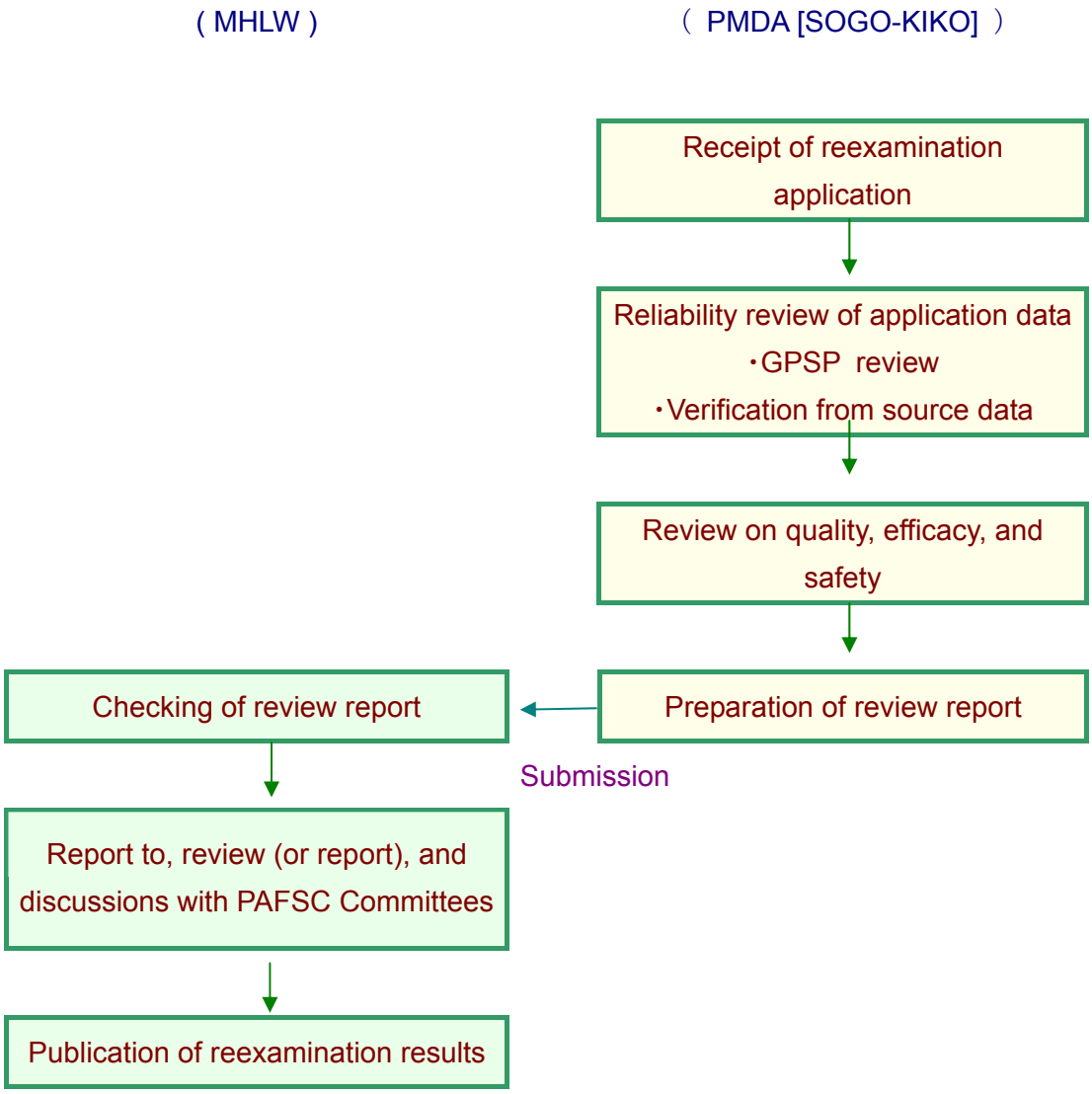


Fig. 13 Reexamination system

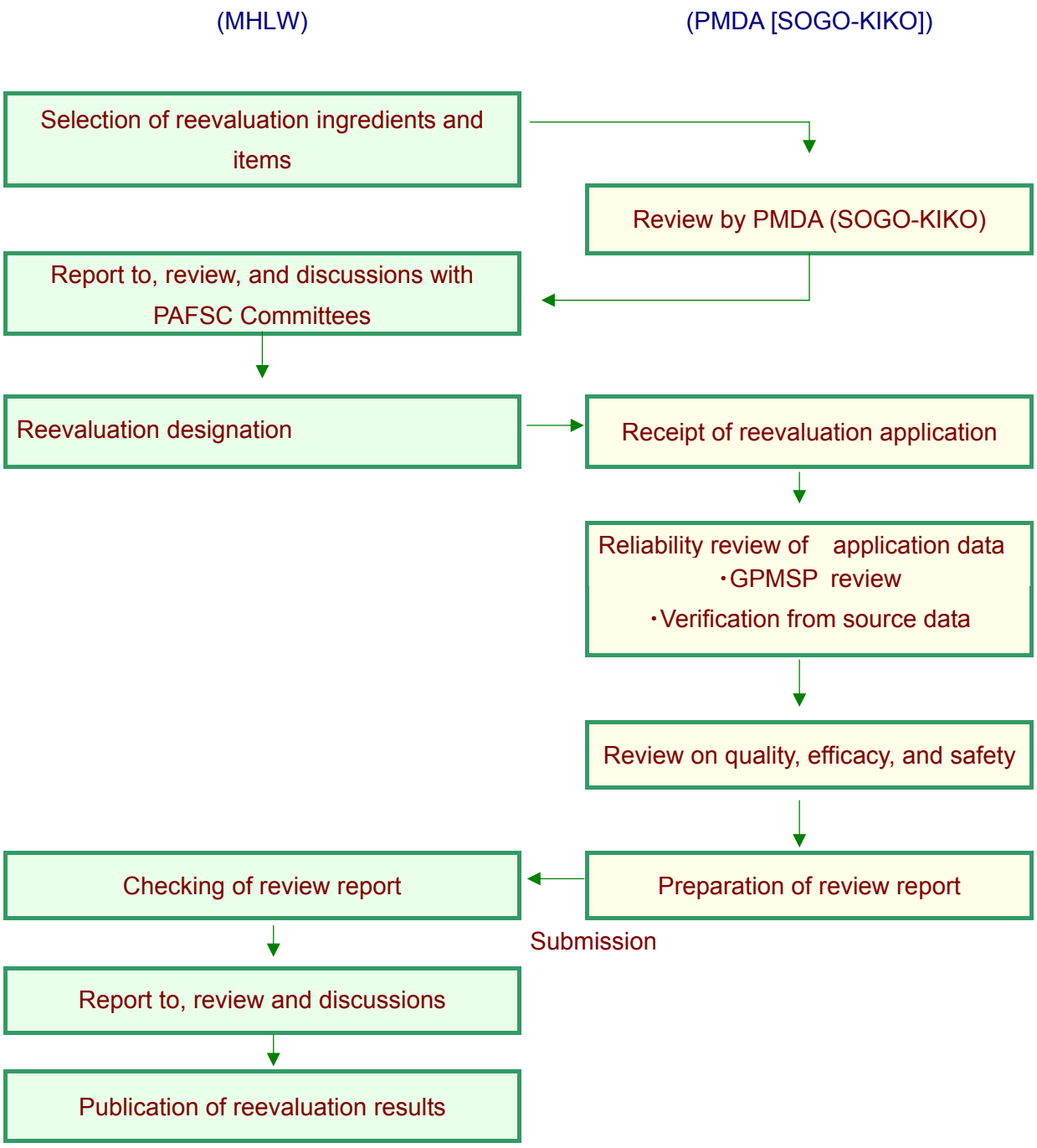


Fig. 14　Reevaluation system

CHAPTER 5

Supply and Dissemination of Drug Information

Marketers of drugs must collect and examine information on proper use of drugs such as information on drug efficacy, safety and quality, and supply this information to medical institutions as specified in the Pharmaceutical Affairs Law. For this purpose, drug marketers should prepare standard operating procedures based on the provisions in the GVP ordinance and endeavor to establish a comprehensive system for the supply and dissemination of information on proper and safe use of drugs.

