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Pharmaceutical Administration and Regulations in Japan

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Pharmaceutical Administration and Regulations in Japan

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http://www.jpma.or.jp/jpmalib/ (Japanese)

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This file contains information concerning pharmaceutical administration, regulations, and new drug development in Japan updated biannually by the English RA Info Task Force, International Affairs Committee, Japan Pharmaceutical Manufacturers Association. The contents are not abstracts of governmental rules or regulations but concise descriptions of the most current practices by the regulatory agencies and the industry that the working group complies. The file does not contain anything related to forecasts. The file is available also at the homepage of National Institute of Health Science (http://www.nihs.go.jp/mhlw/jouhou/yakuji/yakuji-e0202.pdf).

Japan Pharmaceutical Manufacturers Association

http://www.jpma.or.jp/index.html

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Chapter 1

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

The **Ministry of Health, Labour, and Welfare** (**MHLW**) (**Kosei-roudou-sho** in Japanese) was established by merger of the Ministry of Health and Welfare (**MHW**) and the Ministry of Labour, on January 6, 2001 according to 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 succeeds 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 Social Insurance Council, Pharmaceutical Affairs and Food Sanitation Council (PAFSC), and other institutions. Affiliated institutions are national hospitals, National Institute of Health Science, and other institutions. Local branches are regional bureaus of health and welfare and prefectural labour bureaus. The external organizations are the Social Insurance Agency and the Central Labour Relations Commission (**Fig. 1**).

The MHLW is in charge of pharmaceutical regulatory affairs in Japan. The **Pharmaceutical Affairs Bureau** (**PAB**) was reorganized on July 1, 1997 in conjunction with the enforcement of the revised Pharmaceutical Affairs Law on April 1, 1997 to cope with the greater complexity and internationalization of health administration. Some of the functions of the PAB were entrusted to other bureaus, and a new system of pharmaceutical regulation was initiated. The main features of this reorganization were the establishment of the new office, **Pharmaceutical and Medical Safety Bureau** (**PMSB**), which was renamed as **Pharmaceutical and Food Safety Bureau** (**PFSB**) in October 2001 and which 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 and distribution policies, i.e., functions related to pharmaceutical companies. The **Pharmaceuticals and Medical Devices Evaluation Center** (**Evaluation Center**) established in the **National Institute of Health Sciences** has been undertaking to strengthen approval reviews since July 1, 1997.

This new reorganization consists of three parts: currently, (1) the Pharmaceutical and Food Safety Bureau (PFSB) of the MHLW, (2) the Evaluation Center, and (3) the **Organization for Pharmaceutical Safety and Research** (**OPSR [KIKO]**). It handles a wide range of activities from clinical studies to approval reviews, reviews though the post-marketing stage, and safety measures (**Fig. 2**).

1. Pharmaceutical and Food Safety Bureau (PFSB)

The Pharmaceutical and Food Safety Bureau (PFSB) 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**). 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) General enforcement of the Pharmaceutical Affairs Law.

(3) Enforcement of the Pharmacists Law.

(4) Issues related to the Pharmaceutical Affairs

and Food Sanitation Council (PAFSC).

(5) Supervision of OPSR (KIKO).

* **Office of Drug Induced Damages**

This office undertakes guidance and supervision of OPSR (KIKO) and clerical work related to damage caused by adverse drug reactions (ADRs).

* **Office of Access to Information**

This office was established in April 2000 to assure smooth publication of information in accordance with the promulgation of the Law Concerning Access to Information Held by Administrative Organs established on May 14, 1999.

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.

(2) Manufacturing or import business licenses and approvals to manufacture or import drugs, quasi-drugs, cosmetics and medical devices.

(3) Reexamination and reevaluation of drugs and medical devices.

(4) Issues related to the Japanese Pharmacopoeia (JP).

(5) Standards and specific precautions concerning drugs, quasi-drugs, cosmetics and medical devices.

(6) Designation of orphan drugs and orphan medical devices.

(7) Enforcement of laws pertaining to poisonous and deleterious substances (excluding areas under the control of the Compliance and Narcotics Division).

(8) Regulations related to evaluation of chemicals that might cause damage to human health from the standpoint of the environment and public health, as well as regulations concerning the manufacture, import, use, and other handling of such chemicals.

(9) Control of household products containing harmful substances Control of household products containing harmful substances.

(10) Establishment of tolerable daily intake (TDI) of dioxins and related compounds.

(11) Work related to the National Institutes of Health Sciences (limited to overall management of clerical work concerning reviews required for approvals to manufacture or import drugs, quasi-drugs, cosmetics and medical devices or for reexaminations and reevaluations of drugs and medical devices.).

(12) Work related to OPSR (KIKO) (limited to promotion of research and development of orphan drugs, etc. and assurance of quality, efficacy, and safety of drugs, etc., excluding matters related to the Health Policy Bureau)

(13) Guidance and supervision of designated review organizations for medical devices.

(14) Enforcement of the Industrial Standardization Law for medical devices.

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.

(2) Reviews of the safety of drugs, quasi-drugs, cosmetics and medical devices (excluding work undertaken by the Evaluation and Licensing Division).

(3) Guidance and advice concerning preparation of records of designated medical devices.

(4) Work related to OPSR (KIKO) in collecting adverse drug reaction data and disseminating drug information.

(5) Safety management of hospitals, clinics and maternity clinics.

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.

(2) Guidance and supervision related to advertising of drugs, quasi-drugs, cosmetics and medical devices.

(3) Testing and government certification of drugs, quasi-drugs, cosmetics and medical devices.

(4) Matters related to pharmaceutical inspectors (including GMP compliance inspectors).

(5) Matters related to inspectors of poisons and powerful drugs.

(6) Matters related to health care inspectors.

(7) Enforcement of the Narcotics and Psychotropics Control Law, Cannabis Control Law, Opium Law and Stimulants Control Law.

(8) Issues related to surveys and statistics of narcotics, psychotropics, cannabis, opium and stimulants.

(9) Employment of narcotics control officers and staff as judicial police officials.

(10) Cooperation with international criminal investigations concerning narcotics, etc.

(11) Work related to local narcotics control offices.

(12) Issues related to narcotics, psychotropics, cannabis, opium and stimulants other than that in the above items.

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.

(4) Assurance of stable supply of blood products other than those specified in (2) and (3).

(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) Planning, surveys and coordination related to production and trade of drugs, quasi-drugs, medical devices, sanitary materials and other hygiene-related products (drugs, etc.).

(2) Financial services and other work related to fostering and promotion of production and distribution of drugs, etc.

(3) Enforcement of laws concerning production and distribution of drugs, etc.

(4) Handling of materials required for pricing and production of drugs, etc.

(5) A forum acting on behalf of companies and the industry as a whole in areas related to the drug pricing system and entries in and revisions of the reimbursement price list, hearing of opinions and coordination with the Medical Economics Division, Health Insurance Bureau, in charge of the health insurance system.

(Refer to the procedures related to drug pricing in the health insurance system in Chapter 6).

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

Office of Direction for Health-Related Services

(1) Clerical work related to restrictions on contracting out the work of managers of hospitals, clinics and maternity

clinics.

(2) Guidance concerning work related to improvement of management of hospitals, clinics and maternity clinics.

(3) Issues related to Health Centers.

Office of Industry Research

(1) This office collects information on pharmaceutical and related companies to provide information on the companies and the pharmaceutical industry as a whole and support the drafting of industrial policies by the Health Policy Bureau.

(2) It also serves as a forum for exchanges of information and opinions through consultations with industry.

2.2 Research and Development Division

The functions of this division are as follows:

(1) Planning, surveys and coordination related to research and development of drugs, etc.

(2) Issues related to fostering and promotion of R&D of drugs, etc., including financial services.

(3) Guidance and supervision of OPSR (KIKO) concerning basic research, promotion of research and promotion of development of orphan drugs, etc.

(4) Matters related to the cultivation and production of medicinal plants.

(5) Matters related to the cultivation and production of medicinal plants, general research such as drug discovery and development of anti-HIV drugs via the Japan Health Sciences Foundation*****, and basic research in the field of health promotion and medical treatment and financing and investment in research via OPSR (KIKO).

The **Office of Medical Technology and Information Development** was established with the following functions:

(1) Issues related to installation and use of medical devices.

(2) Maintenance of the health care information management system.

(3) Surveys and planning related to the evaluation of medical technology.

*** 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, etc., 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, poisons and powerful drugs, the Institute oversees the Pharmaceuticals and Medical Devices Evaluation Center which was newly established in July 1997 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.

4. Pharmaceuticals and Medical Devices Evaluation Center (Evaluation Center)

This Center was new established on July 1, 1997 in the National Institute of Health Sciences (formerly the National Institute of Hygienic Sciences) to enhance the expertise and speed-up approval

reviews for drugs, etc. and to strengthen the review system. The Center whose review teams made up to experts in such fields as medicine, pharmacology, veterinary science, and statistics works together with OPSR (KIKO) and conducts reviews ranging from clinical studies to approval reviews and post-marketing reviews, including reevaluations, of drugs, etc., in order to assure the safety of drugs, etc. and prevent recurrences of health damage. The Center consists of four divisions: the Planning and Coordination Division and Evaluation Divisions I, II, III, and IV.

4.1 Planning and Coordination Division

This division consists of two sections.

- **Office of General Affairs**:

  This section is responsible for planning and coordinating various activities of the Center. It is also responsible for the administrative management of Center's review activities.

- **Office of Information**:

  This section is responsible for collecting, analyzing, and distributing review-related information within the Center. Management of clinical trial notifications and adverse drug reaction reports received during the conduct of clinical trials is also coordinated through this section.

4.2 Evaluation Division I

This division undertakes approval reviews, and reviews required for reexamination and reevaluation of new drugs including anti-AIDS drugs, anti-viral drugs, antibiotics, gastrointestinal drugs, chemotherapeutics, and anti-cancer drugs.

4.3 Evaluation Division II

This division undertakes approval reviews, and reviews required for reexamination and reevaluation of new drugs including cardiovascular drugs, new prescription combination drugs, CNS acting drugs, respiratory drugs, anti-allergic drugs, and urogenital drugs.

4.4 Evaluation Division III

This division undertakes reviews required for approval and for reexamination or reevaluation of new drugs including biological products, blood products, and radiopharmaceuticals and approval review of drugs other than new drugs and *in vitro* diagnostics, over-the-counter (OTC) drugs, quasi-drugs, and cosmetics.

4.5 Evaluation Division IV

This division undertakes approval reviews, and reviews required for reexamination or reevaluation of medical devices and approval review of *in vitro* diagnostics.

5. Pharmaceutical Affairs and Food Sanitation Council (PAFSC)

The Pharmaceutical Affairs and Food Sanitation Council (PAFSC) serve as an advisory body to the MHLW, and reviews and discusses important pharmaceutical and food sanitation-related matters (Fig. 3). 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 Section** and a **Food Sanitation Section**. The latter comes under the Food Sanitation Law and the former under other laws.

The Council has as members experts in various fields* including the medical and pharmaceutical sciences whose duty is to examine and review important pharmaceutical matters. The CPAC had 18 committees and 16 subcommittees, but the PAFSC has 16 committees and 21 subcommittees.

The frequency of committee meetings differs. For example, the First Committee on Drugs and the Second Committee on Drugs, which review new drug applications, each meet approximately eight times a year. New drugs are then reviewed or reported and approved by the Pharmaceutical Affairs Council that meets four times a year.**

* Nursing, life sciences, applied biochemistry, mathematics and statistics, law and economics

** For recent new drugs, refer to the Appendix

and homepage on drug information.
(http://www/pharmasys,gr.jp/)

6. National Institute of Infectious Diseases

In April 1977, 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 collection, epidemic surveillance, and supply of information pertaining to infectious diseases, issues certification and performs tests and research for the quality control of antibiotics and other biological products, as well as manufactures biological products that are technically difficult for private companies to produce.

- **Infectious Diseases Information Center**

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

- **AIDS Research Center**

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

7. Organization for Pharmaceutical Safety and Research (OPSR [KIKO])

The Drug Fund for ADR Relief Law was enacted in 1979 to establish the Drug Fund for ADR Relief with the approval and under and supervision of the MHLW in order to provide rapid relief for damages caused by ADRs occurring in humans in spite of correct usage of licensed drugs in accordance with their proper purpose.

This law was partially revised in 1987 and 1994 and the name was changed each time. The current names are the Drug Fund for ADR Relief and Research Promotion, and the Organization for Pharmaceutical Safety and Research (OPSR [KIKO]).

OPSR (KIKO), in addition to providing relief for individuals suffering health damage caused by adverse drug reactions (ADRs), promotes basic research on pharmaceutical technology, supports private pharmaceutical R&D activities, promotes development of orphan drugs, and conducts equivalence reviews for drug approval applications. From April 1, 1997, OPSR (KIKO) began consultation services on planning and conduct of clinical studies, reviews of clinical study protocols, and reviews of the suitability of data attached to pharmaceutical approval applications (**Fig. 2**).

7.1 General Affairs Department

This Department undertakes overall coordination and drafts management plans for OPSR (KIKO).

7.2 ADR Relief Department

This Department undertakes work related to ADR relief including the provision of medical costs, disability pensions, survivor pensions and funeral costs for individuals whose health has been damaged by ADRs. It also provides funds, including medical costs, on request for SMON patients and individuals who were infected with HIV by tainted blood products.

7.3 R&D Promotion Department

This Department undertakes investment in R&D projects aimed at R&D of technology related to the production and distribution of drugs, quasi-drugs, cosmetics, and medical devices, as well as major improvements industrial technology levels or technological reforms in the health care field, provides partial financing for expenses to consolidate research results such as patent fees, and financing of R&D from which concrete results can be expected to overcome important problems in the health care field, and provides support for private R&D activities. It also undertakes collaborative projects with national research institutes and universities or contract research on basic research topics, and promotes the results of such research.

7.4 Product Review Department

At the request of the Minister of the MHLW, this Department undertakes reviews for comparison with source data and certification of data attached to

approval applications for generic drugs in connection with "**compliance with the application data reliability standards**" specified in the Pharmaceutical Affairs Law, including whether or nor the data was compiled correctly based on test results; reviews of equivalence of "drugs, etc. with drugs, etc. of confirmed efficacy and safety which have already been approved"; and **GLP compliance reviews**.

This Department also provides medication consultation for consumers. This Department gives financial support to companies or other organizations developing designated drugs, etc. to promote the development of orphan drugs, and approves R&D expenses so that companies receiving financial support can obtain tax exemptions under the Special Taxation Measures Law. It also forms alliances with the MHLW and provides guidance and advice on R&D for companies, etc.

In addition, this Department reviews certification of drugs for export at the request of the MHLW, and provides medication consultation for consumers and drug information***.**

* To promote the safe use of prescription drugs, information on prescriptions drugs provided by the MHLW and the manufacturers is available via the Internet for health professionals and others who may be interested (http://www/pharmasys,gr.jp/).

7.5 Clinical Trial Review & Guidance Department

This Department provides consultation on clinical studies to assure the safety of subjects and the development of more effective and safer drugs. This consultation is in the form of guidance and advice on clinical studies on new drugs for approval reviews and reviews required for reexamination or reevaluation in response to consultation applications from pharmaceutical companies.

At the request of the Minister of the MHLW, this Department also reviews data attached to applications for approval to manufacture or **import drugs concerning compliance with GCP**.

This Department reviews initial clinical trial application (clinical studies for the first time on human subjects in Japan) on new drugs with new active ingredients to assure the safety of subjects.

7.6 Compliance Review Department

At the request of the Minister of the MHLW, this Department undertakes paper reviews to compare with source data and certify data from clinical studies attached to new drug approval applications with respect to **compliance** with the application data reliability standards. It also reviews data attached to applications for reexamination of new drugs for compliance with the reexamination data reliability standards.

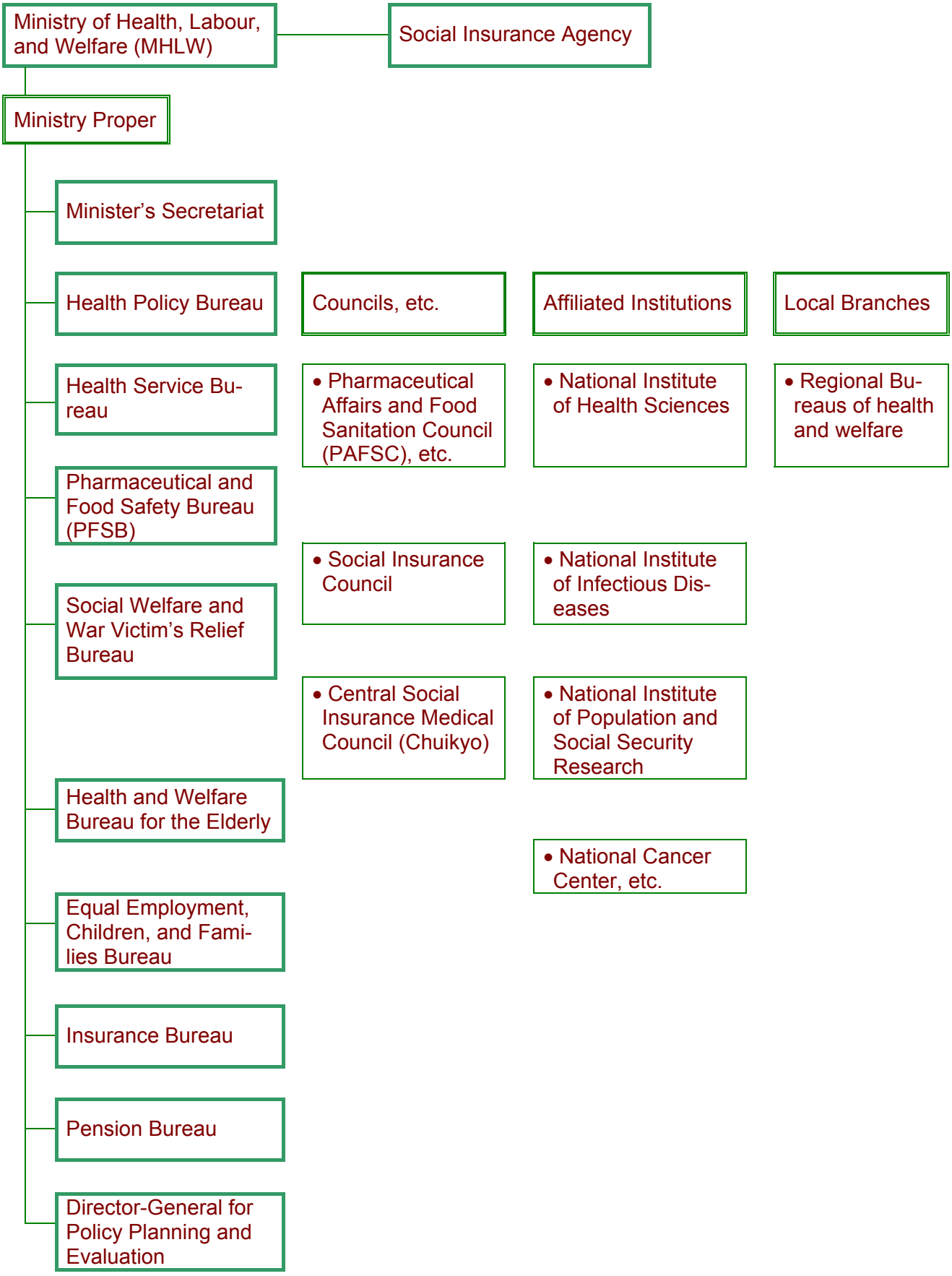


FIG. 1 ORGANIZATION OF MINISTRY OF HEALTH, LABOUR, AND WELFARE (PHARMACEUTICAL AFFAIRS-RELATED OFFICES)

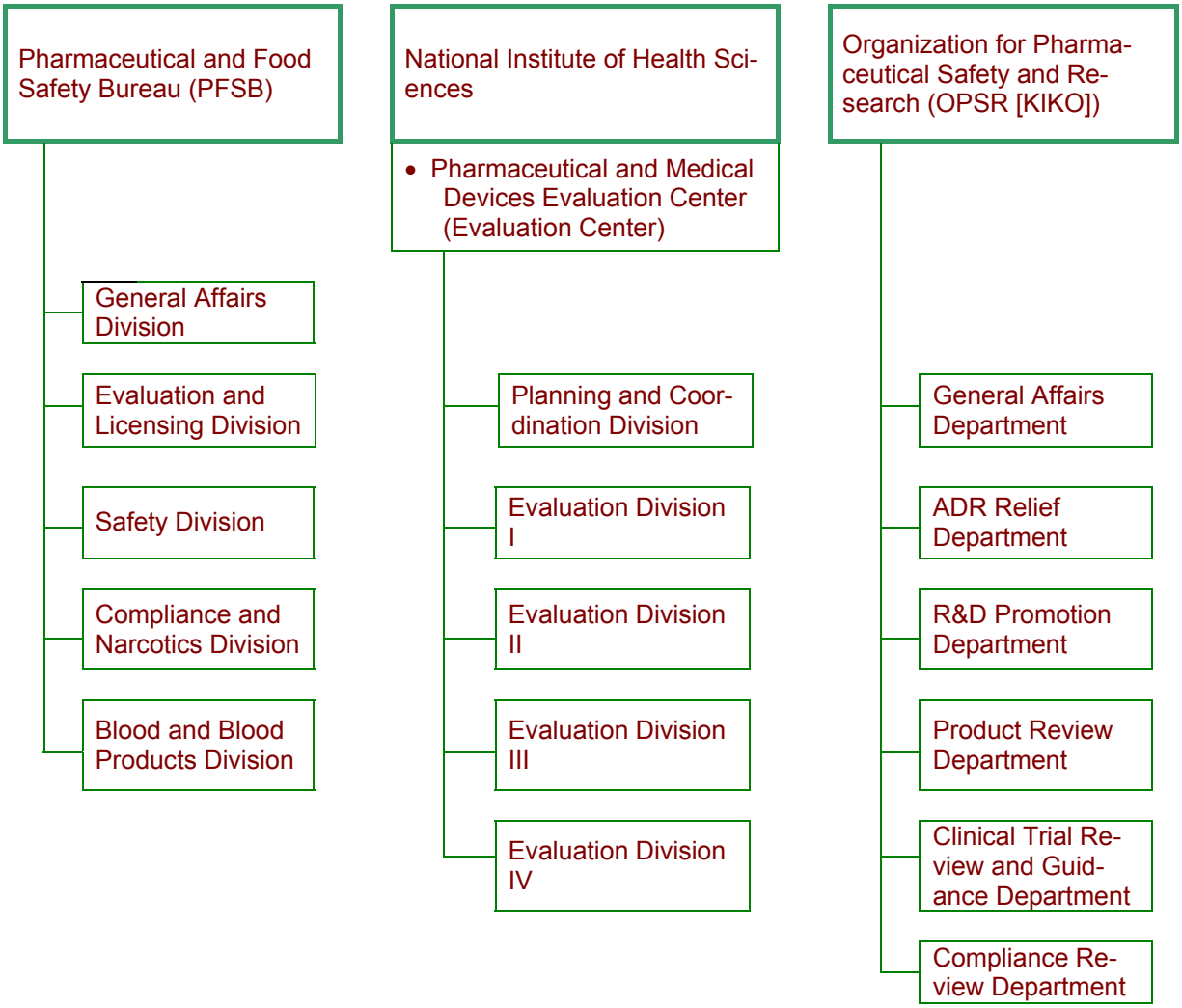


FIG. 2 ORGANIZATION OF THE PHARMACEUTICAL AND FOOD SAFETY BUREAU (PFSB), THE PHARMACEUTICALS AND MEDICAL DEVICES EVALUATION CENTER (EVALUATION CENTER), AND THE ORGANIZATION FOR PHARMACEUTICAL SAFETY AND RESEARCH (OPSR [KIKO])

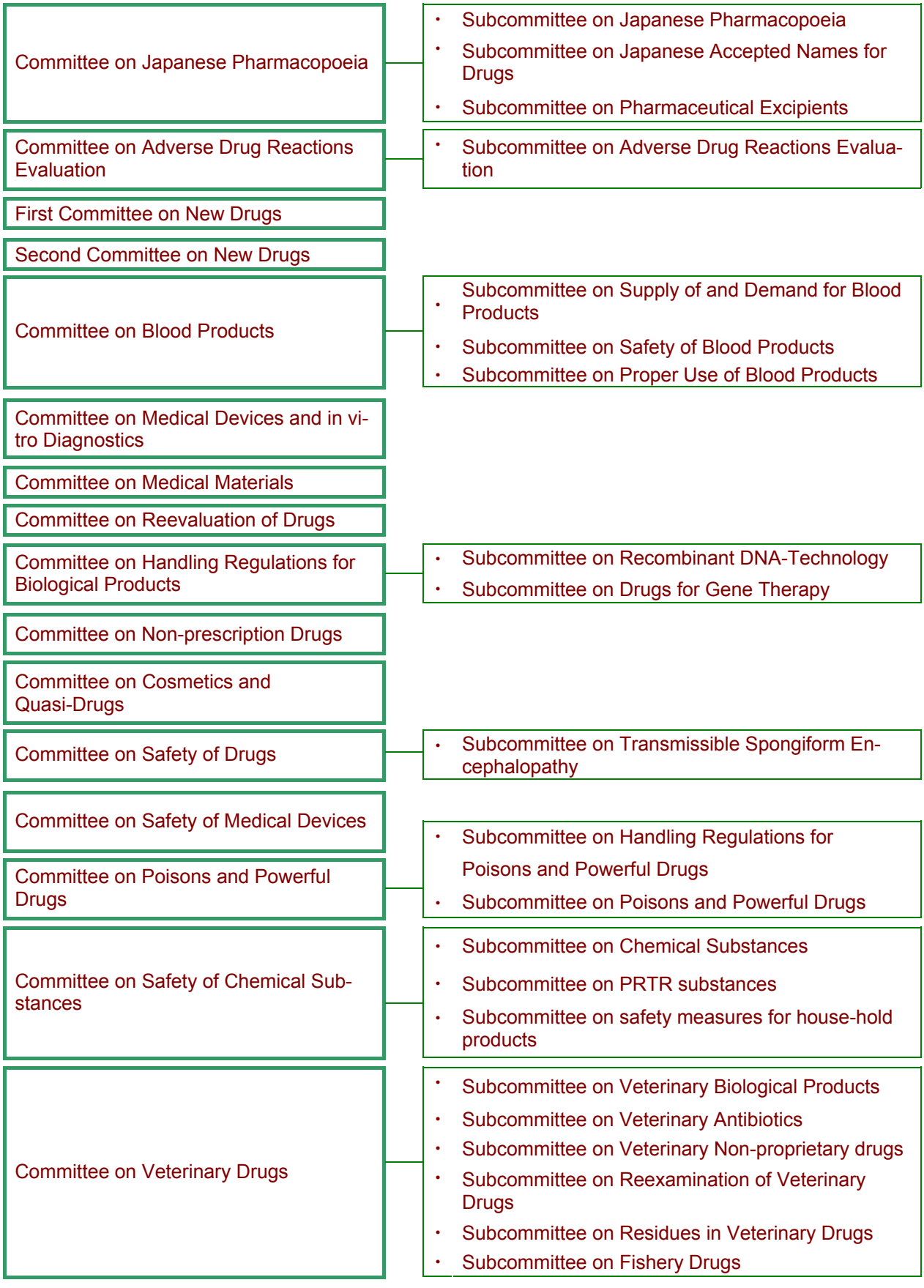


FIG. 3 ORGANIZATION OF THE PHARMACEUTICAL AFFAIRS AND FOOD SANITATION COUNCIL (PAFSC) (16 COMMITTEES AND 21 SUBCOMMITTEES, MARCH 31, 2003)

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) the Pharmacists Law, (3) the law concerning the Organization for Pharmaceutical Safety and Research, (4) the Blood Collection and Blood Donation Services Control Law, (5) the Poisonous and Deleterious Substances Control Law, (6) the Narcotics and Psychotropics Control Law, (7) Cannabis Control Law, (8) the Opium Law, and (9) the 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, Labour, 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 which 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 foreign 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 exceptions for biological products, investigator-initiated clinical trials and adverse drug reaction reports from medical institutions came into effect on July 30, 2003 (Cabinet Order No. 212, April 23, 2003) and provisions related to manufacturing and distribution businesses and manufacturing businesses, as well as provisions related to medical devices will come into effect on April 1, 2005.

The Pharmaceutical Affairs Law has 11 chapters and 89 articles as follows:

Chapter 1: General Provisions (Purpose and definitions of drugs, quasi-drugs, cosmetics, medical devices, pharmacies, orphan drugs, orphan medical devices and clinical trials)

Chapter 2: Pharmaceutical Affairs Councils (Council on Drugs and Food Sanitation and Local Pharmaceutical Affairs Councils) Council on Drugs and Food Sanitation (establishment of the Pharmaceutical Affairs Section)

Chapter 3: Pharmacies (License standards,

supervision of pharmacies, duty of supervisor, etc.)

Chapter 4: Manufacturers and Importers (License standards for manufacturers or importers, special licenses before approval, approval to manufacture or import, reviews in conjunction with approval reviews performed by OPSR (KIKO), reviews in conjunction with approval reviews of medical devices performed by designated review organizations, reexamination, reevaluation, supervision of manufacture, items requiring compliance by manufacturers, manufacturing approvals for drugs manufactured in foreign countries, etc.)

Chapter 4-2: Designated Review Organizations (Designation standards, staff, review specifications, etc. for designated review organizations for reviews of medical devices)

Chapter 5: Sales of Drugs and Sales and Leasing of Medical Devices (Types of retailing license, restrictions on items sold, and on methods of sale, items requiring compliance by sellers and leasers, etc.)

Chapter 6: Standards and Government Certification for Drugs (the Japanese Pharmacopoeia and other standards, etc.)

Chapter 7: Handling of Drugs (Handling of poisonous and powerful drugs, sale of prescription-only drugs, items to be entered on the immediate container and package inserts, prohibition of sale and manufacture, etc.)

Chapter 8: Advertising of Drugs (Prohibition of 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 (manufacturing supervisors, matters indicated on immediate containers, matters indicated on package inserts, etc., prohibition of retail and manufacture, explanation of specified biological products by appointed health professionals, regular reports on infectious diseases, retention of records on preparations, and guidance and advice).

Chapter 9: Supervision (On-site inspection, emergency orders, orders for improvement, revocation of approval and licenses, hearings, etc.)

Chapter 9-2: Designation of Orphan Drugs and Orphan Medical Devices

Chapter 10: Miscellaneous Provisions (Supply of information, reports of ADRs, recall reports, procedures for clinical trials, etc.)

Chapter 11: Penal Provisions

In April 2005, the remaining provisions in the revised Pharmaceutical Affairs Law concerning the approval and licensing system will come into effect. The revision is outlined in the Attachment. At present, the pharmaceutical system is under review and the Pharmaceutical Affairs Law will be revised based on this review. An outline of this revision is given in the Appendix.

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.

(4) 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. 1115003 of the Pharmaceutical and Food Safety Bureau (PFSB), MHLW dated November 15, 2002).

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 guidance of a physician or a dentist

(2) **Non-prescription drugs**

Drugs other than prescription drugs which are intended for use at the discretion of general consumers by direct purchase in a pharmacy or drug store.

2) Classification according to handling regulations related to safety

Drugs include those which 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.

(1) Poisonous drugs (Article 44 of the Law).

(2) Powerful drugs (Article 44 of the Law).

(3) Drugs requiring directions or 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 requiring record-keeping (Article 14 of the Enforcement Regulations of the Law).

(7) Drugs with restrictions on advertising (Article 67 of the 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 (GCP).

(14) Drugs for post-marketing clinical studies (GCP).

(15) Biological products (Article 2, Paragraph 5 of the Law)

(16) Specified biological products (Article 2, Paragraph 6 of the Law)

3) Biological products and specified biological products

Biological products were classified as follows based on the definition 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 keeps 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, 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 marketing.

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 5 of the Law) are the drugs, quasi-drugs, cosmetics or medical devices shown in Attached Table 1. Specified biological products (Article 2, Paragraph 6 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 Necessity of Manufacturing or Import Approvals

Formal approvals and licenses are required in order to manufacture or import drugs in Japan, and formal approval and/or licenses must first be obtained from the appropriate authorities. Depending on the circumstances, the appropriate issuing authority may be the Minister of the MHLW, prefectural governor, or the local health authority.

Manufacturing or importing and distributing business licenses must be obtained for each facility or business office when operating a drug manufacturing or import business.

Approvals are granted for each product on the basis of reviews of whether the product to be manufactured or imported is appropriate as a drug or not. Licenses for drugs to be manufactured or imported are granted after confirmation that the capacity and facility for manufacturing or importing and distributing drugs are adequate.

3.4 Good Manufacturing Practice (GMP)

GMP specifies general requirements ranging from the building and facilities of the plant through the overall manufacturing process to manufacturing control and quality control as requirements for manufacturing licenses (refer to Chapter 3).

3.5 Regulations for Imported Drugs Management and Quality Control

Regulations for Imported Drugs Management and Quality Control (commonly referred to as GMPI) dated June 2, 1999 have become licensing conditions for pharmaceutical importers, and this new system has been enforced from August 1.

3.6 Drug Seller Licensing

A license must be obtained from the Prefectural Governor in order to sell or supply drugs.

3.7 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.

3.8 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 cautions for use.

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 2003 (refer to Chapter 5).

3.9 Restriction 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 public, 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).

3.10 Good Laboratory Practice (GLP)

GLP specifies standards which must be met by testing facilities for nonclinical safety tests on drugs from the viewpoint of the structure/facility 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) which was enforced on April 1, 1997 to assure greater reliability of application data (refer to Chapter 3).

3.11 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 issued by the Secretary-General of the Ministry on 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 developed 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 studies. This ordinance was set forth 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 Investigation Committee on the Efficient Conduct of Clinical Research reported recommendations to improve systems for actively encouraging voluntary participation of human subjects in clinical studies and for better 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 burdens required of the subject.

(5) Train and develop clinical research coordinators (CRCs).

Based on these recommendations, several measures were taken to improve the conduct of clinical trials. Such measures include 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 public hospitals and public medical schools (Notification No. 196 of the Inspection and Guidance Division, PMSB dated July 2, 1999 and Notification No. 20 of the Inspection and Guidance Division, PMSB, MHW, July 2, 1999).

The current GCP was enacted on October 4, 1998. However, the Investigation Committee on the Efficient Conduct of Clinical Research indicated the need of standardized operational procedures for the proper conduct of clinical studies. One of the working groups in the committee investigated and discussed various items related to the procedures and reported the standard operational guidelines, in particular the acceptance of monitoring requests by the medical institution in view of potential practical

problems at the site of patient care and management (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 Policy Study Group on 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 as clinical research 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.

3.12 Good Post-marketing Surveillance Practice (GPMSP)

GPMSP specifies 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, and it was issued as an MHW ordinance in 1997 (Ordinance No. 10: so-called new GMPSP dated March 10, 1997), which was enforced on April 1, 1997 to further strengthen post-marketing surveillance (refer to Chapter 4).

3.13 Reexamination and Reevaluation

PMS on new drugs must be performed by manufacturers or importers so that efficacy and safety can be reconfirmed by reexamination by the MHLW, in principle, 6 years after approval. All drugs, including those which 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 so-called new GPMSP.

Since April 1, 1997, periodic safety reports must be submitted to the Minister until completion of the reexamination period of the drug concerned for drugs requiring investigation of clinical use.

3.14 Adverse Drug Reaction (ADR) and Infection Reporting

When manufacturers or importers of drugs are informed of any adverse reaction, etc. as specified by MHLW ordinance for trial products or their marketed products, they must report it to the Minister within the specified period.

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 (Notification No. 164 of the Safety Division and Notification No. 1843 of the Evaluation and Licensing Division, PMSB dated December 28, 1999).

Since October 27, 2003, electronic adverse drug reaction reports have been accepted. They can be sent via the Internet or brought to the Ministry or mailed in the form of a disk etc. together with the paper copy.

3.15 Dissemination of Information

Manufacturers or importers, wholesalers, and foreign manufacturers with manufacturing approval or their **in-country caretakers** must endeavor to supply physicians, pharmacists and other health professionals with information concerning the efficacy and safety of the drugs and medical devices, and other information for proper use of the drugs and medical devices (proper-use information), including information of ADRs.

3.16 Measures related to the Law Concerning Access to Information Held by Administrative Organs

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

Based on this Law, basically the MHLW must disclose the contents of its reviews (records of meetings of the PAFSC, new drug approval infor-

mation 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). These criteria 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 and narcotics-related documents, (4) blood and blood products-related documents, and (5) other activity-related documents. Actual decisions applied for such accessibility are specified.

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) and 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 those on the manufacturing method, specifications and test methods, impressions of the applicant, etc.) are not disclosed.

3.17 Patent System

The patent term is 20 years from the time of application as a rule. However, if the patent can not be implemented in accordance with laws and regulations to ensure the safety of the drug, etc. the patent term can be extended for a maximum of 5 years. The extension is permitted for the period that the patented invention cannot be implemented, such that the period of extension becomes 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 manufacturing approval for the drug. Since the extension is applied to patents, it does not apply to me-too products as a rule.

Patentees who wish 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 the disposition as drug approval. In cases where it is anticipated that it will not be possible to take disposition of government ordinance by the day before 6 months prior to the date on which the patent expires, a document showing necessary information including patent number must be submitted. If an application for an extension is submitted, it can be considered that the patent term be extended until judgment of rejection becomes final or until the extension is registered (**Fig. 4**).

Japanese language website of the Patent Office: http://www.jpo.go.jp/indexj.htm English website: http://www.jpo.go.jp/index.htm

3.18 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 and Other Activities Involving Controlled Substances Through International Cooperation.

June 26, the last 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 in the form of a third period of stimulant abuse with feelings of resistance and alarm concerning drug abuse waning among young people such as middle and high school students.

A notification has been issued on procedures for handling narcotics by narcotics wholesale dealers (Notification No. 2060 of the Narcotics Division, PMSB dated November 9, 2000).

4. Approval and Licenses

4.1 Drug Manufacturing and Import Approval and Licenses

Drug manufacturing and import approval means the governmental permission for a drug to be manufactured or imported, generally distributed, and used for health care in Japan. Whether or not a substance under application is appropriate for use for human health care is objectively determined in light of the state of the art of medical and pharmaceutical technology. Specifically, the MHLW reviews the name, ingredients, composition, dosage and administration, indications and ADRs, etc. of the substance before giving approval. 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.

Manufacturing and import licenses are issued after ensuring that the applicants are able to manufacture or import and to distribute the approved drugs, e.g., whether manufacturing or business facilities of the applicants have sufficient structure and equipment, manufacturing and quality control systems and human resources to properly deal with the approved drugs. In order to manufacture or import and to distribute drugs, manufacturers or importers must obtain a drug manufacturing or import license for each of their manufacturing plants or business facilities from the prefectural governor and a manufacturing or import license for each product from the MHLW.

Issuing of licenses under the authority of the Minister was delegated to the local health authorities (regional bureaus of the Ministry) (Article 81-4, the Pharmaceutical Affairs Law) at the merger of the MHW and the Ministry of Labour on January 6, 2001.

From April 2005, the current “manufacturing (import) approvals” will become “manufacturing and distribution approvals” and the current “manufacturing (import) licenses” will become “marketing licenses” as specified in the Pharmaceutical Affairs Law revised in 2003.

4.2 Approval Reviews

Application forms for approval to manufacture or import drugs are usually submitted to the prefectural authorities who forward them to the MHLW. When forms for new drugs are received by the Pharmaceuticals and Medical Devices Evaluation Center (Iyakuhin Iryokiki Shinsa Senta in Japanese, PMDEC, Evaluation Center), a reliability review of the application data (certification from source data), **GLP compliance** review are undertaken by OPSR (KIKO). When the reliability and compliance of the data are confirmed, a detailed review is undertaken by a team of experts for the field concerned at the Evaluation Center, and the team prepares a team review report.

A new system, consisting of meetings of specialists, has been introduced for review and evaluation of new drug applications. These meetings, consisting of team reviewers and medical experts (consultants), focus on the discussion of key issues. The subcommittees will eventually be dissolved.

The evaluation process followed by the Evaluation Center (announced in a November 30, 2000 notification) is as follows

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

(2) Team review

(3) Inquiries and checks

(4) Report (1)

(5) Specialists’ meeting (includes at least three clinical experts)

(6) Hearing (main agenda items and specialist committee attendees communicated to an applicant 2 weeks prior to meeting; presentation)

entation)

(7) Follow-up specialist meeting

(8) Report (2)

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

Then, a report is submitted to the Pharmaceutical Affairs Section (Committees on New Drugs) of the PAFSC for review and discussion as required on the basis of the review report, and sent to the MHLW where the Minister grants the new drug approval (Fig. 5). A **New Drug Approval Information Package (NAIP)** is prepared from the review data and published so that accurate information concerning the quality, efficacy and safety obtained during the approval review process and required for proper use of the drug can be supplied to medical institutions, etc.

In reviews of new drugs with new active ingredients, drug samples are requested for special reviews, and the specifications and testing methods are usually checked by the National Institute of Health Sciences, or by the National Institute of Infectious Diseases in the case of biological products and antibiotics. When the active ingredients, dosage, administration route, and indications are the same as those of approved drugs, a review is undertaken by the Evaluation Center after reviews on drug equivalence and compliance by OPSR (KIKO), and approval is granted.

A basic notification concerning drug approval reviews was issued on April 8, 1999 and will come into force for approval reviews of drugs from April 1, 2000.

On February 8, 2000, a notification was issued on completion of approval application forms for new drugs; the notification includes general rules for completion the forms and exceptions.

Also, 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 hearing is held within 6 months after application (excluding the time taking by the applicant to prepare replies, etc.).

With the agreement 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).

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

These guidelines will be enforced from July 1, 2003 but approval applications can be filed from July 1, 2001 using these guidelines (refer to Chapter 3).

Based on the review period of 1 year, the time for responding to inquires for the applicant has also been set at 1 year as a rule or 2 years as a maximum. The applicant is asked to withdraw the application in case a longer time is required for responding to inquiries or conducting additional studies.

Since additional expenses are required for reduction of the review period, an increase in application fees for all new drugs submitted after April 1, 2000 was implemented. Further changes in the fees were made on April 1, 2004.