1. PACKAGE INSERTS

The most basic tool for supplying information on drugs to health professionals is package inserts, and the contents of package inserts for prescription drugs have been specified by the Pharmaceutical Affairs Law. These package inserts are public documents that pharmaceutical marketers are obliged to prepare for the purpose of supplying to physicians, dentists and pharmacists the information necessary to assure the safety of patients administered the drug and to promote the proper use of the drug concerned based on the provisions of the Pharmaceutical Affairs Law. The Law specifies items which must be included in the package inserts, points to consider when preparing the package inserts and items which are prohibited in package inserts. It also specifies penalties for not complying with these provisions and for including false or exaggerated information in package inserts. The MHLW has also issued notifications that provide guidelines on the actual items to be included and the order of their inclusion in package inserts, as well as guidelines on the preparation of Precautions for package inserts. Important information on adverse reactions, etc. obtained and evaluated in post-marketing surveillance on product safety must be reflected in package inserts. Because of the limitations on space and the amount of information that can be presented in package inserts, manufacturers and distributors may prepare various types of information to supplement the package inserts.

The necessity of a complete reconsideration of package inserts was pointed out in the final report of the Council on 21st Century Pharmaceuticals entitled "Proper use of drugs in future health care and the role of the regulatory authorities" in May 1993, and in the interim report of the Study Committee on Measures to Promote

Appropriate Use of Drugs in July 1995. At about the same time, the Sorivudine incident involving a very severe adverse reaction caused by the interaction of this antiviral agent and an anticancer drug occurred, and the MHW (currently MHLW), health professionals and pharmaceutical companies considered emergency measures to assure proper supply of information on drug safety, mainly related to interactions (Notification No. 999 of PAB and Notice No. 1445 of the Japan Pharmaceutical Manufacturers Association).

To cope with this problem, the MHW (currently MHLW) established three study groups on the revision of pharmaceutical package inserts, which completed their work and submitted reports in May 1996. Based on these reports, guidelines for package inserts and for Precautions were completely revised, and the following three notifications were issued in April 1997:

(1) Guidelines for **Package Inserts for Prescription Drugs** (Notification No. 606 of PAB dated April 25, 1997).
(2) Guidelines for Package Inserts for Prescription Drugs (Notification No. 59 of the Safety Division, PAB dated April 25, 1997).
(3) Guidelines for Precautions for Prescription Drugs (Notification No. 607 of PAB dated April 25, 1997).

The main points in these notifications are as follows:

- Package inserts have been revised to make them easier to understand and to use by health professionals.
- The purpose is to supply scientifically accurate information.

Two notifications concerning package inserts for biological products were issued in May 2003: “Entries in package inserts for biological products” (Notification No. 0515005 of the PFSB dated May 15, 2003) and “Guidelines for entries in package inserts of biological products” (Notification No. 0520004 of the Safety Division, PFSB dated May 20, 2003). These notifications came into effect from July 2003.

Labeling was changed with the amendment of the Pharmaceutical Affairs Law in April 2005. “Manufacturer and importer” was changed to “marketer.”

“Drug requiring a prescription” was changed to “prescription drug” based on Notifications No. 0331008 of the Compliance and Narcotics Division, PFSB dated March 31, 2005, “Handling of labeling of drugs in the amended Pharmaceutical Affairs Law” and No. 0210001 of the PFSB dated February 2005 “Designation of prescription drugs.” “Caution: Use under prescription from a physician, etc.” is entered.

To improve the supply of information on generic drugs, Notification No. 0324006 of the Safety Division, PFSB dated March 24,

2006 was issued. This notification specifies the entry of bioequivalence study data in the “Pharmacokinetics” section of the package insert.

1.1 Summary of the New Guidelines

1) Coordination of Formats

(1) Items considered important must be entered close to the beginning of the package inserts.

(2) "Warnings" and "Contraindications" must be entered at the beginning of the package inserts. Package inserts with "Warnings" have a red bracket-shaped band printed in the right margin. The "Warnings" must be in red letters encased in red and "Contraindications" must be encased in red.

(3) Overlapping entries under two or more headings should be avoided, in principle.

(4) The size of the package insert should be within four A4 size pages, in principle.

2) Improved Contents

(1) The "Precautions" must follow "Indications" and "Dosage and Administration" in that order.

(2) The incidence of adverse reactions must be given in numerical values with appropriate classifications whenever possible.

(3) "Adverse Reactions," "Interactions" etc. must be as clearly visible as possible using tables, etc.

(4) The former headings "Drug Characteristics and Development Process" and "Non-clinical Studies" have been abolished, and the required information must be supplied in a scientifically accurate manner by improvement of the information given under such headings as "Clinical Pharmacology" and "Pharmacokinetics."

3) Addition of New Headings

(1) The new heading "Conditions for Approval" has been added.

(2) This heading consists of a list of the dates of entry in the NHI Reimbursement Price List, initial marketing in Japan, publication of the latest reexamination and/or reevaluation results, latest approval of (additional) indications, the international birth date, etc.

1.2 Headings and Their Sequence in Package Inserts

The actual headings and the sequence in which they are entered in package inserts for prescription drugs are shown below. Refer to **Fig. 15** (Layout of a

Package Insert for a Prescription Drug (with "Warning")) for the layout.

All of the headings should be included whenever possible, but when no appropriate information is available, the heading may be omitted.

For details of the contents of the headings in package inserts, please refer to the three MHW notifications mentioned above (Notifications No. 606 and 607 of the PAB and Notification No. 59 of the Safety Division, PAB) and notifications related to biological products (Notification No. 0515005 of the PFSB and Notification No. 0520004 of the Safety Division, PFSB). For changes in entries in package inserts with the enforcement of the amended Pharmaceutical Affairs Law in April 2005, refer to Notification No. 133 of the Japan Pharmaceutical Manufacturers Association (JPMA) dated March 4, 2005 and Notification No. 0324006 of the Safety Division, PFSB dated March 24, 2006 concerning supply of information on generic drugs.

*** Headings and their Sequence in Package Inserts**

1) Date of preparation and/or revision(s) of the package insert
2) Standard Commodity Classification No. of Japan, etc.
   - Standard Commodity Classification No. of Japan (SCCJ)
   - Approval number
   - Date of listing in the national health insurance (NHI) reimbursement price list
   - Date of initial marketing in Japan
   - Date(s) of latest reexamination
   - Date(s) of latest reevaluation
   - Date(s) of latest approval of additional indication(s)
   - International birth date
   - Storage, etc. (storage, expiration date, shelf-life, etc.)
3) Therapeutic category
4) Regulatory classification (specified biological products, biological products, poisonous substance, deleterious substance, habit-forming drug, prescription drug, etc.)
5) Name(s) [brand name, non-proprietary name, Japanese Accepted Name (JAN), etc.]

◆ At the beginning of the package insert
Precautions concerning specified biological products (encased in black)

6) Warning(s) (in red letters encased in red)
7) Contraindications (in black letters encased in red)
   (1) Contraindications
   (2) Relative contraindications
8) Composition and description
   (1) Composition

(2) Product description

9) Indication(s)

(1) Indication(s)

(2) Precautions related to Indications

10) Dosage and administration

(1) Dosage and administration

(2) Precautions related to dosage and administration

11) Precautions (Refer to Notifications No. 606 of PAB, No. 59 of the Safety Division, PAB, No. 607 of PAB, No. 0515005 of PFSB, and No. 0520004 of the Safety Division, PFSB) (Refer to Sections 1.3 and 1.5)

12) Pharmacokinetics

13) Clinical studies

14) Clinical pharmacology

15) Physicochemistry (active ingredient)

16) Precautions for handling

17) Conditions for approval

18) Packaging

19) References and reference requests

♦ Information of drugs with limited administration periods

20) Manufactured and/or distributed by: (name and address)

1.3 Precautions

The Precautions are prepared voluntarily by the manufacturer of the drug concerned or under the guidance of the MHLW based on the guidelines in the MHLW notifications listed previously. Information obtained from post-marketing drug use results (clinical experience) surveys, and foreign and domestic case reports and research reports is collected and evaluated, and the Precautions are revised to incorporate the latest data as required. Revisions based on the results of reexaminations and/or reevaluations are undertaken as required.

The headings* used in the Precautions are as follows. Refer to the following MHW notifications: (1) No. 606 of PAB, (2) No. 59 of the Safety Division, PAB and (3) No. 607 of PAB, and notifications related to biological products (Notification No. 0515005 of the PFSB and Notification No. 0520004 of the Safety Division, PFSB) for details concerning the contents of Precautions.

* Headings Used with Precautions

1) "Warning" (in red letters and encased in red at the beginning of "Precautions")

2) "Contraindications" (in black letters and encased in red following "Warning" in principle. However, at the beginning of the Precautions when there is no "Warning")

(1) Contraindications ("This product is contraindicated in the following patients.")

(2) Relative contraindications

("As a general rule, this product is contraindicated in the following patients. If the use of this product is considered essential, it should be administered with care.")

3) Precautions related to indications (In the event of such precautions, they are entered under the heading "Precautions" following "Indications" in the package insert.
4) Precautions related to dosage and administration (In the event of such precautions, they are entered under the heading "Precautions" following "Dosage and Administration" in the package insert.
5) Careful administration ("This product should be administered with care to the following patients.")
6) Important precautions
7) Drug interactions
   (1) Contraindications for coadministration ("This product should not be coadministered with the following drugs.") (in black letters and encased in red, with simple explanation provided under "Contraindications" above.)
   (2) Precautions for coadministration

   The MHW issued an office communication stressing that the Drug Interaction section must be based on the most recent scientific findings [office communication dated December 25, 2000 as a supplement of Notification No. 607 of PAB, MHW].
8) Adverse reactions (incidence shown in numerical values whenever possible)

   * A key to the frequency of adverse reactions should be provided at the beginning.

   (1) Clinically significant adverse reactions
   (2) Other adverse reactions
9) Use in the elderly
10) Use during pregnancy, delivery, or lactation
11) Pediatric use (low birth weight infants, newborns, infants, small children, children)

Reference: Age classification for pediatric use (basic standards)

- Children: under 15 years of age
- Small children: under 7 years of age
- Infants: under 1 year of age
- Newborns (neonates): under 4 weeks of age
- Low birth weight infants

(premature infants): body weight of less than 2,500 g (according to the WHO recommendation)

12) Effects on laboratory tests
13) Overdosage
14) Precautions concerning use
15) Other precautions (toxicity obtained in animal studies requiring particular caution, etc.)

1.4 Labeling of Excipients

When excipients such as stabilizers, preservatives, and vehicles are used in products listed in the Japan Pharmacopoeia (JP), in the Minimum Requirements for Biological Products or in the Radiopharmaceutical Standards, the names and quantities of these excipients must be included in the relevant package inserts or on the containers or wrappers.

Since safety problems considered to be caused by excipients have appeared, the names and quantities of excipients specified in Notification No. 853 of the PAB dated October 10, 1988 must be included in the relevant package inserts or, if necessary, on the containers or wrappers of all prescription drugs since October 1988.

The labeling of excipients in non-prescription drugs is the same as that for prescription drugs based on a voluntary agreement of the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ) (FPMAJ Notification No. 165 dated March 27, 1991; Office Communication of the Safety Division, PAB dated June 3, 1991).

All ingredients of both prescription and non-prescription drugs must be included in the package insert based on a voluntary agreement of the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ) (FPMAJ Notification No. 170 dated March 13, 2002) because of the social responsibility to disclose as much information as possible related to drugs as life-related products. For non-prescription drugs, the names of excipients, including designated ingredients entered voluntarily, must be labeled on the outer container or the equivalent (the above FPMAJ Notification No. 165 is canceled by the voluntary agreement concerned). The above Office Communication of the Safety Division, PAB dated June 3, 1991 was canceled by Notification No. 0409001 of the Safety Division, PFSB dated April 9, 2002.

1.5 Entries for Biological Products

Specified biological products

1) Regulatory classification
   Specified biological products
2) Name
   For genetic recombinants, “recombinant” is included immediately after the non-proprietary name
3) Beginning of the package insert (before the “Warning”)

(2) Risk of spread of infections derived from raw materials can not be completely eliminated.
(2) Summary of safety measures undertaken to prevent spread of infection.
(3) Use must be kept to a minimum after careful investigation of necessity in treatment of disease.

4) Composition and description
(1) Names of ingredients among raw materials and packaging materials derived from humans or other organisms
(2) Names of parts of humans or other organisms among raw materials
(3) Name of country where blood was collected as a raw material and collection methods (donor blood or non-donor blood)

5) Precautions, Important Precautions
Health professionals such as physicians must explain to persons using the drug the efficacy and safety and other measures required for proper use of the drug concerned.

6) Precautions concerning use
Health professionals such as physicians must record the names and addresses of persons using the drug and preserve such records in medical institutions, etc.

7) Other items required for proper use

Biological products (excluding specified biological products

1) Regulatory classification:
Biological product

2) Name:
For genetic recombinants, (recombinant) is included immediately after the non-proprietary name

3) Composition and description:
(1) Names of ingredients among raw materials and packaging materials derived from humans or other organisms
(2) Names of parts of humans or other organisms among raw materials
(3) Name of country where blood was collected as a raw material and collection methods (donor blood or non-donor blood)

4) Other items required for proper use

1.6 Brand Names of Prescriptions Drugs

Principles for naming of brands of prescription drugs have been specified in Notification No. 935 of the PMSB dated September 19, 2000 to prevent medication accidents.

The application fee for revising brand name was lowered in April 2005. The timing of brand name revision for preventioin of medical accident is the time for NHI price listing twice a year.

1.7 Information on Package Inserts in English

Information on package inserts in English of some drugs prepared by marketers in Japan has appeared on the JPMA homepage basically once a year since 2001.

http://www.e-search.ne.jp/~jpr/

2. INFORMATION TO SUPPLEMENT PACKAGE INSERTS

Because of space limitations in Japanese package inserts, the following media are also use to provide more detailed information about pharmaceutical products.

2.1 Outline of Prescription Pharmaceutical Product Information

The Outline of Prescription Pharmaceutical Product Information prepared by manufacturers and distributors is intended to provide accurate and appropriate information to health professionals to assure proper use of their drugs.

This document is prepared on the basis of Guidelines for Preparation of Outlines of Prescription Pharmaceutical Product Information published by the Japan Pharmaceutical Manufacturers Association (JPMA) in March 1999, but the contents also follow the MHLW notification on Guidelines for Preparation of Package Inserts. The document must also comply with the Promotion Code.

New drugs approved during or after October 2001 are marked with a logo indicating that the drug is under early post-marketing surveillance for a period of time as specified in the labeling (refer to Chapter 4, 1. GVP).

2.2 New Drug Approval Information Package (NAIP)

The MHLW issues a "New Drug Approval Information Package (NAIP)" which consists of "Review Reports" and an NDA Summary for each product to promote appropriate use of new drugs and assure transparency of the approval review process. This Information is distributed via the homepage of the Pharmaceuticals and Medical Devices Agency (PMDA, SOGO-KIKO) (refer to Section 4 below).

2.3 Summary Basis of Reexamination (SBR)

The Summary basis of Reexamination (SBR) is an outline of post-marketing surveillance, including drug use results (clinical experience) surveys, special surveys, and post-marketing clinical trials, as well as post-marketing safety management information such as adverse reaction reports, based on reexamination application data evaluated by the PAFSC. SBR have been prepared 5 times to promote proper use of drugs; they have not

been published since December 1999).