4.3 Priority Review System

Drug approval reviews are normally processed in the order that the application forms are received, but with this system, applications are reviewed on a priority basis for drugs, which have been designated as orphan drugs and other drugs, which are considered to be especially important from a medical standpoint. The latter drugs include those indicated for serious diseases, and those which are particularly excellent medically with respect to efficacy and safety when compared with existing drugs.

A study group concerning priority reviews met to discuss selection of products subject to priority reviews and products for priority clinical trial consultations, and the following opinions were presented.

1. Products other than orphan drugs or orphan medical devices should be selected based

on the seriousness of the indicated diseases and an overall assessment of therapeutic usefulness

(1) Seriousness of indicated diseases

① Diseases with important effects on patient's lives (fatal diseases)

② Diseases with marked effects on daily life (progressive irreversible diseases)

③ Others

(2) Overall assessment of therapeutic usefulness when there is no existing method of treatment or with respect to existing treatment

① There is no existing method of treatment.

② Therapeutic usefulness with respect to existing treatment

i) Standpoint of efficacy

ii) Standpoint of safety

iii) Reduction of physical and mental burden on the patient

2. Concepts concerning the selection of products subject to priority reviews and products for priority clinical trial consultations should be coordinated. To achieve a more efficient priority review system it is necessary to achieve closer coordination between the priority review and priority clinical trial systems.

3. Selection of products for priority clinical trial consultations should be based on data that can predict usefulness for products of fixed quality such as Phase II clinical trial results including overseas data.

4.4 Special Licensing System before Approval

Unless a drug has been approved, it normally cannot be granted a license for manufacture or import, but with the revision of the Pharmaceutical Affairs Law in June 1996, a system of special licenses before approval was initiated to cover emergencies.

The drugs to which this system applies are those used in emergencies to prevent the spread of diseases, which might have a major effect on the people's lives and health. It also applies to drugs for diseases for which the drug concerned is the only method of treatment and which are marketed in foreign countries. Such drugs may be granted a license for manufacture or import even though they have not received approval for manufacture or import.

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, excellent usefulness of the drug from the medical standpoint, etc. 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.

4.6 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 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, multiple applicants in the same codevelopment group are regarded as a single applicant under the new rules, and requirements for data submitted by individual companies for approval application have been simplified.

4.7 Transfer of Approvals

Manufacturing (import) approvals can be transferred to legally authorized manufacturers and importers through succession, merger, contracts, etc. provided that all data and related information are transferred from the original approval holders.

4.8 Approval Applications for Drugs Manufactured in Foreign Countries

Pharmaceutical manufacturers outside Japan can apply directly under their own name for manufacturing 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**).

However, the applicants must designate an **'in-country (domestic) caretaker'**, resident in Japan, who can fulfill the following responsibilities required in Japan. In-country caretakers, together with the foreign manufacturers, are obliged to adhere to all provisions in the Pharmaceutical Affairs Law.

- Receive reexaminations and reevaluations of the drug
- Report ADRs to the Ministry
- Provide necessary information to the importer for appropriate handling of the drug

In-country caretakers must be appointed when a foreign manufacturer applies directly to the MHLW for manufacturing approval. In-country caretakers must be resident in Japan and must meet certain criteria specified by MHLW ordinance. They must fulfill criteria equivalent to those for supervisors for drugs or responsible technicians for medical devices, which apply to Japanese manufacturers.

4.9 Issuing of Certificates by MHLW

Notifications on issuing export certificates for drugs and medical devices were partially revised and the certificates for the items related to 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 manufacturing (import) of drugs, etc., manufacturing (import) approvals for drugs, etc., attached documentation for new drug manufacturing or applications, GLP compliance for drugs, clinical investigation of drugs, business licenses for manufacture (import) and marketing of medical devices, manufacturing (import) approvals for medical devices, certification of pharmaceutical products, and statements of approval and licensing status of pharmaceutical products. The Ministry desires to issue using formats specified by the WHO; however, they accept country-specific format when necessary. The request for issuing export certificates on drugs, quasi-drugs, and medical devices should be sent to OPSR (KIKO) (Table 2). Certificates for the Items Related to Clinical Study Protocol Notices for Drugs and the Items Related to Conformity of Drug Manufacturing Factories with GMP can be obtained by requesting directly to the Compliance and Narcotics Division of the MHLW.

4.10 Issuing Certificates Based on the WHO Certification System

In principle, export certificates for drugs approved and licensed by the MHLW are issued according to the WHO certification systems from January 1998: certificates are not issued item-wise but totally describe the approval status, GMP compliance, and product information by certification of pharmaceutical products and statements of approval and licensing status of pharmaceutical products.

5. Japanese Pharmacopoeia and Other Standards

5.1 Japanese Pharmacopoeia (JP)

Japanese Pharmacopoeia (JP) was established and published to regulate the properties and qualities of drugs by the MHLW after hearing the opinion of the Pharmaceutical Affairs and Food Sanitation Council (PAFSC). The JP consists of Part I and Part II. Part I covers mainly widely used bulk drugs and

basic preparations, as well as drugs essential for health care. Part II covers combination preparations and their bulk components, drugs produced from natural substances and basic substances required for pharmaceutical formulations.

Since it was first published in June 1886, the JP has been revised several times. Based on the Pharmaceutical Affairs Law, the JP is 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 Committee on the Japanese Pharmacopoeia to cope with recent progress in the medical and pharmaceutical sciences in November 2001. As a result, the following policies for revisions were issued for the 15th edition of the JP (JP 15).

(1) The "basic policies" are as follows:

(a) Complete entries of all drugs important in health care

(b) Rapid revisions as required and the resulting smooth application of government policies

(c) Promotion of international harmonization

(d) Assurance of transparency concerning revisions of the JP and widespread application of JP

(e) Promotion of introduction of the latest analytical methods and coordination of reference substances.

(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 essential 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

Supplement 1of the 14th edition of the JP had been issued and came into effect during a period from April 2001 to January 2003. Future plans include Supplement 2 to be issued in January 2005 and the 15th edition scheduled to come into effect in April 2006. In addition, partial revisions will be made as required.

(4) Selection of products for entry in the JP

Items selected for entry in the JP must be those important in health care based on the necessity of the drug in medical practice, wide application and experience of use. Products with definite significance and specifications will be entered in the JP, and reasons and standards of individual drugs for entry in the JP would be confirmed.

Opinions of related organizations should be obtained for entry as required.

(5) Organization of the JP Panels

The organization consists of 11 panels: Panel on general affairs, physical test methods, medicinal chemicals, biological test methods, antibiotics, crude drugs, nomenclature, excipients, biological products, as well as a subpanel on general affairs and a PDG (Pharmacopoeial Discussion Group)-related panel.

5.2 Standards Based on Article 42 of the Pharmaceutical Affairs Law

For drugs, which 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

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 all 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 provisions of Article 42 (Standards of Drugs, etc.) of the Law. These standards 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.

5.4 Quality Standards Based on Notifications

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

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

5.5 Government Batch Test

Government supervision and certification based on batch tests are specified for drugs, which 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, biological products are subject to such testing.

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

6. Inspections

6.1 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 and 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.

6.2 Procedure of Product Recalls

Based on the provisions of the Pharmaceutical Affairs Law, the Minister of the MHLW or prefectural governors may appoint "**pharmaceutical inspectors**" to work in the prefectures in connection with the rationalization of pharmaceutical manufacture, import, quality, labeling, advertisements or distribution. This pharmaceutical inspection system covers falsely labeled drugs, drugs of poor quality, drugs, which have not been approved or licensed, false or exaggerated advertising, and nosocomial infections. When violations are discovered, the inspectors may issue various orders including administrative measures as required. The main measures are as follows:

- Revocation of approval, changes in approved items.
- Revocation of licenses, business suspension.
- Temporary suspension of sales and disposal of the drug concerned.
- Recall orders.
- On-site inspections of pharmacies, hospitals, clinics, pharmaceutical manufacturers or importers, etc.
- Improvement orders in cases where the buildings and facilities, etc. of pharmaceutical manufacturing plants do not comply with the GMP.

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). Companies have been requested to pay respond positively to this notification.

6.4 Safety Measures Against Bovine Spongiform Encephalitis

Bovine spongiform encephalitis (BSE) frequently broke out 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 medicinal products to be manufactured by using 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 medicinal products 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 Pharmaceutical and Food Safety Bureau dated April 14, 2002 concerning bovine-derived raw materials that require precautions related to the site or 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.

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 given.

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 (Notifications No. 906 of the PMSB dated July 30, 1999 and No. 1314 of the PMSB dated December 26, 2000).

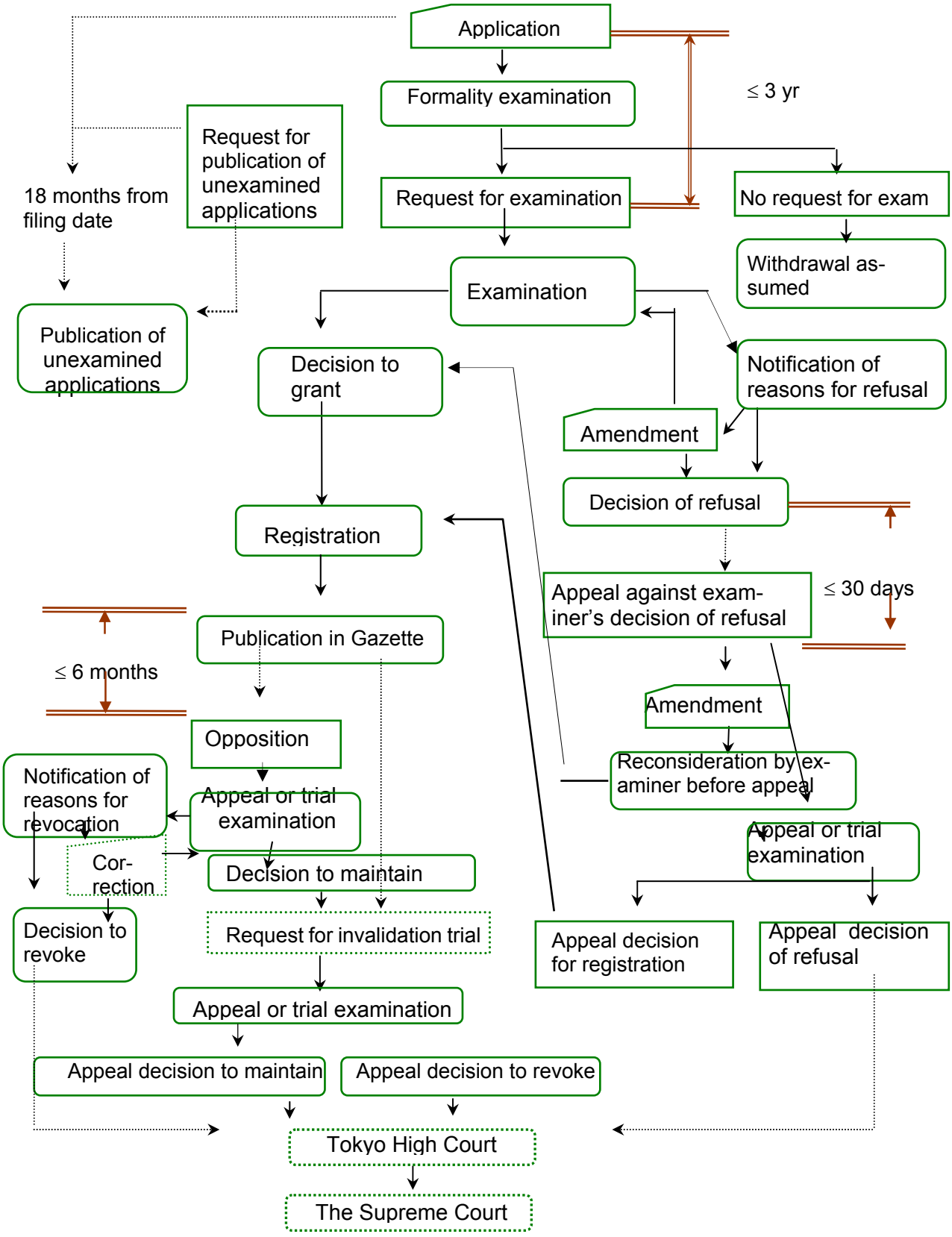


Fig. 4 Flowchart of Patent Application and Objection

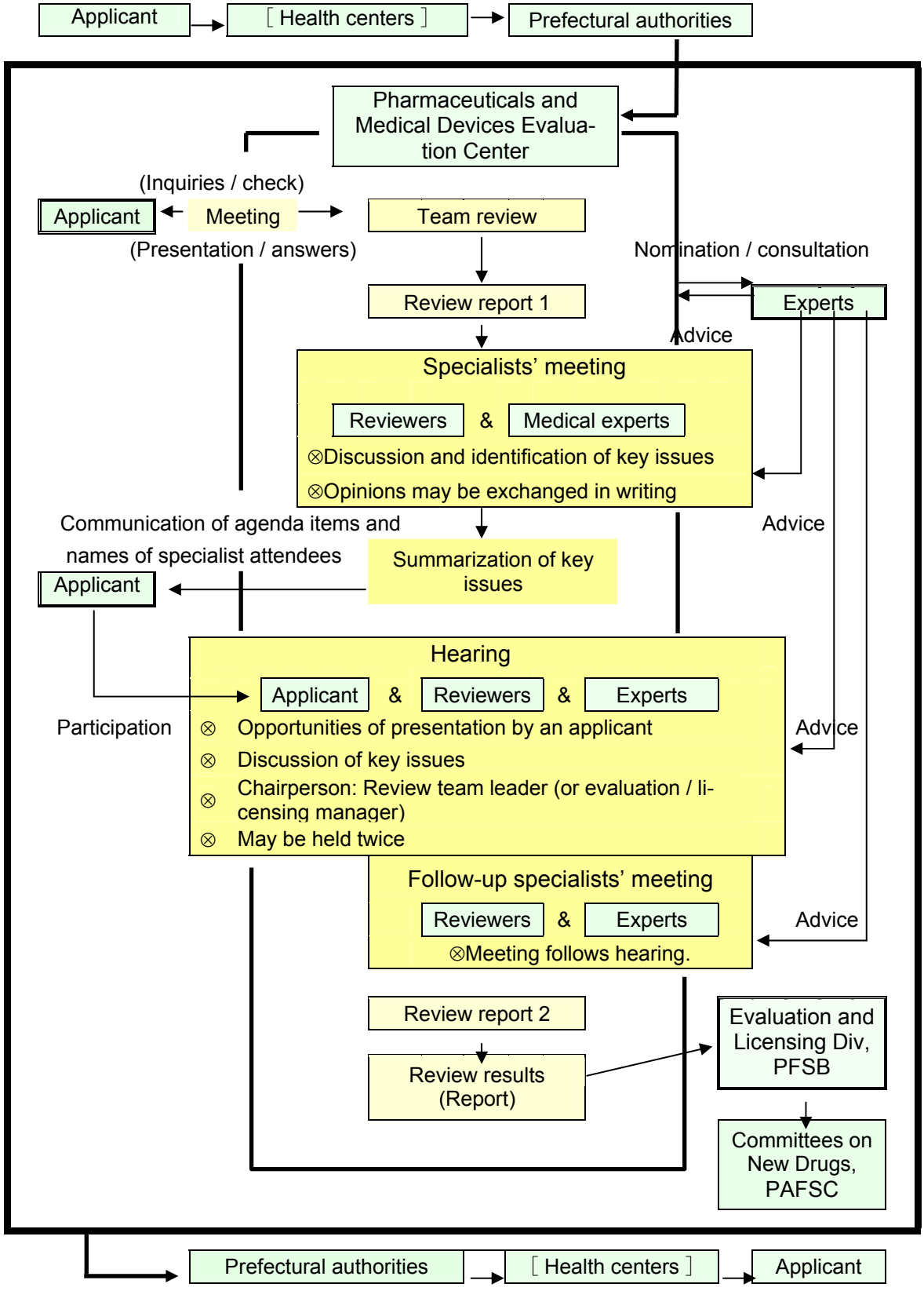


FIG. 5 FLOWCHART OF APPROVAL REVIEW

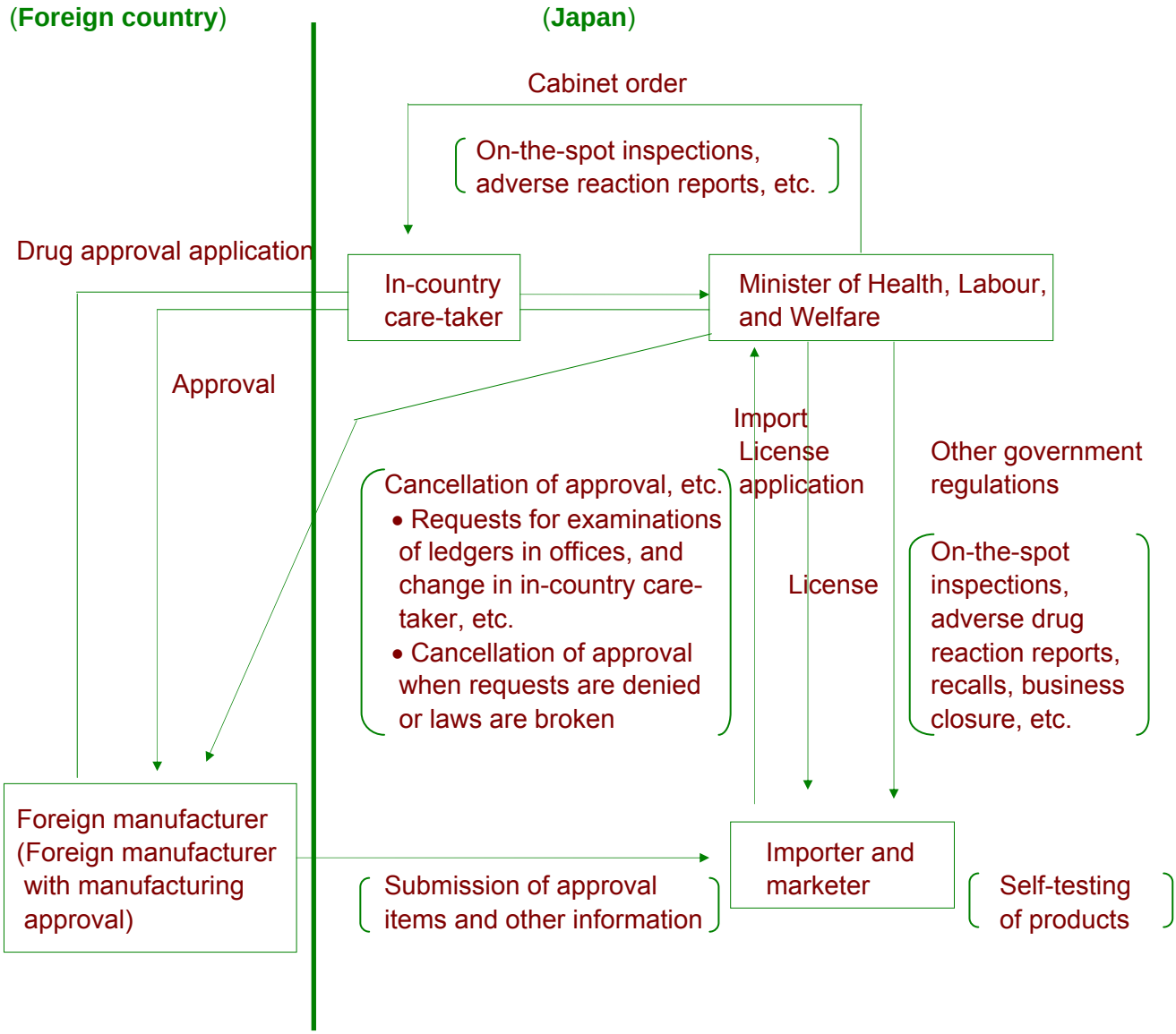


FIG. 6 CASE WHERE PERSONS MANUFACTURING DRUGS IN FOREIGN COUNTRIES OBTAIN APPROVALS DIRECTLY FROM THE MINISTRY OF HEALTH, LABOUR, AND WELFARE

TABLE. 1 LIST OF MAIN CONTROLLED SUBSTANCES

Classification	Characteristics
Poisons and powerful drugs	Poisons and powerful drugs 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-only drugs	Prescription-only drugs are designated by the MHLW as drugs which may be sold or supplied only under the prescription or direction of a physician, dentist or veterinarian.
Habit-forming drugs	Habit-forming drugs are drugs designated by the MHLW as habit-forming.
Designated drugs	Designated drugs are designated by the MHLW as drugs for which sale or supply by drug retailers with second-class licenses is prohibited.
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.
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.