2.4 Pharmaceutical Interview Forms (IF)

Pharmaceutical Interview Forms also serve to supplement package inserts. The IF basically specifies questions to be asked by pharmacists to obtain detailed information on pharmaceutical products in interviews with pharmaceutical company medical representatives (MRs). However, in order to reduce the burden on physicians and MR, the replies (detailed information) to the questions are already entered, and the IF are supplied to health professionals as material to be used in explanations and discussions concerning the product.

The Japanese Association of Hospital Pharmacists published new preparation guidelines in September 1998, and interview forms (IF) have been prepared in the new format for new drugs approved from January 1999.

3. SUPPLY AND DISSEMINATION OF SAFETY MANAGEMENT INFORMATION

For the proper use of drugs, it is important that the necessary information be supplied and disseminated in an appropriate and timely manner to health professionals.

Extremely urgent and important information on the safety of drugs is distributed as emergency safety information in the form of a 'Dear Doctor' letter. In addition to emergency safety information, other information including notices of revision of Precautions is also distributed.

The procedures for dissemination are based on the provisions in the GVP.

Standard operating procedures are prepared by manufacturers and distributors, and the MHLW has specified guidelines on the dissemination of emergency safety information.

3.1 Distribution of Emergency Safety Information (Doctor Letters)

1) Preparation Criteria

Emergency safety information is prepared by the drug manufacturer and distributor on the basis of an order issued in cases where it is judged necessary to take the following measures based on an review by the PAFSC. Guidelines for the preparation of such information were specified in an MHW notification in 1989 (Notification No.160 the Safety Division, PAB dated October 2, 1989).

(1) New or revised Warnings: New or important revisions of warnings.
(2) Revisions of Precautions: Urgent and important revisions based on cases of death, disability, or events that may lead to death or disability, or irreversible ADRs suspected to be due to the drug concerned.
(3) Changes in indications: Important changes in indications for reasons

related to safety.

(4) Changes in dosage and administration: Important changes in dosage and administration for reasons related to safety.

(5) Changes in regulatory classification: Changes in the regulatory classification, such as designation as a poisonous substance, deleterious substance, prescription drug or habit-forming drug, for reasons related to safety.

(6) Discontinuation of marketing or recall: Discontinuation of marketing or recall of a drug for reasons related to safety.

(7) Cancellation of approvals: Cancellation of approvals for reasons related to safety.

(8) Others: Other measures that require the dissemination of urgent and important information for reasons related to safety.

2) Format and Content

Emergency safety information must be prepared in the format specified in the guidelines, using yellow paper, etc.

3) Methods of Distribution

(1) The staff (MR) [refer to **Appendix**] in charge of drug information of the drug manufacturer and distributor directly distributes the information to physicians, pharmacists, and other health professionals in medical institutions. The manufacturer and distributor must also ascertain that wholesalers market all of the drugs concerned currently in stock with the revised package insert included.

(2) Efforts must be made to disseminate the information as widely as possible by publishing it in journals of medical or pharmaceutical organizations, such as the Journal of the Japan Medical Association, Journal of the Japan Pharmaceutical Association and the Journal of the Japanese Association of Hospital Pharmacists, and, if needed, in the Journal of the Japan Dental Association.

4) Distribution

Distribution of emergency safety information to medical institutions must be completed within 4 weeks of receipt of the order, according to the plan and method of distribution. The marketer must report to the MHLW when distribution has been completed as specified in the order.

3.2 Distribution of Information by 'Notices of Revision of Precautions'

1) Preparation Criteria

(1) Cases where the MHLW orders revision of the Precautions, based on the results of an investigation by the PAFSC.

(2) Cases where the manufacturer and distributor voluntarily revises the Precautions (revisions are to be notified to the MHLW beforehand).

2) Format and Contents

The paper must be not yellow.

3) Method of Distribution

The MR distributes these notices directly to physicians, pharmacists, and other health professionals in medical institutions, in principle, in cases corresponding to 1)-(1) above. However, if direct distribution is difficult because of the remote location, etc., distribution can be entrusted to wholesalers. All such drugs in stock at wholesalers must be sold with written notices on the safety information received from the manufacturer and distributor included. In cases corresponding to 1), (2) above, the drug marketer takes measures based on the above as required.

4) Distribution

Distribution of the notices to medical institutions must be completed as soon as possible after receipt of the order or the decision to make a voluntary revision. Based on the instructions of the Safety Division, PFSB for 1) (1) above, the marketer must submit a Notice of Change for items in the Precautions of the drug concerned to the PMDA.

3.3 Dissemination of Information for Drugs That Have Completed Reexamination or Reevaluation

Once the reevaluation results and reexamination results are available, the marketer of the drug concerned disseminated information by preparing a “Notice of reevaluation results” and “Notice of reexamination results” as required, which they distribute to medical institutions. The FPMAJ compiles all of the reevaluation results and publishes a “Notice of Prescription Drug Reevaluation Results” in the journals of the Japan Medical Association, Japan Dental Association, and Japan Pharmaceutical Association.

3.4 Dissemination of ADR Information by the Pharmaceuticals and Medical Devices Safety Information (Information on Adverse Reactions to Drugs)

Among the case reports and scientific reports on adverse reactions collected from manufacturers and distributors, and ADR reports collected from or submitted by health professionals, the MHLW compiles commentaries and Notices of Revisions of Precautions concerning important ADRs. They are supplied in digest form as "Pharmaceuticals and Medical Devices Safety Information" to health professionals who submitted ADR reports, and also published in the media, on the PMDA Home Page (http://www.info.pmda.go.jp/), and in various publications such as the Journal of the Japan Medical Association and the Journal of the Japanese Association of Hospital Pharmacists. An English version is sent to WHO.

The digest was published bimonthly from June 1973 and then monthly from June 2001 (from Issue No. 167) with 240 issues as of September 2007.

3.5 Distribution of Information by Drug Safety Update

The Society of Japanese Pharmacopoeia and the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ) have been jointly editing and publishing the Drug Safety Update (DSU), which includes information on ADRs of prescription drugs (revisions of the Precautions) under supervision of the MHLW since September 1992 (10 times per year) (published by the FPMAJ since Issue No. 128 dated April 2004). The journal is distributed by mail to medical institutions nationwide including approximately 10,000 hospitals, 90,000 clinics and 60,000 dental clinics, as well as about and 70,000 pharmacies and dispensing facilities within one month after printing.

3.6 Commentaries on "Precautions" in Package Inserts

Commentaries on "Precautions" in Package Inserts are prepared by manufacturers and distributors of drugs to provide the most basic safety information on new drugs. Manufacturers and distributors must prepare easy-to-understand “commentaries” concerning the basis and contents of Precautions, and their MRs distribute the commentaries to medical institutions before new drugs are used in medical practice in order to assure proper use of new drugs.

With the revisions of the guidelines for the preparation of package inserts and Precautions in April 1997, a guide for preparation of these commentaries was issued (Notification No. 88 of the Safety Division, PAB dated June 27, 1997). Thereafter, companies started to prepare commentaries on their new drugs. New drugs that are approved after October 2001 are marked with a logo indicating that the drug is subject to early post-marketing surveillance for such a period of time as specified in labeling (refer to Chapter 4, 1. GVP).

4. ELECTRONIC INFORMATION DISSEMINATION

The MHLW received a report from its study group on policies to supply drug information to health professionals, etc. using the Internet and started operation of a "Drug Information System” to supply such information via the Internet at the end of May 1999 (currently PMDA Home Page, http://www.info.pmda.go.jp/).

The information supplied includes information on package inserts of prescription drugs, safety information disseminated by the MHLW, cases of suspected adverse reactions collected by the MHLW, as well as information on Dear Doctor Letters, drug guide for patients, the manual for handling disorders due to

adverse drug reactions, drug approval applications, drug recalls, etc.

With this system, package insert information for prescription drugs is provided in SGML (Standardized Generalized Markup Language) format to facilitate downloading and processing of the information for various purposes. In addition, the MHLW provides all information in PDF (Portable Document File) format in view of the inherent convenience.

The supply of package insert information for non-prescription drugs was started in 2006.

5. PACKAGE INSERTS OF NON-PRESCRIPTION DRUGS

The MHLW established a study group to improve package inserts of non-prescriptions drugs in August 1996 following the revision of the guidelines for package inserts of prescription drugs, and this group issue its report in September 1998.

The MHLW issued notifications in August 1999 on entry methods for Precautions and information that should be included on the outer containers.

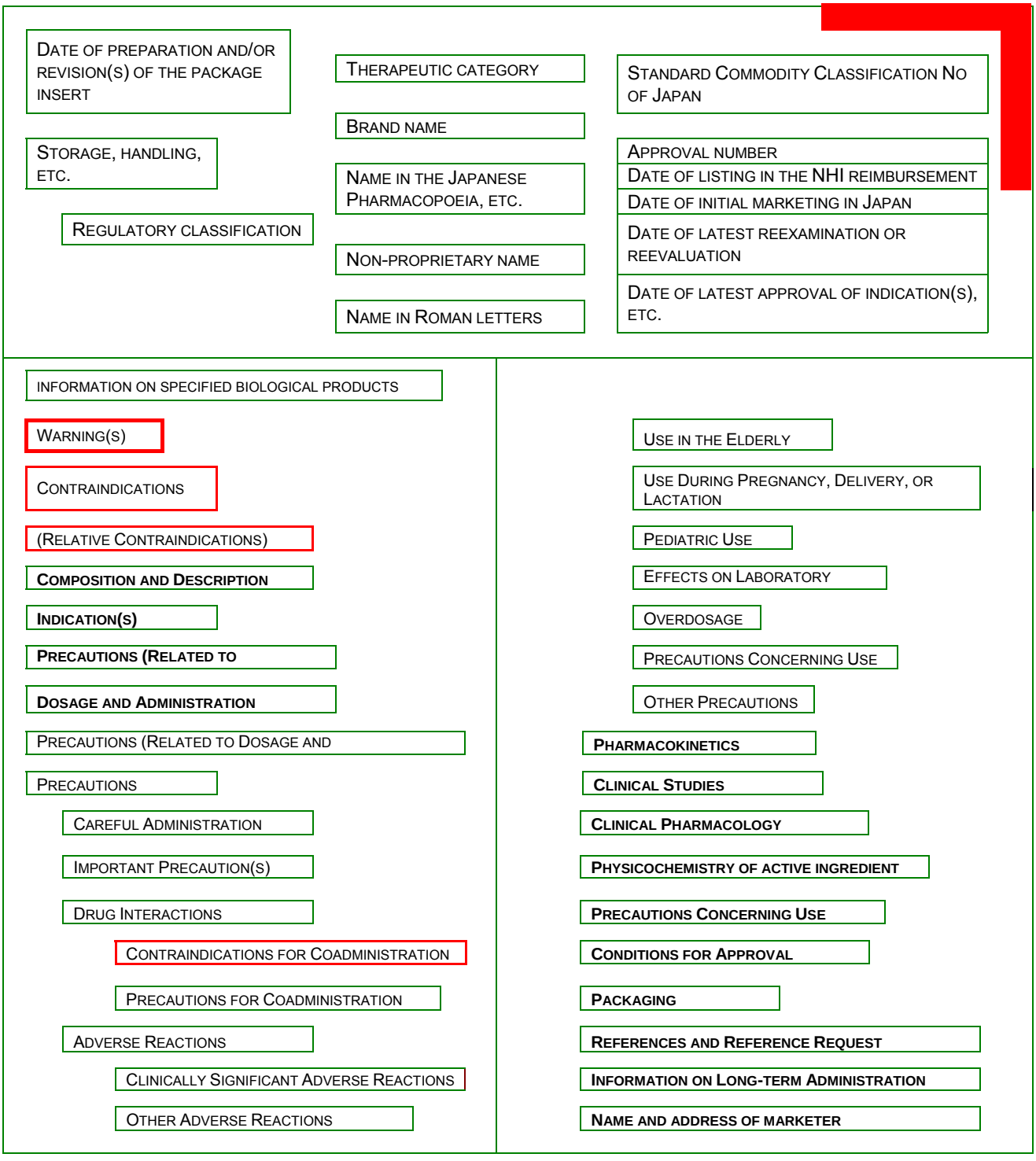
Labeling requirements of excipients of non-prescription drugs are the same as those for prescription drugs according to a voluntary agreement of the JPMA (Notification No. 165 of the JPMA dated March 27, 1991) and Office Communication of the Safety Division, PAB dated June 3, 1991. Based on a voluntary agreement of the JPMA (Notification No. 170 of the JPMA dated March 13, 2002), all ingredients must be included in package inserts by March 31, 2004 and the names of excipients including voluntarily designated ingredients must be included on the outer container (or its equivalent).

Based on this voluntary agreement, Notification No. 165 of the JPMA was canceled and the Office Communication of the Safety Division, PAB dated June 3, 1991 was canceled by Notification No. 0409001 of the Safety Division, PFSB dated April 9, 2002.

For the background of labeling of drug excipients, refer to Section 1.4 on pharmaceutical excipients.

Fig. 15 Layout of a Package Insert for a Prescription Drug (with "Warning")

Package inserts consist of specified headings in a specified order (See Chapter 5: Section 1.2). Efforts are made to carefully analyze collected information and include all headings whenever possible, but some headings are omitted when appropriate information is not available. The layout may differ to some extent.



Note: Sections in refer to Precautions

(PMS Subcommittee, Drug Evaluation Committee, JPMA)

CHAPTER 6

Health Insurance Programs and Drug Pricing in Japan

1. HISTORY OF HEALTH INSURANCE PROGRAMS

Health insurance programs in Japan began in 1922 with enactment of the Health Insurance Law which was aimed only at workers for the purpose of ensuring sound development of national industries through increases in labor efficiency and close cooperation between workers and employers by eliminating workers' anxiety about their daily life. This law was implemented in 1927. The National Health Insurance Law, enacted in 1938, and the Employees' Health Insurance Law and the Seamen's Health Insurance Law, both enacted in 1939, were subsequently enforced. In 1961, it was ruled that every citizen was required to join either one of the various society-managed employees' health insurance programs or the NHI, which is a regional insurance program. At this point, "health insurance covering the entire population" was established.

Increasing efforts were made thereafter to improve the structure of medical benefits given under various health insurance programs. In addition, under the Law for the Welfare of the Aged, all medical costs for the elderly have been provided free of charge since 1973. These measures all helped to alleviate the burden placed on patients by high medical costs.

Because of the long-term deficit in the health insurance system, radical measures as well as temporary financial measures were conceived.

Free medical care for the elderly resulted in sharp increases in the cost of their medical treatment, which seriously affected the financial status of the health insurance program. In addition, it created an imbalance in the contributions for medical costs of the elderly between the different health insurance programs due to differences in the proportion of elderly persons covered under each program. This made it necessary to radically review the health insurance system in Japan, and as a result, the Health and Medical Services Law for the Aged was enacted and was enforced in 1983.

This law encourages general health related projects for the elderly, including the prevention and treatment of diseases and rehabilitation efforts. A new system was introduced in which medical costs for the elderly are shared by public expenditure and by contributions from individual health insurance programs in order to distribute the costs more fairly.

Thereafter, anxiety increased concerning home care because of the aging of society and changes in family function, and the excessive burden of home care on families has become a social problem. Another problem is stringency on health insurance finances by social hospitalization, i.e., long-term hospitalization of the elderly for nursing care. There are limits on solving the home care problem under the current system, and a reform of the health insurance system together with the introduction of a new social security system was debated. The Home Care Insurance Law was passed together with the third revision of the Medical Service Law on December 19, 1997 and it was enforced from April 1998. It is amended every 5 years.