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 or import and distribution of drugs, etc. 2. Items related to manufacturing or import approvals for drugs, etc. 3. Items related to attached documentation for new drug manufacturing or import 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 notices for drugs 6. Items related to business licenses for manufacture or import and marketing of medical devices 7. Items related to manufacturing or import approvals for medical devices 8. Items related to certification of pharmaceutical products 9. Items related to statements of approval and licensing status of pharmaceutical products
Compliance and Narcotics Division	- Items related to conformity of drug manufacturing factories with GMP

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 or import or those listed in the JP. Applications for approval of new drugs must be submitted to the Ministry of Health, Labour 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 are usually consisted 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 14-3. Related ordinances include the Ordinance on **Standards for Conduct of Clinical Trials** (MHW Ordinance No. 28, March 27, 1997, partially revised by MHLW Ordinance No. 106 dated June 12, 2003) (**GCP**); the Ordinance on **Standards for Conduct of Nonclinical Studies on the Safety of Drugs** (MHW Ordinance No. 21, March 26, 1997) (**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 OPSR (KIKO) at the request of the MHLW.

1.2 Reviews and Guidance by the OPSR (KIKO)

The OPSR (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 (Refer to GLP Article 3.1.3)

The OPSR (KIKO) 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. 705 of the OPSR dated July 9, 2001) of the OPSR (3.1.4. GLP).

2) Review of Clinical Study Protocols

The OPSR 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 Evaluation Center at the request of the Minister of Health, Labor and Welfare.

3) Clinical Trial Consultation

The OPSR has established a consultation system for clinical study protocols to improve and reinforce the quality of clinical studies. Clinical study consultations by the OPSR consist of four types for

clinical studies performed during the course of development of new drugs:

(1) Clinical trial consultations for new drug development

① Consultations before start of Phase I studies

② Consultations before start of Phase II studies

③ Consultations after completion of Phase II studies

④ Pre-application consultations

(2) Clinical trial consultations for reexminations and reevaluations

① Consultations when planning clinical trials for reexminations and reevaluations

② Consultations on completion of clinical trials for reexminations and reevaluations

(3) System-related clinical trial consultations

① Consultations on procedures

② Consultations on quality

③ Consultations on safety

④ Additional consultations

4) Compliance Reviews

Following revision of the Pharmaceutical Affairs Law in June 1996, the OPSR 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

Paper reviews are based on "Guidelines for Paper Compliance Reviews for New Drugs" (Notification No. 357 of the Evaluation and Licensing Division, Pharmaceutical and Medial Safety Bureau, MHLW dated March 31, 1998) when the applicant provides the OPSR with data. The review assures that the approval review data has been collected and compiled in accordance with the above criteria. In August 2001, the OPSR has shown a checklist for self-compliance review by the applicant prior to approval applications.

- On-site reviews

In these reviews, the OPSR 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 (Notifications No. 629 of the Evaluation and Licensing Division, PMSB dated May 16, 2001). The revised guidelines were applied from September 1, 2001.

The reviews are generally performed in the applicant's offices and facilities and the medical institutions performing the clinical study (four facilities). 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 3 shows the GCP on-site reviews conducted between April 1, 1997 and March 31, 2003.

1.3 Approval Reviews

A detailed team review as well as discussion with specialists designated by the Committee or Subcommittee chairperson of the PAFSC is performed by the teams of specialists and review staff in the Pharmaceuticals and Medical Devices Evaluation Center in the National Institute of Health Sciences (Evaluation Center) after the reliability is confirmed in the compliance review by the OPSR (KIKO). For the main points concerning reviews, refer to "Points to Consider for Approval Application Data for New Drugs" (Office Communication of January 28, 2002). 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, Labour, and Welfare (Refer to 4.2 Approval Reviews, Chapter 2). **Fig. 7** 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 pro-

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 5.2: 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, Pharmaceutical and Medial Safety Bureau, MHLW dated April 8, 1999). These notifications were issued in consideration of the globalization of drug development from April 2000.

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 Pharmaceutical and Medical Safety Bureau, 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, Pharmaceutical and Medical Safety Bureau, dated June 21, 2001, partially revised: Notification No. 0701004 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, dated July 1, 2003) was issued to specify guidelines for preparation of data to be attached to approval applications based on the CTD. The structure of the data 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.

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 poison, powerful drug, 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)

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 in Notification No. 663 of the PMSB and No. 899 of the Evaluation and Licensing Division, PMSB dated June 21, 2001 and the attachments 1 and 2-(1) were also revised. The guidelines for preparation of data to be attached to approval applications can be applied as present in approval applications (after enforcement of CTD related-notifications on July 1, 2003) for drugs corresponding to 7: Drugs with Additional Formulations, 7.2: Combination Prescription Drugs with Similar Prescriptions, and 8: Other Drugs in Table 3.

2.1.2 Non-prescription Drugs

The range of data to be submitted with applications for non-prescription drugs is also specified in Notification No. 698, which was revised as shown in Table 4 of Notification No. 481 of the PMSB dated April 8, 1999. 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 application for non-prescription drugs as in the past. Application categories and handling of data to be attached to approval applications were partially revised in Notification No. 0827003 of the PFSB dated August 27, 2003 “Approval applications for non-prescription drugs,” which came into effect from October 1, 2003.

3. Guidelines Concerning Drug Approval Applications

Guidelines outlining standard test methods and essential criteria for reference in the preparation of data for drug manufacturing or import 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 Pharmaceutical and Medical Safety Bureau dated August 8, 1998) and Ethnic Factors to be Considered in the Acceptance of Foreign Clinical Trial Data (Notifica-

tion No. 672 of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau dated August 11, 1998). 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 concluded that the clinical study outcome in 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 OPSR (KIKO).

The data attached to applications for approval to manufacture or import drugs must be in Japanese, but as part of the deregulation process, it was specified in Notifications No. 256 of the Pharmaceutical and Medical Safety Bureau and No, 265 of the Evaluation and Licensing Division, PMSB, both dated March 18, 1998, that documents in English 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” (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)” (Notification No. 571 of the Evaluation and Licensing Division, PMSB dated May 1, 2001). These new 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 (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) (Notification No. 571 of the Evaluation and Licensing Division, PMSB dated May 1, 2001

(3) Text (items) on Analytical Validation (Notification No. 755 of the Pharmaceuticals and Cosmetics Division, PAB dated July 20, 1995)

(4) Text (items) on Analytical Validation (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 (Notification No. 877 of the Pharmaceuticals and Cosmetics Division, PAB dated September 25, 1995)

(6) Guidelines on Impurities in Drug Preparations (Notification No. 539 of the Pharmaceuticals and Cosmetics Division, PAB, dated June 23, 1997)

(7) Guidelines on Residual Solvents in Drug Preparations (Notification No. 307 of the Evaluation and Licensing

Division, PMSB dated March 30, 1998)

(8) Handling of Pharmacopoeia-related Approved Items in JP for International Harmonization (May 1, 2001)

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 (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, Notification No. 0603001 of the Evaluation and Licensing Division, PFSB dated June 6, 2003). New stability test guidelines have also be established for approval applications outside the three ICH regions (EU, Japan and the US) (Notification No. 0603007 of the Evaluation and Licensing Division, PFSB dated June 6, 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 (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 (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) (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 (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 re-

placed by these guidelines:

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

(2) Guidelines for Reproductive and Developmental Toxicity Studies (Notification No.316 of the Pharmaceuticals and Cosmetics Division, PAB dated April 14, 1997 and 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) (Notification No.443 of the Pharmaceuticals and Cosmetics Division, PAB dated July 2, 1996).

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

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

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

(7) Timing of Preclinical Studies in Relation to Clinical Trials (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)

Data on the following studies which should be conducted in accordance with the above guidelines are required for the review and evaluation of a new drug application by the Ministry:

(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” (Notification No. 325 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 or import 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 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 OPSR 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 OPSR are performed on the basis of the “GLP compliance guidelines” specified by the OPSR (Notification No. 151 of the OPSR dated June 6, 1994; No. 705 dated July 9, 2001; partially revised in Notification No. 1226 dated December 27, 2002). GLP compliance conditions are evaluated in the following three categories by the GLP Evaluation Committee established by the OPSR 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. 253 of the Evaluation and Licensing Division and No. 29 of the Safety Division, PAB dated March 27, 1997). 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 Guidelines for General Pharmacological Studies Required for Applications for Approval to Manufacture (Import) Drugs issued in 1991 show basic approaches and test items required for general pharmacological studies conducted in research and development of new drugs and related products. The major objectives of general pharmacological studies include: (1) to generally determine the types and magnitudes of pharmacological effects the investigational product exerts in addition to its therapeutic effects in order to clarify its pharmacological profile; (2) to predict ADRs that may occur in humans and to collect information necessary to cope with them; and (3) to evaluate adverse effects of the product and which may not be found in toxicity 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 efficacy pharmacology, secondary/safety pharmacology, and other pharmacology. In the part related to secondary pharmacology studies, the guidelines on general pharmacology are used as reference. The safety pharmacology guideline (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. 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).

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 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).

In addition, 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) 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).

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

(4) 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).

3.2 Clinical Studies

1) Basic Requirements

As stated in the General Guidelines for Clinical Evaluation of New Drugs published by the MHW in June 1992, 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.

Since the General Guidelines for Clinical Evaluation of New Drugs were published in 1992, 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**).

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) 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 or import 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**.

Studies must be designed and data analyzed or evaluated according to the above clinical guideline. **Fig. 9** 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 procedure 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: human pharmacology)

Phase I entails the initial administration of an investigational new drug to humans. The most typical study is that on clinical pharmacology. Although human 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.

(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 surveillance to assess efficacy and safety in special populations, and post-marketing clinical studies to obtain additional information. These studies are called Phase IV studies and PMS (Chapter 4).

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 co-administered, it is usually important that drug interaction studies be performed in nonclinical and, if appropriate, in human 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 adequately documented 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 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 (Notification No. 1047 of the Evaluation and Licensing Division, PMSB dated November 30, 1998), 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 February 2002, the following 27 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 Antimalignant Tumor Drugs (Notification No. 9 of the New Drugs Division, PAB dated February 4, 1991).

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

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

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

[2] Guidelines common for clinical evaluation

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

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

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

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

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

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

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

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

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

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

[3] Other guidelines

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

(22) Research on Evaluation Methods of Blood Preparations, Especially Plasma Fraction Preparations (1984).

(23) Guidelines on Clinical Evaluation Methods of Antiarrhythmic Drugs (1984).

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

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

(26) Guidelines on Clinical Evaluation Methods of Antianginal Drugs (1985).

(27) 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).

* ICH guidelines

6) **Requirements** for **Conduct of Clinical Studies**

Regarding the conduct of clinical studies to collect data to be submitted with approval applications for new drug manufacturing or import, the Pharmaceutical Affairs Law and the **GCP** (MHW Ordinance No.28, March 27, 1997) 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 studies, 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 studies conducted after the drug goes on the market.

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 Evaluation Center (at least 2 weeks for subsequent notifications). The sponsor must report to the authorities any severe adverse reactions or infections which 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 OPSR (KIKO) 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 OPSR (KIKO) gives guidance and advice concerning study protocols has also been established (refer to 1.2-3 Clinical Trial Consultation of this Chapter).

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 which 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 which might result in disability
- Other medically serious condition
- Congenital diseases or abnormalities in the next generation

(b) Predicted deaths or events which 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.

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 studies 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 1 and Article 48, Paragraph 1); and data concerning the results of clinical studies performed by individuals 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.
- Information on adverse reactions, etc. required for proper conduct of the trial must be collected and examined, and provided to the medical institutions performing the trial.
- 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.

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 studies to be submitted for reexaminations or reevaluations, but taking account of the nature of post-marketing clinical studies, 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 OPSR (KIKO) 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 OPSR (KIKO) 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 (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 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, **Standards for Manufacturing Control and Quality Control (GMP)** were specified in Notification No. 801 of the PAB dated September 14, 1974 and they were enforced from April 1976 with some exceptions. With the partial revision of the Pharmaceutical Affairs Law in October 1979, the GMP became legally binding. The control part of the GMP is specified in **Drug Manufacturing and Quality Control Regulations** in MHW Ordinance No. 31, 1980, and the part concerning buildings and facilities is specified in the revision of the Regulations for Buildings and Facilities for Pharmacies, etc. in MHW Ordinance No. 32, 1980 based on Article 13 of the Pharmaceutical Affairs Law.

Thereafter, provisions related to validation, recall, self-inspections, and education and training were added and the revised Regulations for Manufacturing Control and Quality Control of Drugs (MHW Ordinance No.3, January 27, 1994) and Regulations for Buildings and Facilities of Pharmacies, etc. (MHW Ordinance No.4, January 27, 1994) were issued and went into effect from April 1, 1994.

Provisions required to assure the quality of biological products,* including prevention of contamination by microorganisms, were added to the Regulations for Manufacturing Control and Quality Control of Drugs (Drug GMP) (MHW Ordinance No.71, September 25, 1997) and to the Regulations for Buildings and Facilities of Pharmacies, etc. (MHW Ordinance No. 57, April 30, 1999) since biological products require handling of animals and microorganisms in the manufacturing process, and a high level of control in accordance with the features of individual products such as utilization of biological reactions.

Regulations for Manufacturing Control and Quality Control of Drugs were revised to apply to some quasi-drugs (MHW Ordinance No. 16, March 12, 1999).

To eliminate the risk of spreading infections from cell and tissue-derived drugs and medical devices, the regulations for buildings and facilities for biological products have been applied, the period of retention reference substances and records has been extended and donor screening has been added (MHLW Ordinances No. 54, 55, 56, 57, 58 and 59 dated March 28, 2001).

* Biological products also include drugs manufactured using DNA recombinant technology, drugs manufactured using cell culture technology, and drugs using plants or animals or their components as raw materials or other materials.

4.1 Requirements for Buildings and Facilities (GMP Hardware)

Requirements concerning buildings and facilities of drug manufacturing plants (GMP hardware specifications) are specified in Chapter 2, Manufacturers of Drugs, etc., of "Regulations for Buildings and Facilities for Pharmacies, etc." (buildings and facilities regulations) in the MHW ordinance (Ordinance No. 57, April 30, 1999).

When buildings or facilities in plants do not meet these requirements, the Minister of the MHLW or the prefectural authorities may refuse to grant the license.

4.2 Requirements for Manufacturing Control and Quality Control (GMP Software)

The requirements for manufacturing control and quality control methods in pharmaceutical plants (GMP software specifications) are specified in "Regulations for Manufacturing Control and Quality Control of Drugs and Quasi-Drugs" in the MHW Ordinance No.16, March 12, 1999). The requirements for manufacturing control and quality control methods for drug substance should be referred to the Guidelines on GMP for Drug Substance (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.

When the manufacturing control and quality control methods in the plant do not comply with these regulations, the Minister of the MHLW or prefectural authorities may refuse to grant the license.

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 occurs, Bio-GMP 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 bear responsibility for these operating procedures. 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 lie with the drug manufacturing control manager designated in each plant under the Pharmaceutical Affairs Law.

Article 2 of the control regulations specifies that the plant must be organized so that there is a quality control unit independent of the manufacturing unit, and a quality control manager and a manufacturing control manager must be appointed as the persons with the ultimate responsibility in the respective units. Under the manufacturing control manager, managers controlling each manufacturing process or managers controlling manufacturing hygiene may be designated if necessary. 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

Manufacturers must prepare manufacturing control standards for each factory and also manufacturing hygiene control standards for each manufacturing facility. Work related to manufacturing control must be performed appropriately by the manufacturing control manager based on the product standards, manufacturing control standards and manufacturing hygiene control standards. Records concerning manufacturing, storage, shipment and manufacturing hygiene control must be retained for a period of 3 years from the date of preparation or one year longer than the expiration date in the case of products with an expiration date (10 years from the expiration date for cell and tissue-derived drugs). For biological products, records concerning the handling of microbes used in tests must be prepared and retained for 5 years from the date of preparation (10 years from the expiration date for cell and tissue-derived drugs).

4) Quality Control

Manufacturers must prepare quality control specifications for each plant and the quality control supervisor must carry out work related to quality control of drugs based on the product specifications and the quality control specifications.

Quality control supervisors must evaluate the test results and report there results in writing to the drug manufacturing control managers and manufacturing control supervisors. The records concerning test results must be retained for 3 years from the date of preparation or for drugs with an expiration date, the period until the expiration date plus one year (when the drugs concerned are cell or tissue-derived drugs, the period until the expiration date plus 10 years). In the case of biological products, records concerning the handling of microorganisms used in the tests must be prepared and must be retained for 5 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).

5) Documents Concerning Procedures for Validation, etc.

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

6) Validation

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

- The validation results must be reported in writing to the drug manufacturing control supervisor.
- 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 must take appropriate measures when improvement 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 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).

7) Complaints

When manufactures receive complaints concerning products, they must ensure that the following obligations are fulfilled by the manufacturing control manager in compliance with the standard operating procedures.

- To clarify the cause of the complaint, and to take the required measures when improvements in manufacturing or quality control are necessary.
- Compliant handling records including the contents of the complaint, clarification of the cause and measures taken for improvement must be prepared and 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).

8) Product Recalls

When manufacturers decide to recall drugs for reasons related to quality, etc., they must have the following obligations fulfilled by the manufacturing control manager in compliance with the standard operating procedures.

- To clarify the cause of the recall and to take the appropriate measures in case that improvements in manufacturing or quality control are necessary.
- Recall records including the contents of the recall, clarification of the cause and measures taken for improvement must be prepared and 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).

9) Self-inspections

The manufacturer 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.
- Records of the results of self inspections must be prepared and 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 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 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).

10) 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.
- Records of the conduct of education and training must be prepared and must be retained for 3 years from the date of preparation.

The manufacturer 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.

4.3 GMP Compliance Reviews

When an application is submitted for a new drug manufacturing business license or a license to add or change a product manufactured, or renewal, the

plant must be inspected for the authorities to determine if it actually complies with the GMP standards.

Evaluation Rank Criteria

A: (Complied): 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) not rated as A 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.

4.4 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, and negotiations are in progress for such agreements with the United States and Canada. 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 EU as a whole in 2002: public documents were exchanged to enforce mutual approval agreements in November 2001 and the drug GMP came into effect from January 1, 2002. In the future, mutual approvals will begin after a preparatory period is established and confirmation of mutual systems and an inspection system.

4.5 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, the PAB specified Standards for Quality Assurance of Imported Drugs and Medical Devices (Notification No. 380 of the PAB dated April 19, 1993) for items related to manufacturing control and quality control which must be met when drugs are imported. Based on these standards, the Regulations for Imported Drug Management and Control were specified (MHW Ordinance No.62, June 2, 1999) and enacted on August 1, 1999.

These regulations include 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 im-

ported is manufactured under appropriate manufacturing control and quality control, and must import, store and distribute drugs and conduct testing in accordance with the standard code, 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.

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 (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 (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) (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). 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 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. Supplements or attachments have been added to the main notifications related to biological products.

5.3 Summary of New Drug Approvals (Public Disclosure of Information)

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 OPSR dated May 29, 2002).

5.4 ICH

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 Union (EU), European Federation of Pharmaceutical Industries' Associations (EFPIA), Ministry of Health, Labour, 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 50 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. In September 2002, the steering committee reached final agreement on the eCTD (electronic CTD).

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 for the 21st century will appear, including new guidelines for products applied in cutting-edge advanced technology including drugs for gene therapy and the post-marketing safety guidelines for new drugs proposed by Japan.

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

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 February 2003, over 50 guidelines have been approved (Step 4 or 5) based on ICH activities.

Step 5

Quality

Q1A: Guidelines on Stability Testing (Drugs with New Active Ingredients)

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

Q1B: Guidelines on Stability Testing: Photostability

Q1C: Guidelines on Stability Testing: New Formulations and Changes

Q1D: Guidelines on Stability Testing: Bracketing and Matrixing Designs for Stability Testing

Q1E: Guidelines for Evaluation of Stability Data

Q1F: Guidance for a Stability Data Package for Registration Applications in Climatic Zones III and IV

Q2A: Text on Validation of Analytical Procedures: Terminology and Definitions

Q2B: Text on Validation of Analytical Procedures: Methodology

Q3A: Guidelines on Impurities in New Drug Substances: Bulk drugs

Q3AR: Guidelines on Impurities in New Drug Substances (Revise)

Q3B: Guidelines on Impurities in Dosage Forms: Preparations

Q3C: Guidelines on Impurities: Residual Solvents

Q3CM: Guidelines on Impurities (Residual Solvents): Maintenance

Q5A: Quality of Biotechnological Products: Viral safety Evaluation

Q5B: Quality of Biotechnological Products: Genetic Stability

Q5C: Quality of Biotechnological Products: Stability of Products

Q5D: Quality of Biotechnological Products: Cell Substrates

Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drugs (Drug Substance and Products) in harmony of three pharmacopoeia

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

Q7A: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

Safety

S1A: Guidelines on the Need for Carcinogenicity Studies of Pharmaceuticals

S1B: Carcinogenicity Studies: Use of Two Rodent Species

S1C: Guidance on Dose Selection for Carcinogenicity Studies of Pharmaceuticals

S1C(R): Revision of Guidelines on Dose Selection for Carcinogenicity Studies of Pharmaceuticals

S2A: Genotoxicity: Guidance of Specific Aspects of Regulatory Tests

S2B: Specific Aspects of Genotoxicity Tests of Pharmaceuticals: Standard Battery Tests

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

S3B: Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies

S4: Guidelines on Single Dose and Repeated Dose Toxicity Tests

S4A: Guidelines on Duration of Chronic Toxicity Tests (Revisions)

S5A: Guidelines on Tests for Reproductive Toxicity

S5B: Tests for Toxicity to Male Fertility

S5BM: Revision of Guidelines on Tests for Reproductive Toxicity: Male Fertility Studies

S6: Safety Studies for Biotechnological Products

S7A: Safety Pharmacology 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: Clinical Safety Data Management: Periodic Safety Update Reports

E3: Clinical Study Reports: Structure and Content

E4: Dose-Response Information to Support Drug Registration

E5: Ethnic Factors in the Acceptability of Foreign Clinical Data

E6: GCP (Good Clinical Practice): Consolidated Guidelines

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

Multidisciplinary Topics

M1: Medical Terminology

M2: Electronic Transmission of Safety Case Reports

M3: Timing of Preclinical Studies in Relation to Clinical Trials

M4: The Common Technical Document (CTD) for the Registration of Pharmaceuticals for Human Use

eCTD (electronic Common Technical Document)

M4Q: Quality

M4S: Safety

M4E: Efficacy

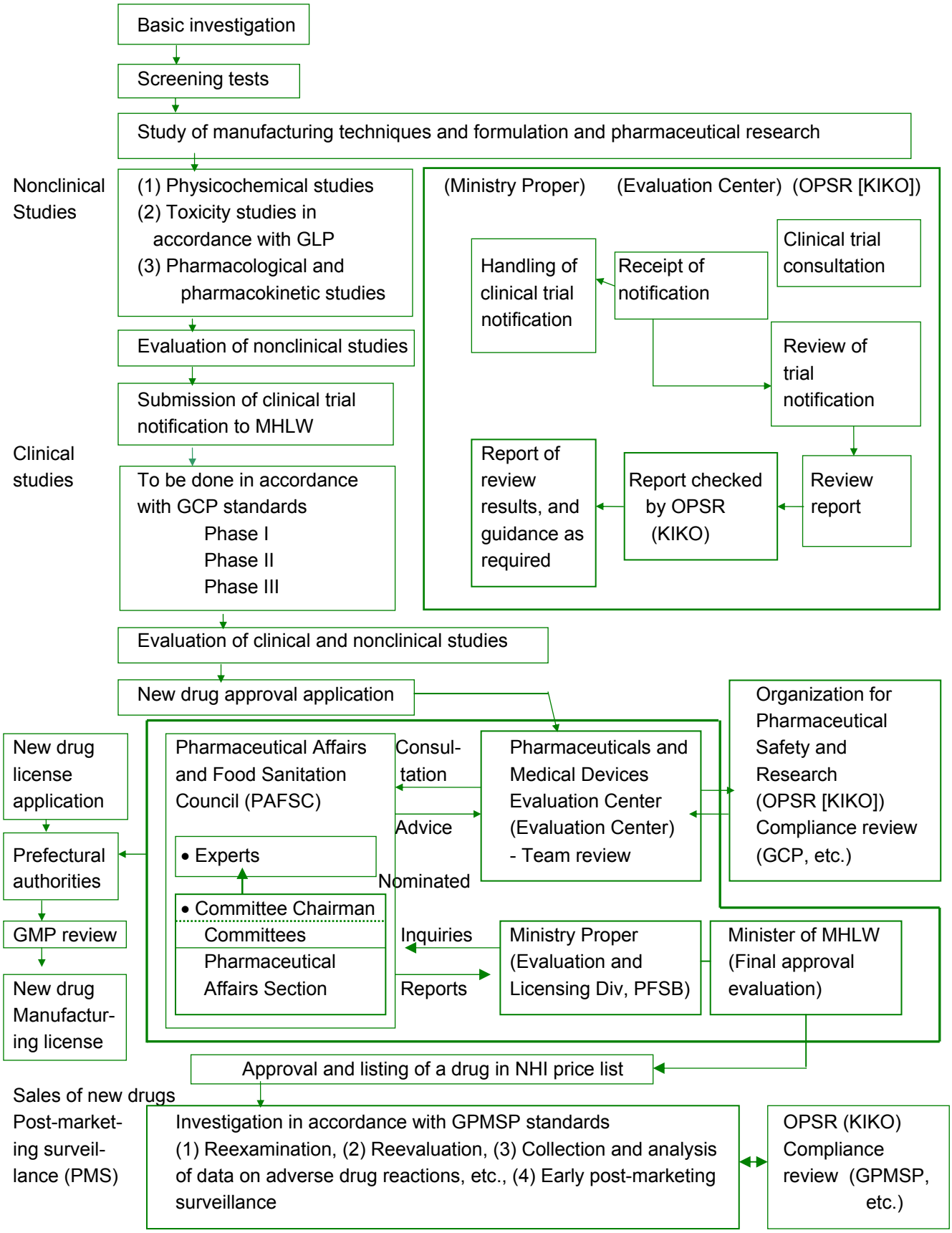


FIG. 7 FLOWCHART OF NEW DRUG DEVELOPMENT AND APPROVAL

TABLE 3 DATA TO BE SUBMITTED WITH AN APPLICATION FOR APPROVAL TO MANUFACTURE/IMPORT: A NEW PRESCRIPTION DRUG (BASED ON THE ATTACHED TABLE 2-1 TO PMSB NOTIFICATION NO. 481)

Data and drugs		1. New drug	2. New combination	3. New route	4. New indication	5. New formulation	6.New dosage	7.1 Additional formulation	7.2 Similar composition	8. Other
a	1. Origin	○	○	○	○	○	○	○	○	×
	2. Foreign country	○	○	○	○	○	○	○	○	×
	3. Comparison	○	○	○	○	○	○	○	○	×
b	1. Structure	○	×	×	×	×	×	×	×	×
	2. Physicochemis-	○	×	×	×	×	×	×	×	×
	3. Standards	○	○	○	×	○	×	○	○	○
c	1. Long-term	○	○	○	×	○	×	Δ	○	×
	2. Severe	○	○	○	×	○	×	Δ	○	×
	3. Accelerated	○	○	○	×	○	×	○	○	○
d	1. Single dose	○	○	○	×	×	×	×	○	×
	2. Repeated dose	○	○	○	×	×	×	×	Δ	×
	3. Mutagenicity	○	×	×	×	×	×	×	×	×
	4. Carcinogenicity	Δ	×	Δ	×	×	×	×	×	×
	5. Reproduction	○	×	○	×	×	×	×	×	×
	6. Local irritation	Δ	Δ	Δ	×	×	×	×	Δ	×
	7. Other	Δ	×	Δ	×	×	×	×	×	×
e	1. Efficacy	○	○	○	○	×	○	×	Δ	×
	2. Safety	○	Δ	Δ	×	×	×	×	Δ	×
	3. Other	Δ	Δ	Δ	×	×	×	×	×	×
f	1. Absorption	○	○	○	Δ	○	○	×	×	×
	2. Distribution	○	○	○	Δ	○	○	×	×	×
	3. Metabolism	○	○	○	Δ	○	○	×	×	×
	4. Excretion	○	○	○	Δ	○	○	×	×	×
	5. Bioequivalence	×	×	×	×	×	×	○	×	○
	6. Other	Δ	Δ	Δ	Δ	Δ	Δ	×	×	×
g	Clinical	○	○	○	○	○	○	×	○	×

○: Date required ×: Data not required Δ: 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. Physicochemical properties, standard, and test methods	1. Chemical structure 2. Physicochemical properties, etc. 3. Standards and test methods
c. Stability	1. Long-term storage tests 2. Tests under severe conditions 3. Accelerated tests
d. Acute, subacute, and chronic toxicity, teratogenicity, and other type of toxicity	1. Single dose toxicity 2. Repeated dose toxicity 3. Mutagenicity 4. Carcinogenicity 5. Reproductive toxicity 6. Local irritation 7. Other toxicity
e. Pharmacological action	1. Tests to support efficacy 2. Secondary pharmacology, Safety pharmacology 3. Other pharmacology
f. Absorption, distribution, metabolism, and excretion	1. Absorption 2. Distribution 3. Metabolism 4. Excretion 5. Bioequivalence 6. Other pharmacokinetics
g. Clinical studies	Clinical trial results

TABLE 4 DATA TO BE SUBMITTED WITH AN APPLICATION FOR A NON-PRESCRIPTION DRUG

Data and drugs		1. New ingredients	2. New ingredients for non-prescription drug	3. New combination	4. Drug (1) (2) (3)		5. Approval standards	6. Other
					4-1 Different pharmacology	4-2 Milder effects		
a	1. Origin	○	○	○	○	○	○	×
	2. Foreign country	○	○	○	○	○	○	×
	3. Comparison	○	○	○	○	○	○	×
b	1. Structure	○	×	×	×	×	×	×
	2. Physicochemistry	○	×	×	×	×	×	×
	3. Specifications	○	○	○	○	○	○	○
c	1. Long-term	○	×	×	×	×	×	×
	2. Severe	○	×	×	×	×	×	×
	3. Accelerated	○	○	○	○	○	○	○
d	1. Single dose	○	Δ	Δ	×	×	×	×
	2. Repeated dose	○	Δ	Δ	×	×	×	×
	3. Mutagenicity	○	×	×	×	×	×	×
	4. Carcinogenicity	Δ	×	×	×	×	×	×
	5. Reproduction	○	×	×	×	×	×	×
	6. Local irritation	Δ	Δ	Δ	×	×	×	×
	7. Other	Δ	Δ	×	×	×	×	×
e	1. Efficacy	○	×	×	×	×	×	×
	2. Safety	○	×	×	×	×	×	×
	3. Other	Δ	×	×	×	×	×	×
f	1. Absorption	○	Δ	Δ	×	×	Δ	×
	2. Distribution	○	×	×	×	×	×	×
	3. Metabolism	○	×	×	×	×	×	×
	4. Excretion	○	Δ	Δ	×	×	Δ	×
	5. Bioequivalence	×	×	×	×	×	×	×
	6. Other	Δ	×	×	×	×	×	×
g	Clinical	○	○	○	Δ	×	×	×

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

(1) Drugs with new active ingred-i ents	(2) Drugs with active ingredi-ents other than new active in-gredients, but which include ingredi-ents which have never been used as active ingredi-ents in any ap-proved non-pre-sciption drug (“new in-gredients of non-pre-scription drugs”)	(3) Drugs with ingredi-ents which have been used as active ingredi-ents in approved non-prescription drugs, but which include active ingredients which have never been approved in the same therapeutic category for which the application for the non-prescription drug has been filed (“already approved ingredients used for new combined preparations”) and drugs with a combination of active ingredients, indi-cations and/or dosage and administration dif-ferent from those of al-ready approved non-prescription drugs in the same therapeutic category (excluding those which fall into type (4) or (5) mentioned in this table or those which meet the approval stan-dards)	(4) Drugs which are the subject of approval ap-plications 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 the same new active ingredients, “new ingredients of non-prescription drugs” and/or “already approved ingredients used for new combined preparations” and a combination of active ingredients that differs from already ap-proved non-prescription drugs, as mentioned in (1) or (2). In order for a non-prescription drug to fall into this type, its dosage, administration, and indications must be identical to those of already approved non-prescription drugs and its formula-tion must be identical to or differ only slightly from that of already approved non-prescription drugs. ---------- (4-1) Only active ingredients with pharmacologi-cal effects qualitatively different from those of new active ingredients, “new ingredients of non-prescription drugs” and/or “already approved ingredients used for new combined preparations” can be different. ---------- (4-2) Same as (1), and ingredient(s) with different pharmacological effects are those that have only mild effects which do not directly contribute to therapeutic efficacy.	(5) Drugs which fall into therapeutic categories for which approval standards have been estab-lished and which deviate from the approval standards with respect to only the formulation, and drugs which fall into therapeutic catego-ries for which no approval standards have been estab-lished and in which only the formulation differs from already approved non- pre-scription drugs in these categories. In both cases, the for-mulation must be unique.	(8) Drugs that fulfill require-ments of approval stan-dards and tho-se which do not fall into any of the five types mention-ed in this table.

a. Origin or background of dis-covery, 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. Physicochemical properties, standard, and test methods	1. Chemical structure 2. Physicochemical properties, etc. 3. Standards and test methods			
c. Stability	1. Long-term storage tests 2. Tests under severe conditions 3. Accelerated tests			
d. Acute, subacute, and chronic toxicity, teratogenicity, and oth-er type of toxicity	1. Single dose toxicity 2. Repeated dose toxicity 3. Mutagenicity 4. Carcinogenicity		5. Reproductive toxic-ity 6. Local irritation 7. Other	
e. Pharmacological action	1. Tests to support efficacy 2. Secondary pharmacology, Safety pharmacology 3. Other pharmacology			
f. Absorption, distribution, me-tabolism, and excretion	1. Absorption 2. Distribution 3. Metabolism		4. Excretion 5. Bioequivalence 6. Other ADME	
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

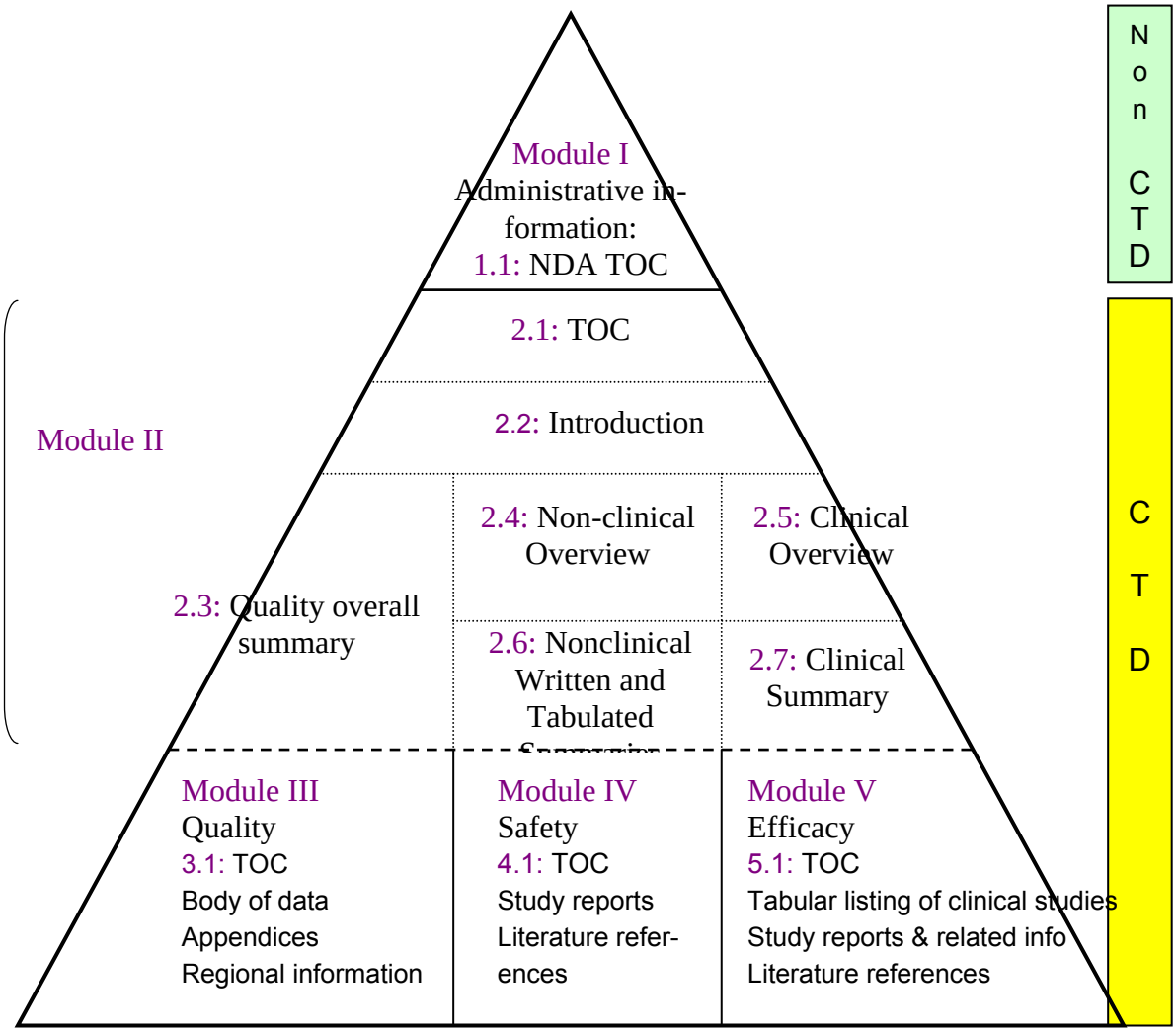


FIG. 8 ORGANIZATION OF ICH COMMON TECHNICAL DOCUMENTS

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.

http://www.nihs.go.jp/dig/ich/m4index-e.html

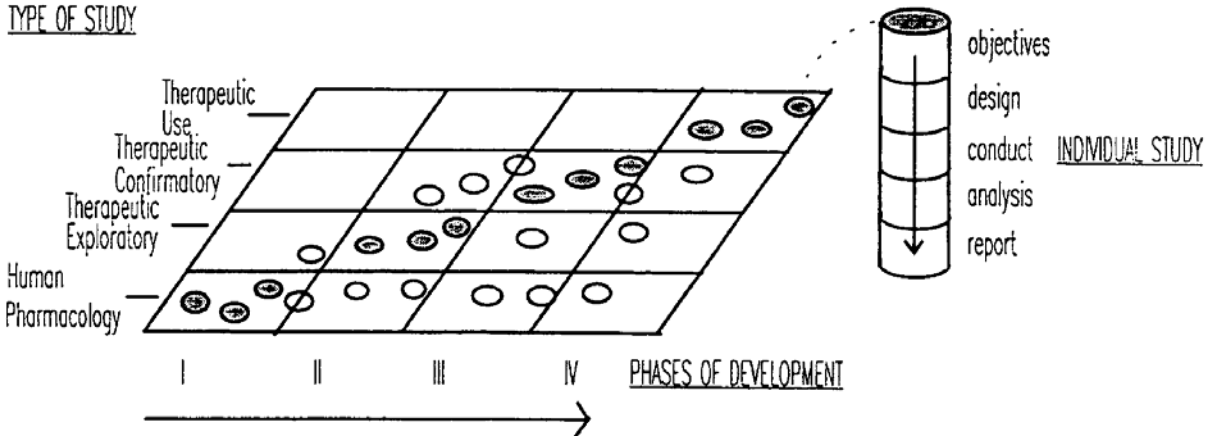


FIG. 9 CORRELATION BETWEEN DEVELOPMENT PHASES AND TYPES OF STUDY

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 re-evaluation system (Fig. 10).

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 Phase Vigilance" 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.

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

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, re-examination 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 about two new versions are published each year. Version 6.1 is now available.

1. GPMSP

GPMSP (Good Post-marketing Surveillance Practice) establishes provisions regarding post-marketing surveillance of drugs, subject to compliance by manufacturers and others. The objective of GPMSP is to ensure the proper implementation of post-marketing surveillance and reliability of the data, and subsequently to prevent risks to public health and to ensure proper use of drugs.

The GPMSP consists of 16 articles containing essentially the following provisions:

(1) The requirement to establish an independent post-marketing surveillance department and to ensure adequate use of qualified personnel for such activities or implementing post-marketing surveillance.

(2) The requirement to ensure ongoing safety measures from the time of drug development throughout the post-marketing period.

(3) Designation of a supervisor of post-marketing surveillance with clearly defined competence.

(4) Designation of a supervisor to implement post-marketing surveillance with clearly defined duties.

(5) The requirement to prepare standard operating procedures and comply with these procedures.

(6) The requirement to collect information on

proper use (proper-use information).

(7) The requirement to examine proper-use information and adopt specific measures based on the results.

(8) A clear distinction among early post-marketing phase vigilance, use-results surveillance, special surveillance, and post-marketing clinical trials.

(9) The requirement to perform in-house inspections.

(10) Requirements for the education and training of personnel conducting post-marketing surveillance.

(11) Provisions for delegation (conclusion of contracts) of duties relating to post-marketing surveillance.

(12) Requirements for preservation of records in connection with post-marketing surveillance.

The following is an overview of the major provisions of the GPMSP:

(1) Purpose (Article 1)

The GPMSP, as the standard for duties related to post-marketing surveillance conducted by manufacturers, etc. of drugs, is applicable to the items described below.

(i) The provisions subject to compliance by manufacturers, etc. regarding the collection of information for reexamination and reevaluation applications and reporting of adverse drug reactions and infections; collection and review of necessary information about the quality, efficacy, safety, and proper use of drugs; and the adoption of appropriate measures based on the results of this information.

(ii) Standards for the collection and preparation of data attached to reexamination and reevaluation applications (compliance standards for application data).

The GPMSP applies to prescription drugs. In vitro diagnostics and pharmaceuticals for batch tests are excluded. With respect to post-marketing clinical trials among the provisions for post-marketing surveillance, the GCP is also applied.

(2) Definitions of Terms (Article 2)

Terms used in the GPMSP such as "post-marketing surveillance," “early post-marketing phase vigilance,” "use-results surveillance," "special surveillance," and "post-marketing clinical studies" are defined below.

(i) "**Post-marketing surveillance**" is defined as collection and examination of information necessary to ensure proper use of drugs (proper-use information), which is related to the quality, efficacy, and safety of marketed drugs, as well as the performance of appropriate measures on the basis of the results.

ii) **Early post-marketing phase vigilance** is defined as vigilance for the first 6 months after marketing for new drugs when MR promote highly cautious use by means of periodic visits to physicians, etc. It is performed to gain a rapid and comprehensive understanding of information on serious adverse reactions and infections.