The MHLW Council on Health Insurance and Welfare issued its final report in November 1996. Using this report, health insurance reform was studied in 1997 and based on an agreement reached by the Health Insurance Reform Council of the ruling parties, and reforms were made to change the coverage on those insured by employee's health insurance to 80% and to introduce a partial cost-sharing for medication. Thereafter, in 2002 the revision of the Health Insurance Law containing the 30% copayment for the insured was passed by the Diet. The 30% burden for the insured was enforced from April 2003 and the partial burden for dispensing fees was abolished.

The law to reform the health insurance system was discussed from 2005 and was enacted in June 2006. From October 2006, persons 70 or older with the same incomes as during their working years were subject to a copayment of 30% and limits on copayments and food costs for inpatients of nursing home increased. The overall reform, including establishment of a new healthcare system for the elderly, will continue until 2012 (refer to **Table 6.** Drug Pricing-related Laws).

2. MEDICAL BENEFITS OFFERED UNDER HEALTH INSURANCE PROGRAMS

As mentioned above, there are several types of health insurance programs in Japan and the medical benefits available vary from one program to another. The percentage of the cost that the insured person is required to pay can also differ from one program to another. Under society-managed health insurance programs, 90% of medical costs of insured persons is covered by health insurance programs according to the revision of the Health Insurance Law in 1984 (80% coverage but this became 90% from April 1986 based on a notification of the Minister of Health and Welfare after approval by the Japanese Diet). From September 1997, coverage was changed to 80% of medical costs to medical institutions where patients are treated under health insurance

programs. A copayment by patients for outpatient medication fees was also introduced with children less than 6 years of age and low-income elderly patients excluded.

Thereafter, problems related to the burden on the elderly were pointed out and the government adopted a policy of exemption of the elderly from outpatient partial cost sharing for medication as an extraordinary measure in July 1999. In December 2000, the Health Insurance Law was promulgated and from January 1, 2001, it became possible to select a copayment system with 10% of the medical expenses as the upper limit or a fixed copayment for the elderly. For family members of insured persons, regardless of type of health insurance program, at least 70% of actual costs are covered by the programs. From October 2002, the burden on elderly patients 70 and older was set at 10% and at 20% for those with a certain level of income. This was revised o 30% from October 2006.

Furthermore, when a patient's medical payment reaches a certain limit, the patient is refunded the excess. Supplementary programs are also available to cover the costs of special treatments including highly advanced treatments and selection of treatment by patients. These all contribute to overall improvement in medical care.

Under these health insurance programs, medical benefits are almost always provided to insured persons in the form of actual treatment rather than as a cash reimbursement. In exceptional cases where this rule is difficult to apply, money is provided to cover treatment costs.

3. REIMBURSEMENT OF MEDICAL FEES

Medical institutions where patients are treated under health insurance programs apply to respective health insurance programs, after treatment has been rendered, for reimbursement of actual treatment costs after subtracting the amount paid directly by patients. Medical fees are set by the MHLW, which consults with the Central Social Insurance Medical Council ("Chuikyo"). The fees are calculated based on the Rules to Calculate Treatment Fees According to the Health Insurance Law (MHW Notification No. 177 issued in June 1958). Under these rules, a point value is assigned for each of the thousands of medical procedures listed. Fees are then calculated by multiplying the number of points by 10. This system, in which medical fees are paid to medical institutions for the procedures performed, is called the “payment for services system” since the basis of the medical cost reimbursement system in Japan. There are many types of points set for lump sum payment for hospitalized treatment, etc. of patients with chronic disease. From April 2003, the Diagnosis Procedure Combination (DPC) was introduced by

university and other large hospitals (university hospitals, National Cancer center, and National Cardiovascular Center: 82 hospitals in total) for diagnosis-based assessment of lump sum payments for emergency admissions and treatments. With this system, medical bills per day per patient are determined using 1,860 diagnosis procedure combinations. The medical bills include basic admission fees, laboratory test fees, imaging diagnosis fees, drug dispensing fees, injection fees and treatment fees of less than 1,000 points. The medical bill is calculated by the following formula.

No. of points per day for each DPC x coefficient by medical institution x number of admissions x ¥10

The coefficient by medical institution is set by the function and past performance records of the hospital. No. of points per day is set for cases of earlier discharge than the mean number of hospitalization days of the DPC.

The number of DPC classification has been further reduced to 1,438 as of April 2006 and the application of this billing system has been extended to 360 hospitals as of July 2006.

Medical procedures, such as medication and injection, require the use of drugs, and the list of reimbursement prices of drugs permitted under health insurance programs is called the **National Health Insurance (NHI) Drug Price List**.

4. NATIONAL HEALTH INSURANCE DRUG PRICE LIST

The National Health Insurance (NHI) Drug Price List is a list drugs for which medical providers can be reimbursed under the health insurance programs as specified in the regulations for hospitals and nursing homes covered by health insurance. The rules used to calculate treatment fees in accordance with the Health Insurance Law state that the reimbursement price of drugs for medical institutions is to be determined separately by the Minister of the MHLW. The invoiced prices for drugs used in hospitals covered by health insurance designated by the Minister of Health, Labor and Welfare are also shown.

5. PRICING FORMULA FOR REIMBURSEMENT PRICE REVISIONS OF DRUGS LISTED IN THE NHI DRUG PRICE LIST

The difference in the purchase price by medical institutions and the NHI reimbursement price (price discrepancy), which provides income for medical institutions, has long been a problem, and various pricing formulas have been used to reduce this price discrepancy and correct the fluctuations in purchase prices, but improvements have not been adequate.

Under these conditions, an attempt was

made to improve the distribution of drugs. From April 1, 1991, the former bulk line method was abolished and a pricing formula based on the weighted average market price was adopted so that the NHI Drug Price List would more accurately reflect market prices, unnatural fluctuations in prices would be corrected and pricing would be simplified. Based on a recommendation submitted by Chuikyo to the MHLW on May 31, 1991, the pricing formula used for drugs listed in the NHI Drug Price List at the time of reimbursement price revisions was revised, and the first overall price revision using the new formula was conducted in 1992.

The revised reimbursement prices are determined by calculating weighted means of sales prices of all existing package sizes by brand and adding a certain percentage of the current reimbursement prices (within a specified price range) to the weighted mean prices obtained. However, the new reimbursement prices must never be higher than the current prices.

Chuikyo believes that this price range, which was intended to take into account the differences in market prices according to differences in terms of sale, should be 10%. Since stable supply of all necessary drug products could not be ensured if the price range was set at 10% from the beginning, Chuikyo recommended that it be set at 15% initially so as not to have too strong an effect on business conditions at the time, and that it be reduced to 13%, 11%, and finally 10% on a step-by-step basis each time the reimbursement prices were revised in the future.

Thereafter, price increases of some products presented a problem, and a Chuikyo recommendation was issued on November 22, 1995. In addition to the usual price revision in April 1996, repricing was undertaken for products that showed a much greater market scale (at least double) that originally expected at the time of listing and for which annual sales (converted to reimbursement prices) exceeded 15 billion yen. Repricing was also undertaken for drugs for which indications were added after the original listing.

The price range decreased gradually from 15% in 1992 to 13% in 1994, 11% in 1996, 10% (8% for products listed for a long time) in 1997, and 5% (2% for high price products with relatively large margin) in 1998. In 2000, the range was set at 2% to secure stable drug supply involved over the need of reimbursement system reform. The pricing formula was changed to the weighted average market price and range adjustment method.

The pricing formulas for drugs included in the list were specified in March 200 to assure transparency of drug pricing. The most recent revision is given in Notification No. 0215002 of the Health Insurance Bureau dated February 15, 2006, “Drug Pricing Standards.”