(iii) "**Use-results surveillance**" " is defined as the survey conducted to assess the incidence of adverse drug reactions and other information on proper use relating to use of the drug concerned in daily clinical settings.

(iv) "**Special surveillance**" is defined as survey conducted to detect and confirm proper-use information regarding the drug concerned in **special groups 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.

(v) "**Post-marketing clinical studies**" "are defined as clinical studies conducted to verify information or obtain additionally required information concerning proper-use of drugs unobtainable by rou-

tine medical practice or concerning the quality, efficacy, and safety of the drug concerned on the basis of an evaluation and analysis of data obtained from clinical studies or other studies conducted after approval has been granted.

(3) Provisions Subject to Compliance by Manufacturers, etc. (Article 3)

Provisions subject to compliance by manufacturers, etc., as stipulated in the Pharmaceutical Affairs Law, are set down in Article 4 through Article 15 of the GPMSP.

(4) Organizations and Personnel Involved in Post-marketing Surveillance (Article 4)

This article provides for establishment of a department (Post-marketing Surveillance Management Department) to manage the duties related to post-marketing surveillance. This department should appoint a supervisor of post-marketing surveillance who has ultimate responsibility and employ adequately qualified and competent personnel. In addition, this department should be independent from all divisions responsible for marketing drugs. In the event that some of the duties of post-marketing surveillance are carried out by departments other than the Post-marketing Surveillance Management Department, each of these other departments must have personnel who are responsible for implementing post-marketing surveillance.

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

Standard operating procedures for post-marketing surveillance, including each of the items specified below, must be prepared in order to implement properly and effectively post-marketing surveillance.

(i) Procedures for collection and examination of proper-use information and for the conduct of specific measures based on these results.

(ii) Procedures for conducting early post-marketing surveillance, use-results surveillance, special surveillance, and post-marketing clinical studies.

(iii) Procedures for in-house inspections.

(iv) Procedures for the education and training of personnel involved in post-marketing surveillance.

(v) Procedures for delegation of duties in post-marketing surveillance.

(vi) Procedures for preservation of records in connection with post-marketing surveillance.

(6) Duties and Functions of the **Post-marketing Surveillance Management Department** (Article 6 through Article 13)

(i) Duties of the supervisor of post-marketing surveillance

- Overall supervision of post-marketing surveillance.
- Preparation of detailed standard operating procedures for post-marketing surveillance.
- Delegation in writing of post-marketing surveillance duties to the department(s) responsible for implementing post-marketing surveillance.
- Offering of opinions required for post-marketing surveillance activities to manufacturers, etc.
- Examination of collected adverse drug reaction information and submission of these reports to the Minister of health and welfare, revision of package inserts, establishing means of distribution of information to health professionals, and submission of information to manufacturers in writing.
- Preparation of education and training protocols.

(ii) Tasks performed by the post-marketing surveillance management department

- Planning, drafting of policies and coordination of post-marketing surveillance.
- Preparation and preservation of basic

protocols for post-marketing surveillance.

- Preparation of protocols to implement early post-marketing surveillance use-results surveillance, special surveillance, and post-marketing clinical studies, as well as implementation of each surveillance or clinical study.
- Verification that post-marketing surveillance is conducted in a proper and effective manner in accordance with the standard operating procedures and protocols.
- Collection of proper-use information such as adverse drug reaction reports.
- Conducting periodic in-house inspections regarding post-marketing surveillance.
- Carrying out planned educational and training activities for personnel involved in post-marketing surveillance on regular basis.

(7) Delegation of Duties of Post-marketing Surveillance (Article 14)

This article provides for delegation of some of the duties of post-marketing surveillance to persons who are capable of properly and effectively carrying out these activities.

(8) Preservation of Records in Connection with Post-marketing Surveillance (Article 15)

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.

(9) Standards for **Compliance of Reexamination and Reevaluation Data** in Connection with Post-marketing Surveillance (Article 16)

In addition to provisions of the GCP MHLW Ordinance, the provisions of Article 4 through Article 12 (excluding applications of Article 4 to 9 regarding early post-marketing phase vigilance), Article 14, and Article 15 of this GPMSP MHLW Ordinance (excluding application of Article 13 regarding education and training) apply, mutatis mutandis, to the collection and preparation of data for reexamination and reevaluation applications in connection with post-marketing surveillance.

2. Data Compliance Reviews and Reviews of Compliance Status of Manufacturers, etc. with GPMSP

GPMSP compliance reviews for reexamination and reevaluation application data and reviews to assess GPMSP compliance status of manufacturers, etc., 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 GPMSP On-site Reviews (Notification No. 613 and 87 of the Evaluation and Licensing Division and the Safety Division, respectively, PMSB dated May 10, 2001) established by the MHLW.

Of these compliance reviews, the reviews concerning reexamination data are conducted by a review team consisting of personnel of OPSR (KIKO), which is commissioned by the MHLW. Reviews regarding reevaluation data and GCP compliance reviews relating to post-marketing clinical studies conducted outside of Japan are carried out by a review team comprised of personnel of the MHLW and the Evaluation Center.

Compliance status reviews are conducted by a review team consisting of personnel from the Pharmaceutical and Medical Safety Bureau of the MHLW or prefectural governments in principle.

On the basis of review reports prepared by each review team, a comprehensive evaluation is conducted by MHLW or prefectural governments, and a determination of "compliance" or "non-compliance" is made and necessary measures are undertaken.

3. Adverse Drug Reaction and Infectious Disease Reporting System

Programs for collecting and reporting safety information on drugs such as adverse drug reactions include the drug safety information reporting system managed by the MHLW, an adverse drug reaction reporting system by pharmaceutical companies in accordance with provisions of the Pharmaceutical Affairs Law, and the WHO International Drug Monitoring Program whereby drug safety information is exchanged among various countries (Fig. 11).

3.1 Drug Safety Information Reporting System of the Ministry of Health, Labour, and Welfare

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.

The information subject to reporting includes adverse reactions associated with the use of prescription medicines, over-the-counter drugs, and medical devices, 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 other pharmaceuticals require especially intensive investigation and collection of information, the MHLW selects medical institutions and, if necessary, performs "special product monitoring reviews" in collaboration with them.

3.2 Adverse Drug Reaction and Infectious Disease Reporting System by Pharmaceutical Companies

This system, based on the Pharmaceutical Affairs Law, requires the reporting of adverse drug reactions and infections by pharmaceutical companies. 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 foreign countries to discontinue manufacturing and/or marketing of a drug due to safety concerns must now be reported.

The collection and examination of domestic and foreign drug safety information, as well as the adoption of specific measures based on this information, must be carried out in accordance with the applicable standard operating procedures for conducting post-marketing surveillance based on the GPMSP.

The provision in the Enforcement Regulations for reporting adverse drug reactions consists of reporting within 15 days and within 30 days. A summary of these provisions is presented below.

(1) Reporting Within 15 Days

The following must be reported to the MHLW 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 abroad. These also include cases where the occurrence of an adverse reaction, its incidence, and/or the conditions of onset were 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 which 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 infections due to use of the drug concerned, including cases both in Japan and abroad (previously known or unknown serious cases).

c) Any implementation of measures by regulatory authorities in foreign countries such as suspension of manufacturing or marketing of the drug.

(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 (1) 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) Any case of a suspected adverse reaction to, or any case of infections attributed to the use of, the drug concerned occurring in Japan. This also includes cases that were not expected on the basis of existing precautions (previously unknown moderate cases: excluding very mild cases).

c) Any suspected development of cancer or another serious disease or disability due to an adverse reaction to, or use of, the drug concerned occurring either in Japan or abroad. This information should also specify the number of occurrences of adverse reactions and infections, their incidence, any conditions of onset, and/or any changes in these factors. Any research reports about the drug concerned, which demonstrate that it does not have an approved indication, should also be included.

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.

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.

3.3 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.

3.4 Evaluation and Communication of Safety Information and Adoption of Specific Measures

Drug safety information reported to the MHLW is evaluated consulting with members of the Pharmaceutical Affairs Section of the PAFSC dealing with adverse drug reactions. Results of discussions

and evaluation are reported or, when necessary, further evaluated by the 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 marketing 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.

As a post-marketing safety measure for drugs, the MHLW introduced the system of periodic safety update reports (PSUR) (Notification No. 32 of the Safety Division, PAB dated March 27, 1997). In the Guidelines for Methods of Use-Results Surveillance of Prescription Drugs (Notification No. 34 of the Safety Division, PAB dated March 27, 1997), the methods to be used for concentrated surveillance immediately after marketing were specified. However, since the number of cases of adverse reactions not evident at the clinical stage appearing immediately after marketing of drugs and the number of cases requiring safety measures has been increasing, Safety Measures for Drugs (Notification No. 25 of the Safety Division, PMSB dated March 11, 1998) and Contents of Drug Adverse Reaction and Infection Report forms (Office Communication) have been issued to promote safety measures further.

3.5 Post-marketing Safety Measures for Drugs

As a post-marketing safety measure for drugs, the MHLW introduced the system of periodic safety update reports (PSUR) (Notification No. 32 of the Safety Division, PAB dated March 27, 1997). In the Guidelines for Methods of Use-Results Surveillance of Prescription Drugs (Notification No. 34 of the Safety Division, PAB dated March 27, 1997), the methods to be used for concentrated surveillance immediately after marketing were specified. However, since the number of cases of adverse reactions not evident at the clinical stage appearing immediately after marketing of drugs and the number of cases requiring safety measures has been increasing, Safety Measures for Drugs (Notification No. 25 of the Safety Division, PMSB dated March 11, 1998) and Contents of Drug Adverse Reaction and Infection Report forms (Office Communication) have been issued. On December 27, 2000, the above Guidelines for Methods of Use-Results Surveillance of Prescription Drugs was abolished and new guidelines were issued under the title of Methods of Implementation of Early Post-marketing Surveillance on Prescription Drugs, etc. (Notification No.166 of the Safety Division, PMSB dated December 27, 2000) to promote safety further.

4. 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 Law).

5. Reexamination System (Article 14-4 of the Law)

The reexamination system is aimed at reconfirmation of the clinical usefulness of drugs by performing use-results or other surveillance as one aspect of the 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 pharmaceutical 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.

5.1 Designation for Reexamination of Drugs

The drugs subject to reexamination include products designated by the MHLW at the time of manufacturing or import 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 for manufacture or import (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 (Notification No. 725 of PAB dated August 25, 1993).

When pharmacoepidemiological surveys or clinical trials to set pediatric doses are performed, the reexamination period can be prolonged as required (maximum reexamination period: 10 years).

(1) Reexamination 10 years after the date of approval:

- Orphan drugs.
- Drugs requiring a comprehensive evaluation utilizing pharmacoepidemiologic methods.
- Drugs for which clinical studies (clinical trials or post-marketing clinical trials) to set pediatric doses, etc. continue during approval applications and after approval.

(2) Reexamination 6 years after the date of approval:

- Drugs containing new active ingredients.
- New prescription combination drugs.
- Drugs with new routes of administration.

(3) Reexamination from 4 to within 6 years after the date of approval:

- Drugs with new indications.
- Drugs with new dosages.

5.2 Periodic Safety Reports (Article 21-4-2 of the Enforcement Regulations of the Law)

Collected post-marketing safety data, primarily in the form of use-results surveillance, had been reported once a year during the period of reexami-

nation 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 use-results surveillance 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 use-results surveillance.
- 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 appropriate product use such as revisions of the precautions.
- Package inserts.
- Future safety measures planned on the basis of surveillance results.

5.3 Data Required for Reexamination Applications and Reexamination Procedures

Post-marketing surveillance to acquire data required for reexamination applications, including use-results surveillance, special surveillance, and post-marketing clinical studies, must be implemented in accordance with the GPMSP. The data must also be collected and prepared in accordance with the GPMSP (post-marketing clinical studies 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 special surveillance and post-marketing clinical studies of the drug concerned in the application. In addition, for any other research data acquired after drug approval relating 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 in foreign countries; summary of post-marketing surveillance; information about safety and efficacy; and references.

(2) Data Attached to Reexamination Applications

This data should include summary of use-results surveillance; special surveillance reports; post-marketing clinical study reports; data from patients who have developed adverse drug reactions or infections; data from research reports; reports of specific measures adopted in Japan and foreign countries; and reports of serious adverse drug reactions.

(3) Compliance Survey Data

This includes data from GPMSP compliance reviews.

(4) Reference Data

This includes, for example, case report forms used in use-results surveillance, package inserts at the time of reexamination application, a summary of the data at the time of product approval, 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 is a flow diagram of this reexamination process. After the application is received, OPSR (KIKO) evaluates compliance with standards such as GPMSP and conducts a reliability survey. The application is next reviewed by the Pharmaceuticals and Medical Devices Evaluation Center and submitted for further necessary review and deliberation to the Food Sanitation Section 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 in appropriate with respect to 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)

6. Reevaluation System (Article 14-5)

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).

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 which 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, PMSB) to guarantee the therapeutic equivalence of generic drugs to the

original drugs. To date (October 2003), certain groups of ingredients and formulations have been designated for the 27th quality reevaluation.

Among the dissolution tests for prescription drugs established after completion of quality re-evaluation, "public dissolution tests" were established 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 (July 2003), the Orange Book has been issued 16 times.