6. RECENT REVISIONS OF THE NHI DRUG PRICE LIST

Based on the 1991 Chuikyo recommendation, the MHW undertook a complete revision of the reimbursement prices of all products already in the NHI Drug Price List using the weighted average pricing formula from 1992.

The actual reimbursement price revisions covers the drugs sold in the month of September of a previous year. A survey of all products in the NHI Drug Price List is conducted on about 4,000 sellers, all first-class wholesalers, and about 3,400 purchasers consisting of hospitals, clinics and pharmacies selected at random using specified sampling fractions in each case. Supplemental price surveys including those on changes with time are performed six times. The new reimbursement price is calculated by adding a reasonable zone (R) to the weighted average marketing price obtained from these surveys in consideration of the consumption tax (refer to the calculation).

Calculation:

New drug price = weighted average value of market price in survey x (1 + consumption tax rate) + current reimbursement price x R/100 (however, the new price shall not exceed the current reimbursement price).

This pricing formula is applied to products that are sold in large quantities, and the prices for drugs sold in lower quantities are adjusted using the revision rate for drugs of the same type and same indications.

From 1992, prices were revised at least every 2 years, but an adjustment was made for the increase of the consumption tax rate in 1997, and as a result, reimbursement prices were reduced for 3 consecutive years: 1996, 1997, and 1998. The reimbursement prices were reduced further by the range-adjustment method in 2000. In 2002, the adjustment range was kept at 2%, but an additional reduction of an average of 5% was made for original drugs of generic drugs (excluding those in the JP) in the case of drugs entered in the NHI price list for a long time. In 2004, a price range of 2% and exceptions for long-listed products were applied. Among JP products entered by brand name, original products for which generic products are available on the market were subjected to an additional price reduction of one half of the rate for non-JP products. In 2006, a further reduction of 2% was applied as an exception for long-listed products.

The results of reimbursement price revisions since 1992 are shown in **Table 7.** Methods of Previous Reimbursement Price Revisions and **Table 8.** Revision Rates of Reimbursement Prices.

7. DETERMINATION OF REIMBURSEMENT PRICES FOR NEW DRUGS

In view of trends in the new drug development environment in recent years, Chuikyo stated in their May 1991 recommendation concerning the reimbursement price of new drugs that a more appropriate premium system should be introduced with a new premium for innovation that would be applicable to only truly innovative new drugs. Specifically, it was recommended that the reimbursement price of new drugs should be determined on the basis of comparison with existing drugs from the same category as before but marked up using premiums for innovation, usefulness, and market size; and that requirements for each premium be clearly defined. The price of a daily dose of a new but non-innovative drug approved on or after April 1, 1966, for which several drugs with similar pharmacological action and indications are already listed and for which the efficacy and safety are objectively evaluated to be about the same as these drugs (excluding drugs within 3 years from the appearance of the first drug or within three drugs with the same pharmacological action) was set at a lower price for a daily dose. Coordination with foreign reimbursement prices was also clarified (maximally twice the foreign price).

The six premium rates as of February 2006 were set at 50–100%, 25–40%, 5–20%, 3–10%, 10%, and 3% for innovation, usefulness I and II, pediatric use (new) and market size I and II, respectively. These rates are allocated in a graded fashion depending on the level of the reimbursement price. Requirements for applying premiums are listed in **Table 9.** Requirements for Applying Premiums.

To assure transparency of the pricing system, drug pricing formulas were make public in March 2003 (the most recent revision is given in Notification No. 0215002 of the Health Insurance Bureau dated February 15, 2006, “Drug Pricing Standards”). Procedures for calculation of drug prices were issued in detail in September 2009 (the most recent revision is given in Notification No. 0215010 of the Health Policy Bureau dated February 15, 2006, “Handling of Entries of Prescription Drugs in the Drug Price Lists”).

Methods for submission of requests for inclusion of prescription drugs in the drug price lists were most recently revised in Notification No. 0215006 of the Health Policy Bureau dated February 15, 2006.

A drug pricing organization was established to undertake scientific surveys concerning selection of products for comparison and the applicability of premiums by experts in the medical and pharmaceutical fields. This organization deals especially with pricing and repricing of new drugs in the NHI drug price list.

With the establishment of the pricing organization, flowcharts of the process from new drug approval until entry in the NHI

price list are shown in **Fig. 16** (Reimbursement Pricing Flow-sheet for New Drugs).

Entries of new drugs in the NHI Drug Price List are made as a rule four times a year.

8. ENTRY OF GENERIC DRUGS IN THE NHI DRUG PRICE LIST

In the past, generic drugs have been entered in the NHI Drug Price List once every 2 years, but the entry has been made once a year from 1994. The reimbursement prices for the drugs listed since 1996 are calculated as follows in principle.

As in the case of new drugs, the drug pricing formulas were issued in March 2000 with the aim of assuring transparency of the generic drug pricing system. (The most recent revisions are given in Notifications No. 0215010 of the Health Policy Bureau dated February 15, 2006, “Drug Pricing Standards,” Notification No. 0215010 of the Health Policy Bureau dated February 15, 2006, “Handling of Entries of Prescription Drugs in the Drug Price Lists” and Notification No. 0215006 of the Health Policy Bureau dated February 15, 2006 “Method for Submission of Requests for Entry in the Drug Price List for Prescription Drugs”).

1) When the original drug is already entered in the list and a generic drug identical to the original drug is entered for the first time, the price of the generic drug is obtained by multiplying the original drug price by a factor of 0.8. When both the original and other generic drugs are already entered, the price of the newly entered generic drug is the same as the lowest of the generic prices.

2) When there are many brands with the same standard, i.e., when the number of products already entered and to be entered exceeds 20, the price of the generic drug to be entered is obtained by multiplying the lowest among all products entered by a factor of 0.9. Generic drugs listed for the first time are excluded.

Table 6. Drug Pricing-related Laws

Date of issue	Main points of amendment	Law
4/2006 (enforced)	• Continuation of the national policy to strengthen the financial base of healthcare	National Health Insurance Law
10/2006	• Revision of burden on elderly patients who are currently employed or have an income (20%→30%) • Revision of food and accommodation expenses for the elderly in convalescent hospitals • Reorganization of combined insured and non-insured healthcare	Health insurance-related laws including Health Insurance Law
	• Initiation of a project for collaborative stabilization of health insurance finances	Health Insurance Law
	• Establishment of regional health insurance societies (unions)	Health Insurance Law
3/2007	• Review of the membership of the Central Social Insurance Medical Council and abolition of regulations on endorsement from organizations	Social Insurance Council Law
4/2007	• Revision of payment rates for illness and delivery benefits	Health Insurance Law
4/2008	• Revision of burden on elderly patients aged 70 to 74 years (10%→20%) • Expansion of liability relief measures (20%) for young children (children not older than 3 years→children before school age)	Health insurance-related laws including Health Insurance Law

	• Revision of the name of the law to “Law for Assuring Healthcare for the Elderly” • Program for the optimal utilization of health expenditures • Obligation to provide preventive medical examinations for citizens covered by health insurance • Establishment of a health care system for the very elderly (older than 75 years of age) • Establishment of a fiscal control system for healthcare spending for the pre-elderly (65 to 74 years old)	Health and Medical Service Law for the Elderly
10/2008	• Public incorporation of government-controlled health insurance programs	Health Insurance Law
4/2012	• Abolition of nursing homes for the elderly	Home-care Insurance Law

Table 7. Methods of Previous Reimbursement Price Revisions

Year	Survey	R zone	Special items
1992	June 1991	15%	
1994	June 1993	13%	Repricing
1996	June 1995	11%	Repricing
1997	Sept. 1996	10% 8%（Long listed products）	Repricing Long listed products
1998	Sept. 1997	5% 2%（Long listed products）	Repricing Long listed products
2000	Sept. 1999	Range adjusted, 2%	Repricing Range adjusted, 2%
2002	Sept. 2001	Range adjusted, 2%	Repricing Long listed products (Special adjustment, 4, 5, 6%)
2004	Sept. 2003	Range adjusted, 2%	Repricing Long listed products (Special adjustment, 4, 5, 6%) 1/2 : JP products entered by brand name

2006	Sept. 2005	Range adjusted, 2%	Repricing Long listed products (Special adjustment, additional 2%, new 8%) 5%: JP products entered by brand name

Table 8. Revision Rates of Reimbursement Prices

Year	Number of products with price decrease	Number of products with price increase	Number of products with price unchanged	Total	Revision rate
1992	7,681	2,121	3,771	13,573	−8.1%
1994	8,613	2,083	2,679	13,375	−6.6%
1996	9,568	1,697	1,604	12,869	−6.8%
1997	7,718	3,394	862	11,974	* −3.0%
1998	9,921	6	1,762	11,692	−9.7%
2000	8,935	61	2,291	11,287	−7.0%
2002	9,096	98	1,997	11,191	−6.3%
2004	9,645	39	2,309	11,933	−4.2%
2006	10,113	75	3,123	13,311	–6.7%

* In 1997, the overall drug price revision was -3.0% when a 1.4% rise based on the increased consumption tax rate is included.

Table 9. Requirements for Applying Premiums

<Premium types, requirements and rates>

(1)	Premium for innovativeness (rate: 50-100%) Applied to new drug products in the NHI price lists meeting all of the following requirements:
	1) The new drug has clinical useful new mechanism of action
	2) The new drug has been shown objectively to have greater efficacy and safety than existing drugs in the same category.
	3) The new drug in the NHI price lists has been shown objectively to improve treatment of the disease or trauma indicated for the newly entered drug product.
(2)	Premium for usefulness I (25-40%) Applied to new drug products in the NHI price lists that meet two of the three requirements listed above
(3)	Premium for usefulness II (5-20%) Applied to new drug products in the NHI price lists that meet one of the following requirements (excluding products to which the innovativeness premium or usefulness premium I is applied):
	1) The new drug has been shown objectively to be more effective and safe than existing drugs in the same category.
	2) The drug has been shown objectively to offer, as a result of formulation improvement, greater therapeutic usefulness than other drugs in the same category.

	3) It has been shown objectively that by listing the new drug, the method of treatment of disease or trauma indicated for the newly listed drug has been improved.
(4)	Premium for pediatric use I (10%) Applied to new drug products in the NHI price lists meeting all of the following requirements:
	1) The new drug has is explicitly shown in the Indications section or Dosage and Administration section to be indicated for children (including infants, suckling infants, newborns, and low-birthweight infants).
	2) New drugs (explicitly shown in the Indications section or Dosage and Administration section to be indicated for children) in the NHI price lists for which there are no drugs with similar pharmacological actions related to the main indications and indications in question.
(5)	Premium for marketability I (10%) Applied to new drug products in the NHI price lists meeting all of the following requirements:
	1) Orphan drugs pursuant to the provisions of Article 77-2 of the Pharmaceutical Affairs Law in the NHI price lists for which the orphan indications for the disease or trauma are the main indications of the drugs concerned.
	2) New drugs in the NHI price lists for which there are no drugs with similar pharmacological actions related to the main indications.
(6)	Premium for marketability II (3%) Applied to new drug products in the NHI price lists meeting all of the following requirements (excluding products to which marketability premium I is applied):
	1) New drugs in the NHI price lists for which the main indications correspond to separately specified indication categories with a small market scale among drug indication classifications specified in the Standard Commodity Classification of Japan.
	2) New drugs in the NHI price lists for which there are no drugs with similar pharmacological actions related to the main indications.

[Gradient distribution (sliding scale) based on daily treatment cost]

In drug pricing, a gradient distribution is applied to the above premium rates in accordance with the daily treatment cost calculated by similar efficacy comparison method I.

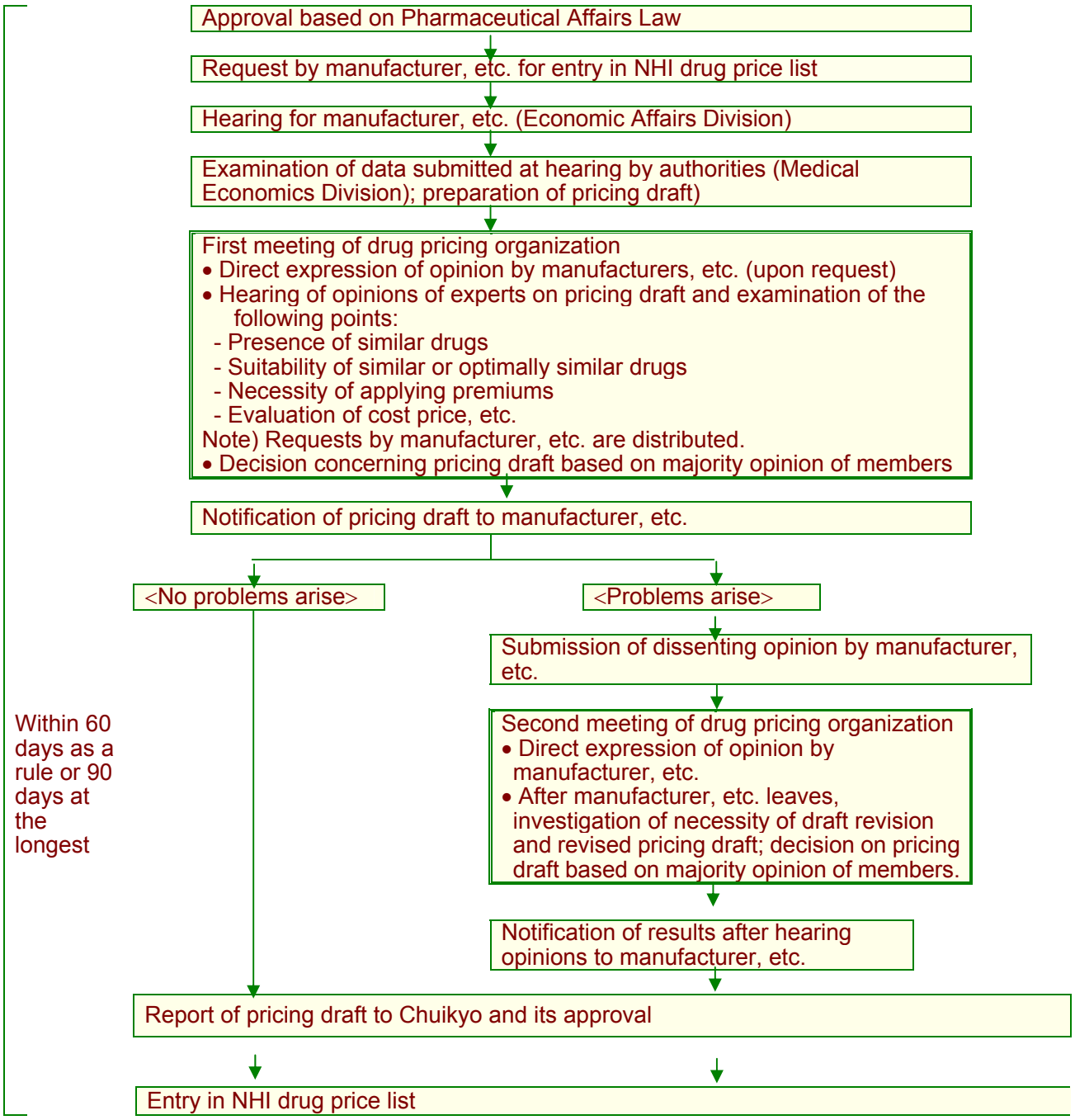


Fig. 16. Reimbursement Pricing Flow-sheet for New Drugs

(Note 1) **The parts in the double box show parts involving the drug pricing organization**

(Note 2) **Time clock (agreed on at MOSS conferences)**

Entry in price list 4 times per year. Listing within 60 days as a rule or 90 days at the longest provided that there are no further problems with the pricing draft.

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