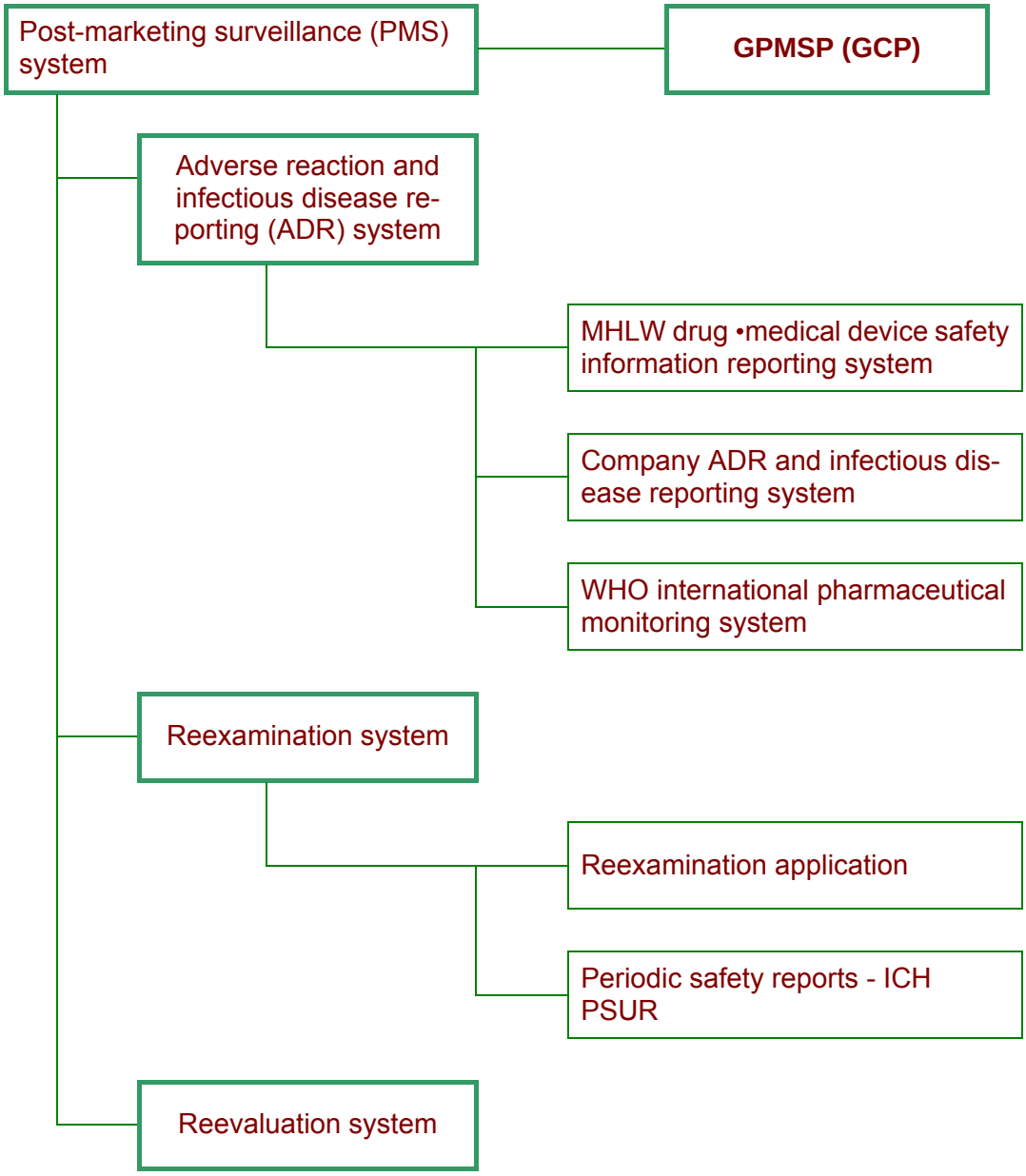


FIG. 10 PHARMACEUTICAL POST-MARKETING SURVEILLANCE SYSTEM

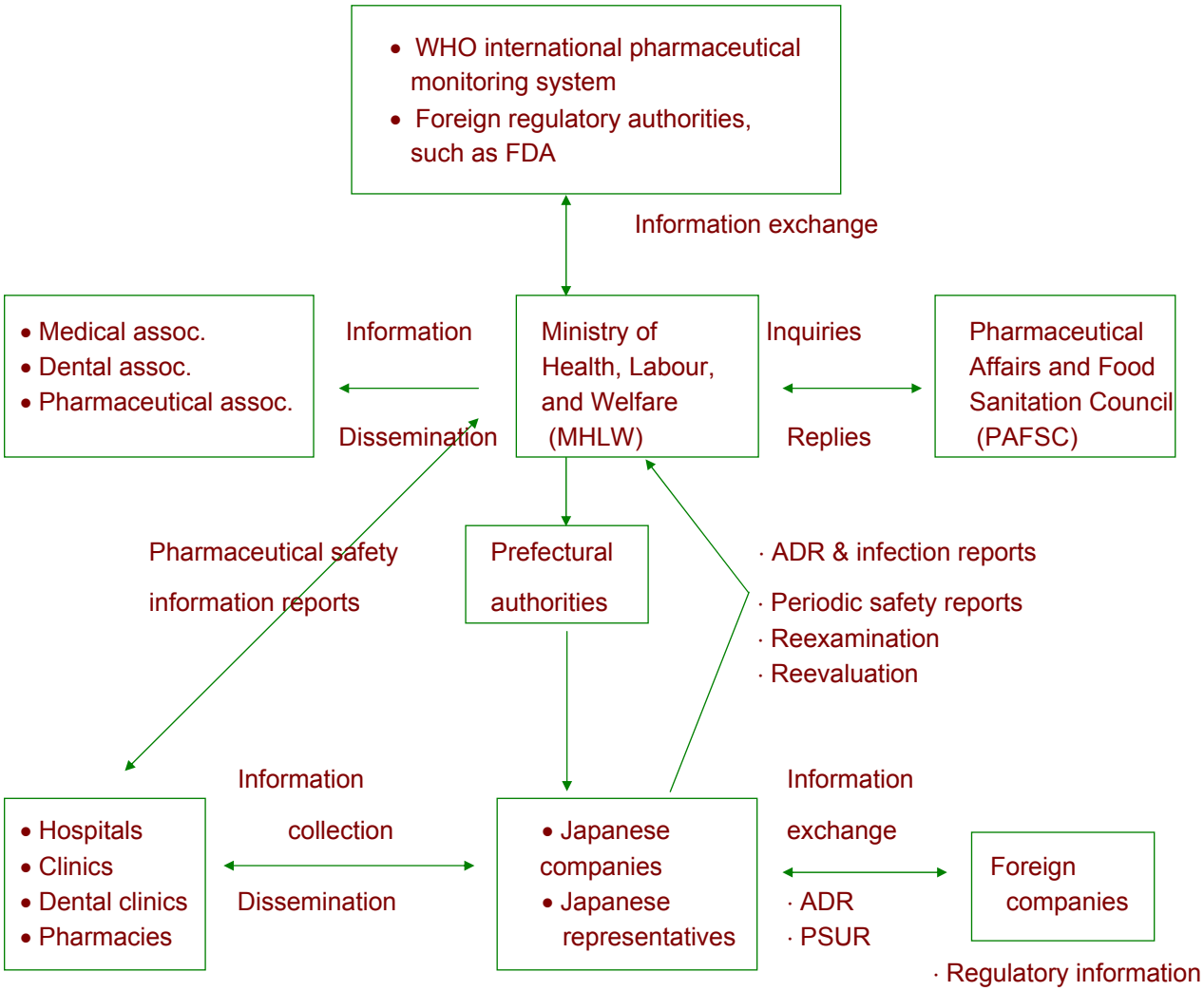


FIG. 11 COLLECTION AND REPORTING OF PHARMACEUTICAL SAFETY INFORMATION

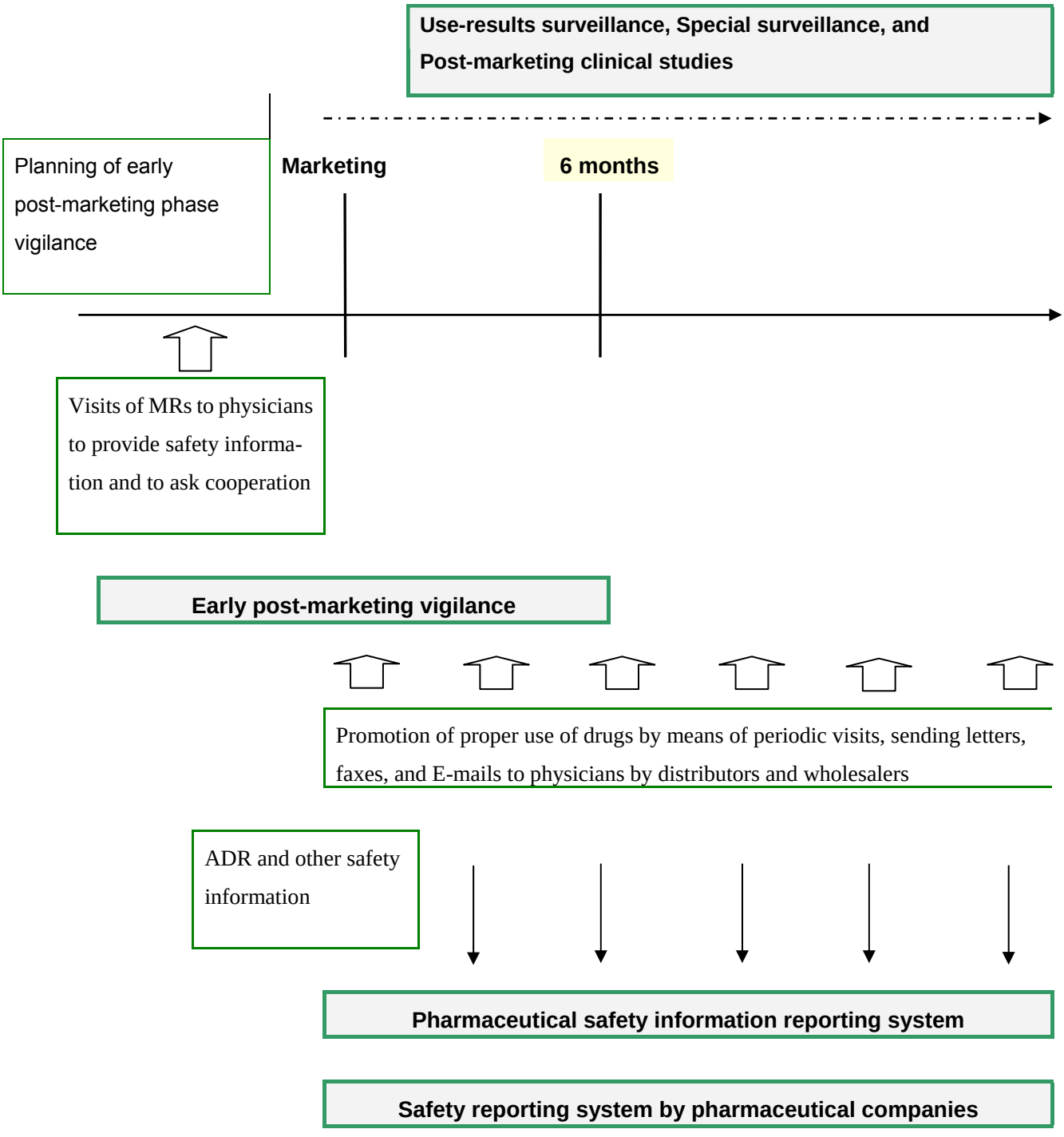


FIG. 12 POST-MARKETING COLLECTION AND REPORTING OF PHARMACEUTICAL SAFETY INFORMATION

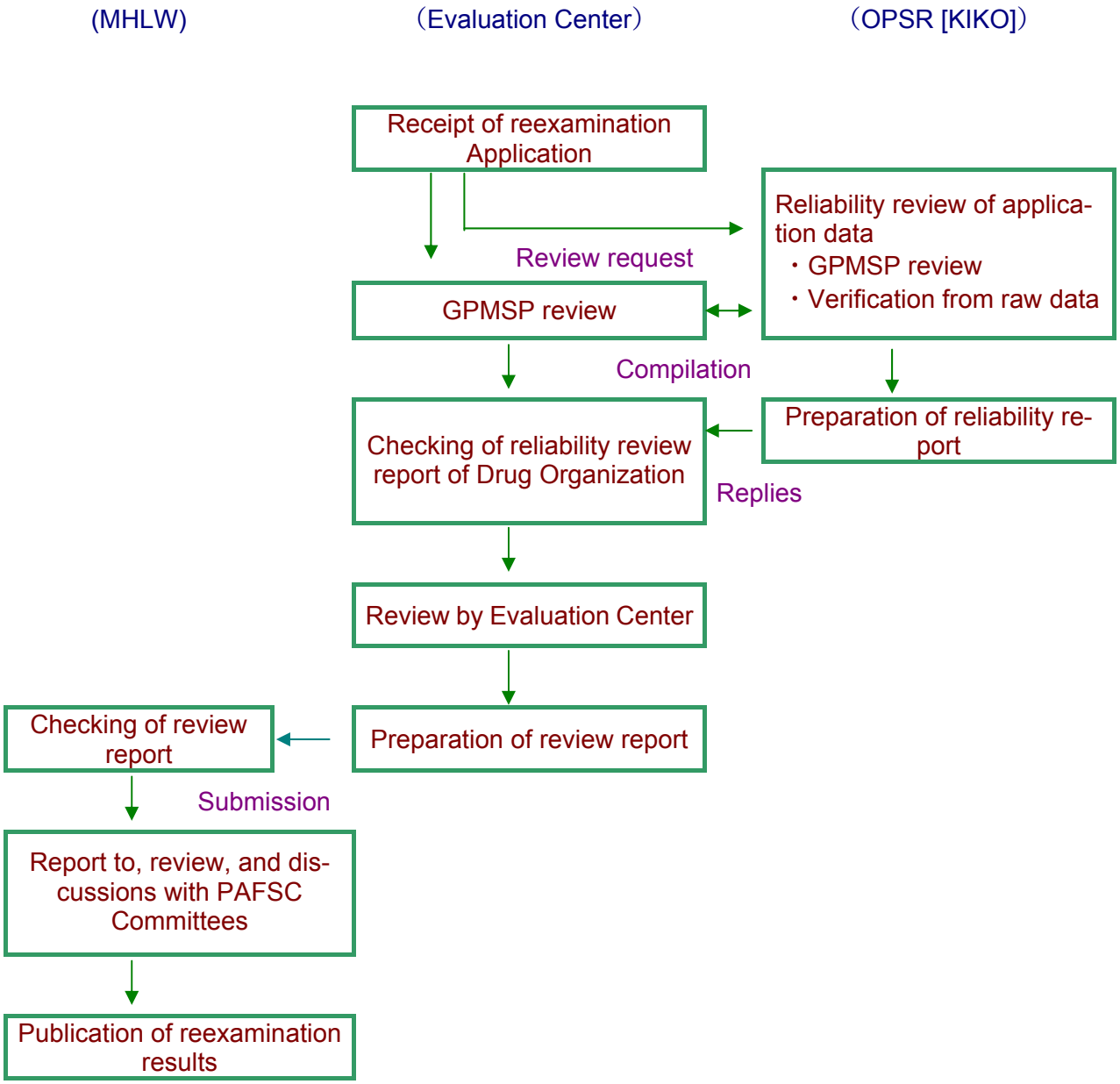
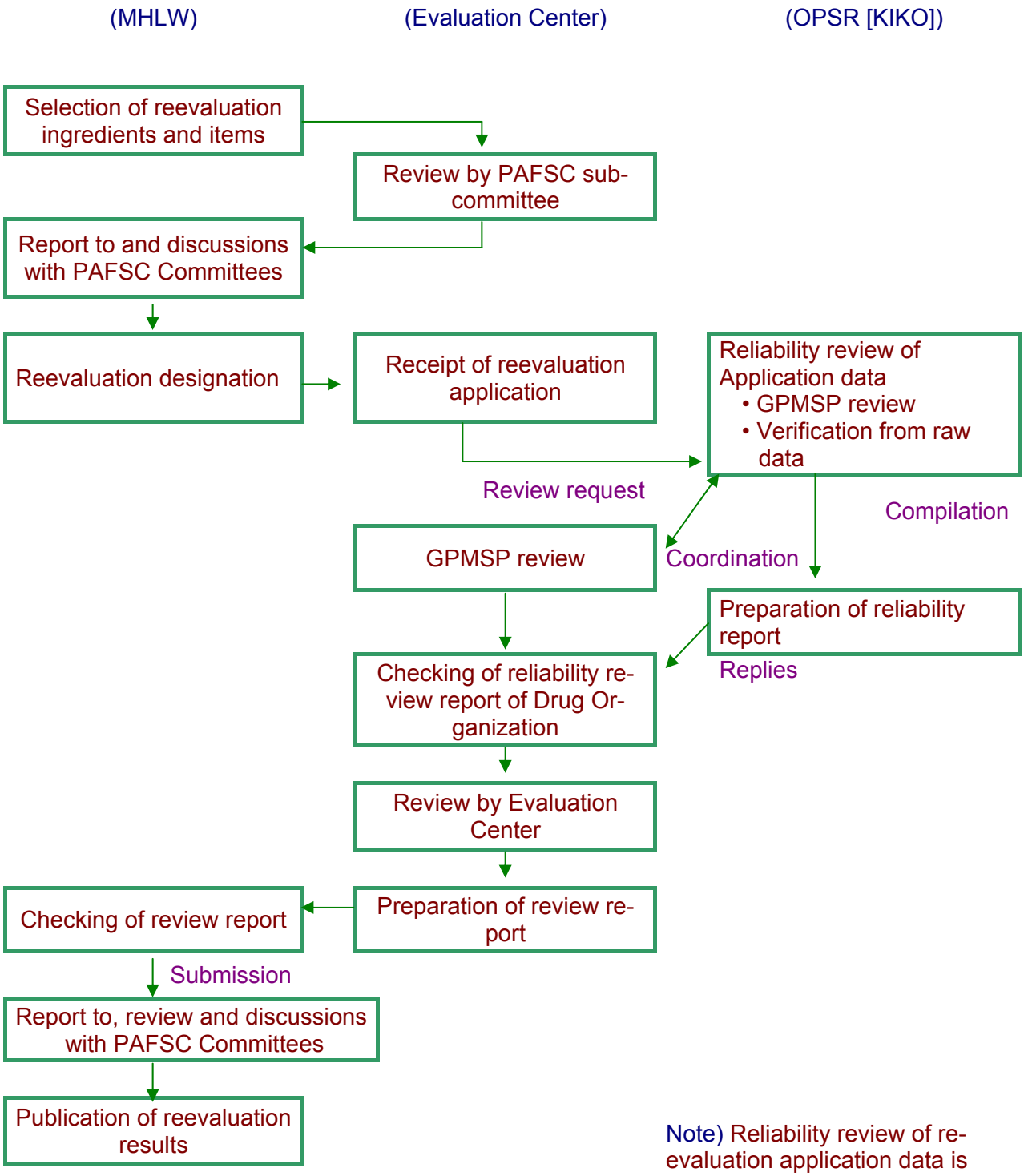


FIG. 13 REEXAMINATION SYSTEM



Note) Reliability review of re-evaluation application data is sometimes performed by Phar-maceuticals and Medical De-vices Evaluation Center

FIG. 14 REEVALUATION SYSTEM

Chapter 5

Dissemination of Drug Information

Manufacturers or importers and distributors of drugs must collect and examine proper-use information 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 manufacturers and importers should prepare standard operating procedures based on the provisions in the GPMSP ordinance and endeavor to establish a comprehensive system for the supply and dissemination of drug information.

1. Package Inserts

The most basic tool for supplying information on drugs to medical 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 which pharmaceutical manufacturers or importers and distributors 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 which 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 must be reflected in package inserts. Because of the limitations on space and the amount of information which can be presented in package inserts, manufacturers 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 information on drugs 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.

1.1 Outline of the New Guidelines

1) Coordination of Formats

(1) Items considered important must be entered nearer the start 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 removed, 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 re-evaluation results, latest approval of (additional) indications, the international birth date, etc. However, the results of quality reevaluations do not apply.

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** 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, 59, and 607) and notifications related to biological products (Notification No. 0515005 of the PFSB and Notification No. 0520004 of the Safety Division, PFSB).

* 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
- Date of initial marketing in Japan
- Date(s) of latest reexamination
- Date(s) of latest reevaluation
- Date(s) of latest approval of indication(s)
- International birth date
- Storage, etc. (storage, expiration date)

3) Therapeutic category

4) Regulatory classification (specified biological products, biological products, poisonous drug, powerful drug, habit-forming drug, prescription-only 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

Information on drug interactions should be provided in details based on current level of science (Supplement to Notification No. 607 of PAB, December 25, 2000).

8) Composition and description

Adverse events should be outlined in the first paragraph of this section.

(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 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 (How supplied)

19) References and reference requests

◆ Information of drugs with limited administration periods

20) Manufactured or imported 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 use-results surveillance, 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 in 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, NHW].

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 (rough indices)

- 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 caution in use, etc.)

1.4 Labeling of Excipients

When excipients such as stabilizers, preservatives, and vehicles are used in preparations listed in the Japan Pharmacopoeia (JP), in the Requirements for Antibiotic Products of Japan (JRAP), 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).

By March 31, 2004, 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 product

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”)

① 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.

1.7 Package Inserts in English

Package inserts in English of some drugs prepared by manufacturers or distributors appeared on the JPMA homepage since 2001.

http://www.jpma.or.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 or importers intends 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 (6-month duration) as specified in the labeling (refer to Chapter 4, 1. GPMSP).

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 Ministry's "Drug Information System" (refer to section 4).

2.3 Summary Basis of Reexamination (SBR)

The Summary basis of Reexamination (SBR) is an outline of post-marketing surveillance, including use-results surveillance, special surveillance, post-marketing clinical studies and adverse reaction reports, based on reexamination application data evaluated by the PAFSC. SBR are prepared to promote proper use of drugs.

The first SBR was published in July 1997 and the fifth in December 1999. The SBR issued to date include those for an erythropoietin product and an antiarrhythmic.

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 MR. 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 discussion concerning the product.

New preparation guidelines were published by the Japanese Society of Hospital Pharmacists in September 1998, and interview forms (IF) were been prepared in the new format for new drugs approved from January 1999.

3. Dissemination of Safety Information

For the proper use of drugs, it is important that the necessary information be disseminated in an appropriate and timely manner to medical 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 GPMSP.

Standard operating procedures are prepared by manufacturers or importers and distributors, and the MHLW has specified guidelines on the dissemination of emergency safety information.

3.1 Dissemination of Emergency Safety Information (the 'Dear Doctor' Letter)

1) Preparation Criteria

Emergency safety information is prepared by the drug manufacturer or importer 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 in Precautions.

(2) Revisions of Precautions: Urgent and important revisions based on cases of death, disability, or events which 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 administration and dosage: Important changes in administration and dosage for reasons related to safety.

(5) Changes in regulatory classification: Changes in the regulatory classification, such as designation as a poisonous drug, powerful drug, prescription-only 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) Revocation of approvals: Revocation of approvals for reasons related to safety.

(8) Others: Other measures which 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 or importer directly distributes the information to physicians, pharmacists, and other health professionals in medical institutions. The manufacturer or importer 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 Society 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 manufacturer or importer must report to the MHLW when distribution has been completed as indicated in the order.

3.2 Dissemination 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 (importer)

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 or importer included. In cases corresponding to 1), (2) above, the drug manufacturer or importer 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. The manufacturer or importer must submit a Notice of Change for items in the Precautions of the drug concerned in the order to the MHLW.

3.3 Dissemination of Information for Drugs Which Have Completed Reexamination or Reevaluation

Once the reevaluation results are available, the manufacturers, importers, or distributors of the drug concerned prepare a “Notice of reevaluation results,” which they distribute to medical institutions. The FPMAJ compiles all of the reevaluation results and publishes a “Notice of Prescription Drug Re-evaluation Results” in the journals of the Japan Medical Association, Japan Dental Association, and Japan Pharmaceutical Association.

Since 1995, the MHLW has been studying the concept of summary basis of reexamination (SBR) to publicize information on the evaluation results, etc. for drugs which have completed reexaminations, and the first SBR were issued in July 1997. To date (December 1999), the SBR has been issued 5 times. (refer to 2.3 SBR).

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 or importers, 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 a digest form as "Pharmaceuticals and Medical Devices Safety Information" to health professionals who submitted ADR reports, and also published in the media, on the Organization for Pharmaceutical Safety and Research (OPSR [KIKO]) Home Page (http://www.pharmasys.gr.jp), and in various publications such as the Japan Medical Journal, the Journal of the Japanese Society of Hospital Pharmacists, etc. An English version is sent to WHO.

The journal has been published bimonthly from June 1973 and then monthly from June 2001 (from Issue No. 167) with 194 issues in October 2003.

3.5 Dissemination of Information by Drug Safety Update

The Society of Japanese Pharmacopoeia and the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ) has been jointly editing and publishing the Drug Safety Update (DSU), which includes information on ADRs to prescription drugs (revisions of the Precautions) under supervision of the MHLW since September 1992 (10 times per year). The journal is distributed to medical institutions including approximately 10,000 hospitals, 80,000 clinics and 60,000 dental clinics, as well as about and 60,000 pharmacies and dispensing facilities within one month after printing.

3.6 Commentaries on "Precautions" in Package Inserts

Commentaries on "Precautions" in Package Inserts is the core means to be prepared by distributors of drugs to provide safety information of new drugs directly after marketing. Manufacturers or importers 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 secure proper use of drugs.

With the revisions of the guidelines for the preparations 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 phase vigilance for such a period of time as specified in labeling (refer to Chapter 4, 1. GPMSP).

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 (http://www.pharmasys.gr.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 approval applications and drug recalls.

With this system, package insert information is provided in SGML (Standardized Generalized Markup Language) format in order 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 conveniences.

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 which should be include on outer containers.

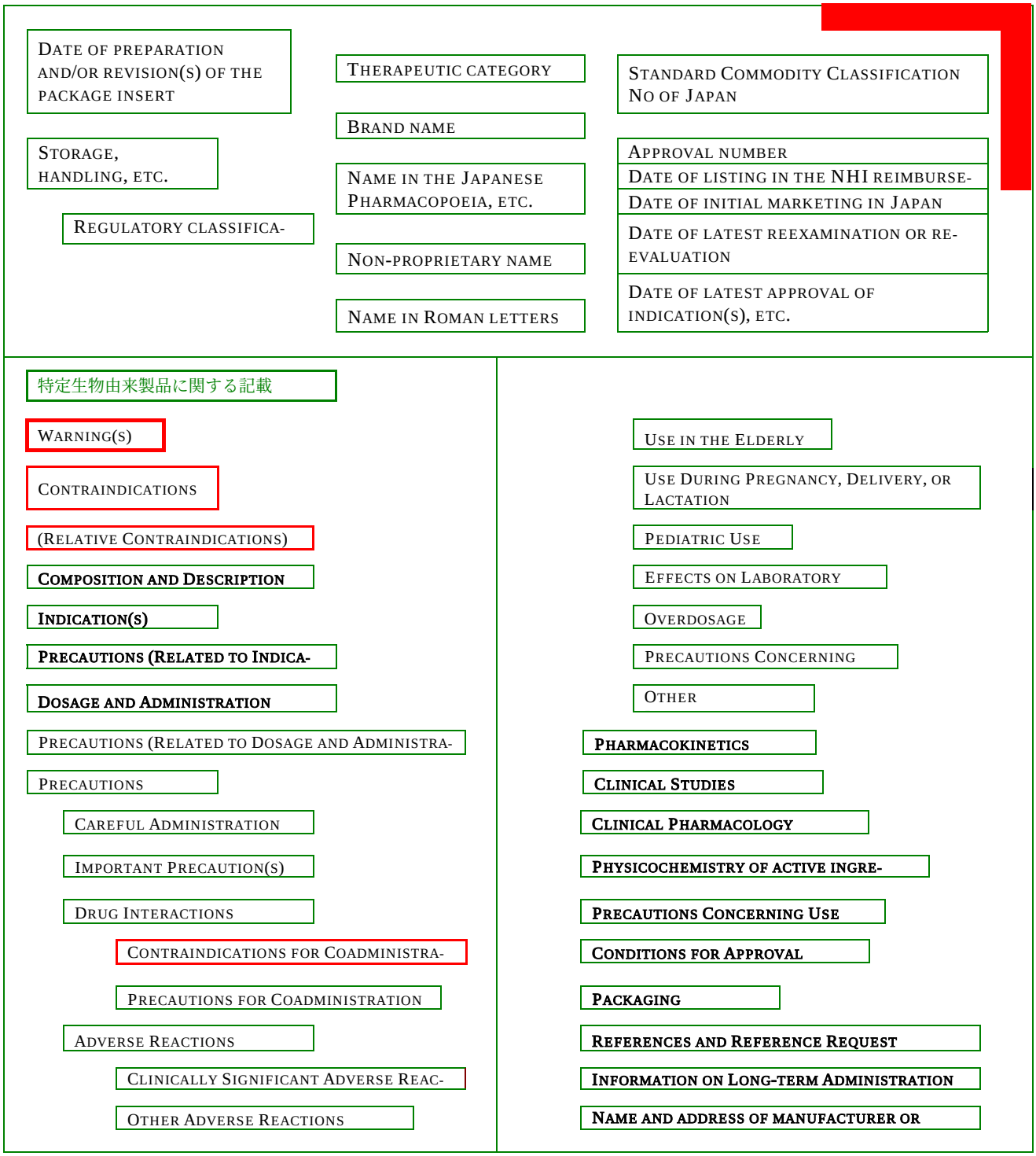
Labeling requirements of excipients of non-prescription drugs are the same as those for prescription drugs according to a voluntary agreement of the JPMA (Notification No. 165 of the JPMA dated March 27, 1991) and Office Communication of the Safety Division, PAB dated June 3, 1991. Based on a voluntary 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 voluntary 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' anxieties 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. Thereafter, the National Health Insurance (NHI) program was put into effect with the intention of providing benefits for the entire population of Japan.

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 put into effect 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 Act was passed together with the third revision of the Medical Service Law on December 19, 1997 and it was enforced from April 1998.

The reform of the health insurance system which was debated at the same time was discussed by the MHLW Council on Health Insurance and Welfare which issued its final report in November 1996. Using this proposal, 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 154th Diet.

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 which 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 Parliament). 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 under 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 out-patient 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 will be set at 10% and at 20% for those with a certain level of income

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, however, 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 who 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. 54 issued in March 1994). Under these rules, a point value is assigned for each of the hundreds 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 by totaling of the fees for the procedures performed is called a “payment for services system.”

Medical procedures, such as medication and injection, require the use of drugs, and the list of reimbursement prices of drugs allowed to be used 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 (reimbursement) fixes the names and prices of drugs for which medical providers can be reimbursed under the health insurance programs. The above mentioned 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.

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 which 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.

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 June of a previous year. A survey of all products in the NHI Drug Price List is conducted on about 3,400 sellers, all first-class wholesalers, and about 2,800 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 eight 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 which 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.

The drug price revisions in 1992, 1994, 1996, 1997, 1998, 2000, 2002 are listed in **Table 7**.

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 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 premium rates as of April 2002 were set at 40-100%, 15-30%, 5-10%, 10%, and 3% for innovation, usefulness I and II, 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 8**, and general rules on reimbursement prices of new drugs are illustrated in **Fig. 18**.

To assure transparency of the pricing system, revised Drug Pricing Rules (Notification 0213008 of the Health Insurance Bureau dated February 13, 2002), and the more detailed and revised Handling of Reimbursement Price Listing of Prescription Drugs (Notification No. 0213011 of the Health Policy Bureau dated February 13, 2002) and Submission of Reimbursement Price Listing Request Forms for Prescription Drugs (Notification No. 0213006 of the Economic Affairs Division, Health Policy Bureau dated February 13, 2002) were issued. 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 **Figs. 16** and **Fig. 18**.

Entries of new drugs in the NHI Drug Price List take place as a rule four times at regular intervals 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. Procedures of pricing for generic drugs are illustrated in **Fig. 17** and **Fig. 19**.

As in the case of new drugs, revised Handling of Reimbursement Price Listing of Prescription Drugs (Notification No. 0213011 of the Health Policy Bureau dated February 13, 2002) and Submission of Reimbursement Price Listing Request Forms for Prescription Drugs (Notification No. 0213006 of the Economic Affairs Division, Health Policy Bureau dated February 13, 2002) also cover generic drugs with the aim of assuring transparency of the pricing system.

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 METHODS OF PREVIOUS REIMBURSEMENT PRICE REVISIONS

Year	Survey	Object	R zone	Special items
1992	June 1991	All products	15%	
1994	June 1993	All products	13%	Repricing
1996	June 1995	All products	11%	Repricing
1997	Sept. 1996	All products	10% 8%（Long listed products）	Repricing Long listed products
1998	Sept. 1997	All products	5% 2%（Long listed products）	Repricing Long listed products
2000	Sept. 1999	All products	Range adjusted, 2%	Repricing Range adjusted, 2%
2002	Sept. 2001	All products	Range adjusted, 2%	Repricing Long listed products (Special adjustment, 4, 5, 6%)

Table 7 shows the results of the reimbursement price revisions in 1992, 1994, 1996, 1997, 1998, and 2000.

TABLE 7 REVISION RATES OF REIMBURSEMENT PRICES

Year	Products	Decrease	Increase	Unchanged	Total	Revision rate
1992	Number	7,681	2,121	3,771	13,573	- 8.1%
	Revision rate	- 8.5%	0.4%	—		
1994	Number	8,613	2,083	2,679	13,375	- 6.6%
	Revision rate	- 6.8%	0.2%	—		
1996	Number	9,568	1,697	1,604	12,869	- 6.8%
	Revision rate	- 7.0%	0.2%	—		
1997	Number	7,718	3,394	862	11,974	* - 3.0%
1998	Number	9,921	6	1,762	11,692	- 9.7%
	Revision rate	- 9.7%	0.0%	—		
2000	Number	8,935	61	2,291	11,287	- 7.0%
	Revision rate	- 7.5%	0.5%			
2002	Number	9,096	98	1,997	11,191	—

* 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 8 REQUIREMENTS FOR APPLYING PREMIUMS

<Premium types, requirements and rates>

(1)	Premium for innovativeness (rate: 40-100%) 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 (15-30%) Applied to new drug products in the NHI price lists that meet two of the three requirements listed above. that meet a or c and b of the three requirements listed above
(3)	Premium for usefulness II (5-10%) 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 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.
(5)	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.

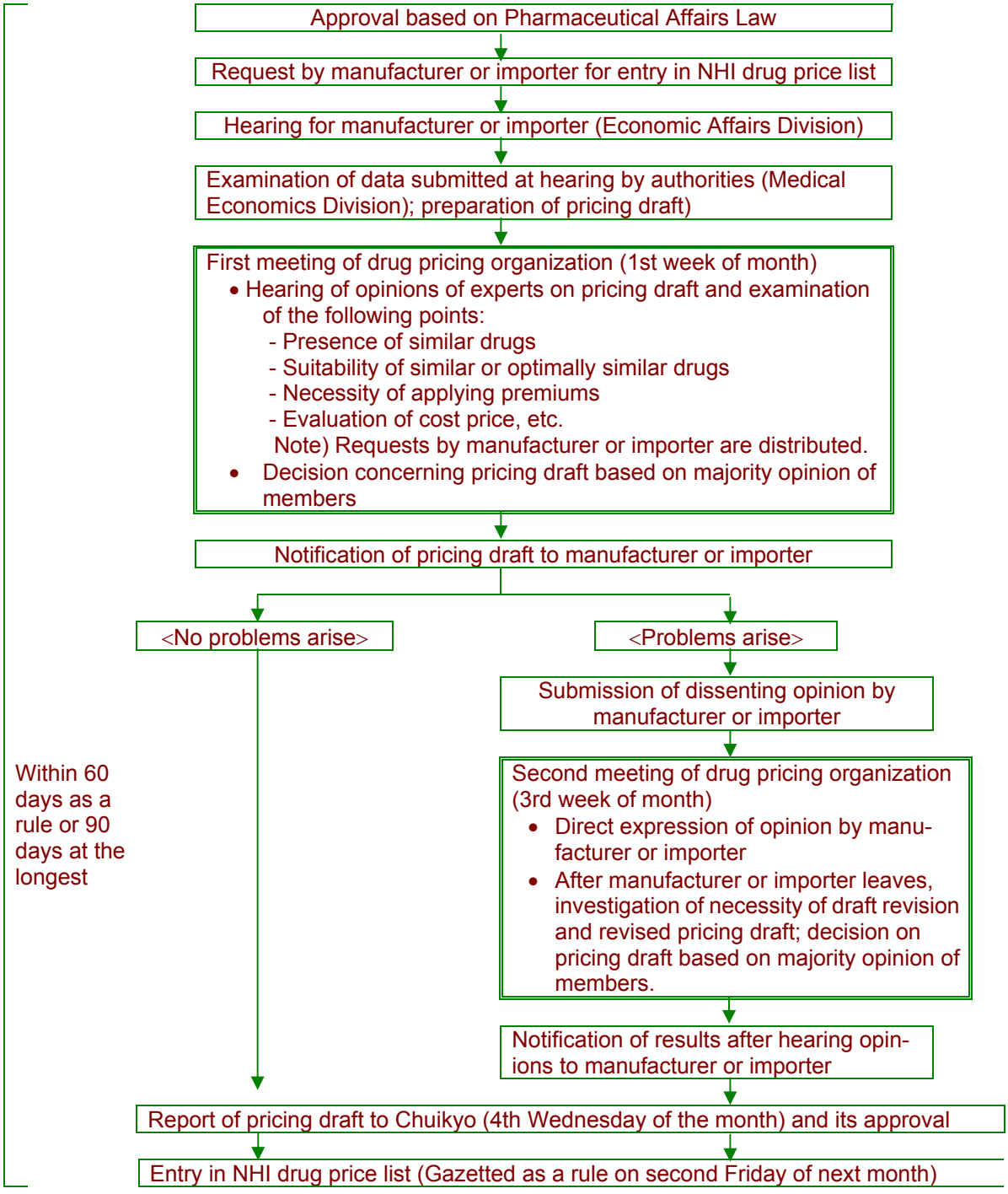


FIG. 16 REIMBURSEMENT PRICING FLOW-SHEET FOR NEW DRUGS

(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.

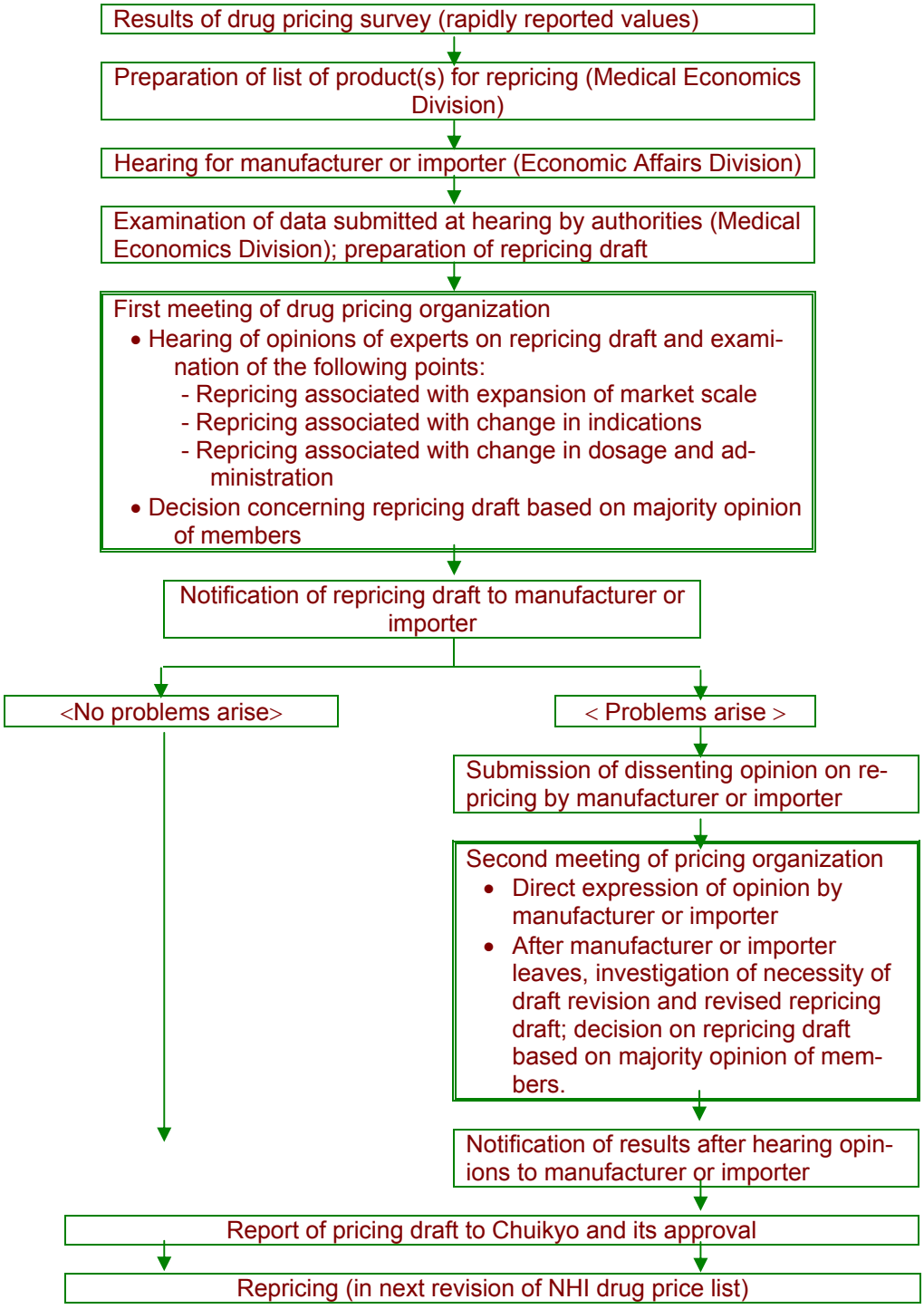


FIG. 17 FLOW-SHEET FOR REPRICING OF DRUGS IN THE NHI PRICE LIST

(Note) The parts in the double box ▭ show parts involving the drug pricing organization

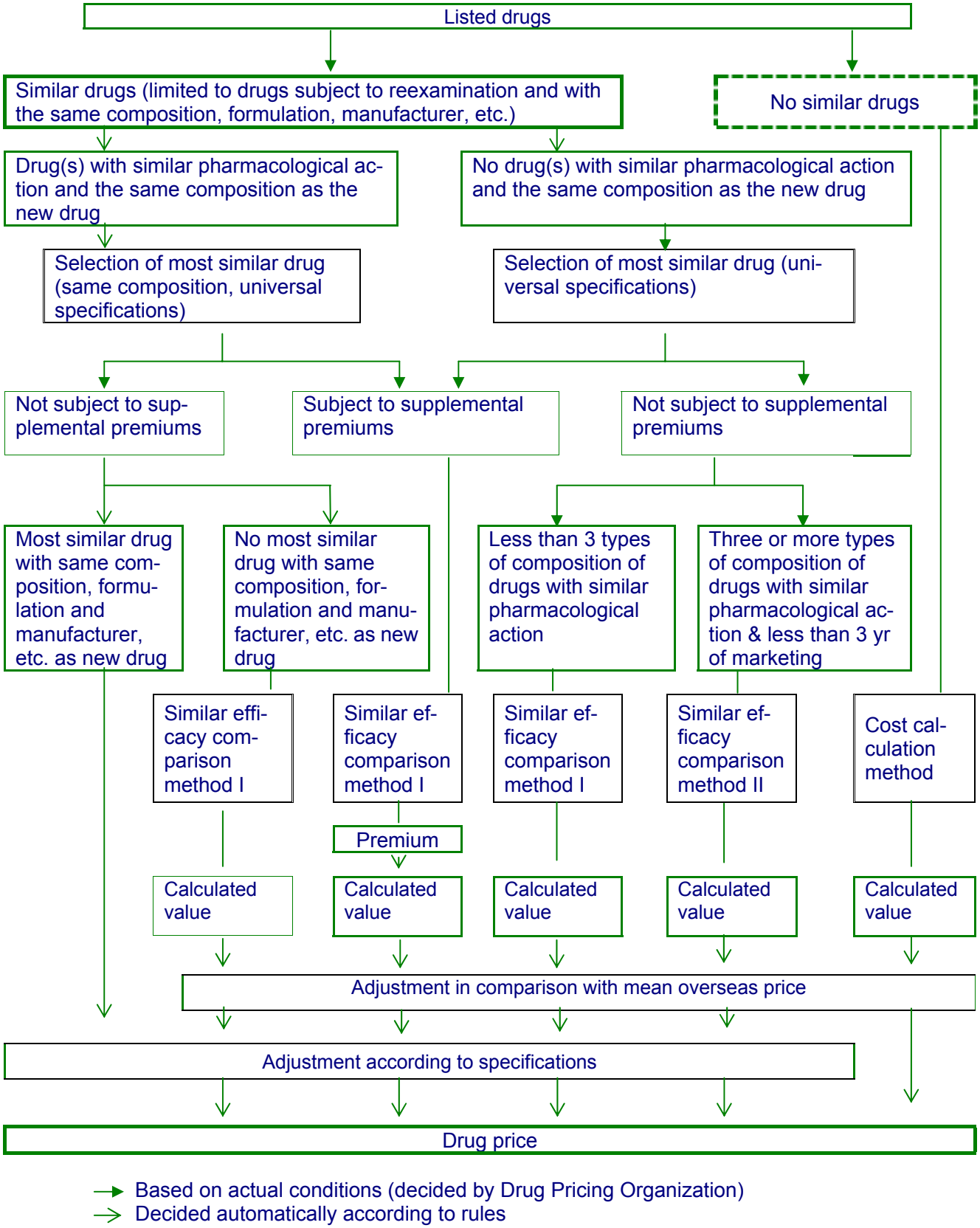


FIG. 18 OVERVIEW OF NEW DRUG PRICING RULES

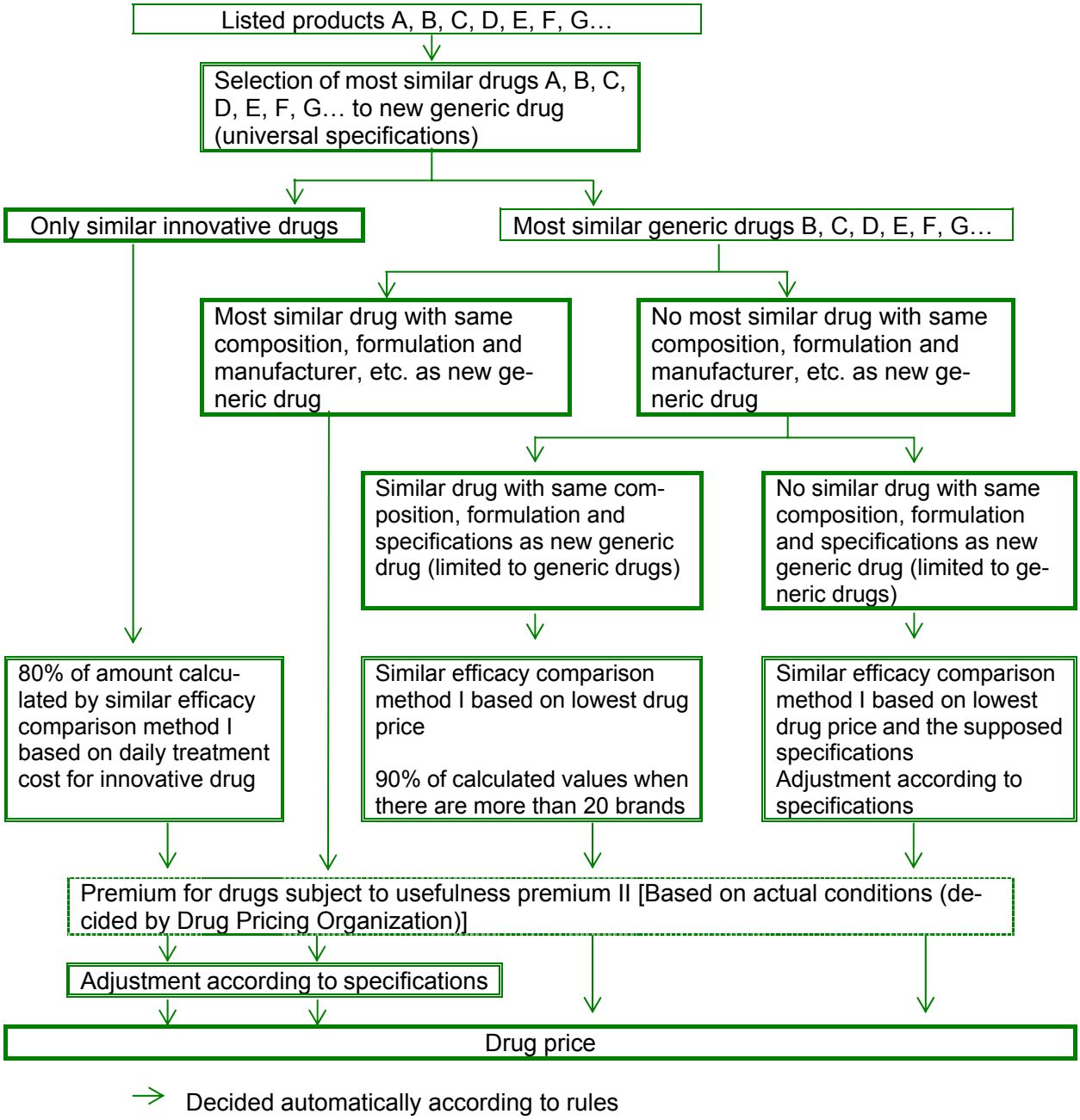


FIG. 19 OVERVIEW OF GENERIC DRUG PRICING RULES

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PHARMACEUTICAL ADMINISTRATION AND REGULATIONS IN JAPAN

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