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**INFORMATION IN ENGLISH ON JAPANESE  
REGULATORY AFFAIRS**

*English Regulatory Information Task Force*

*Japan Pharmaceutical Manufacturers Association*

**Pharmaceutical  
Administration and  
Regulations in Japan**

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## Pharmaceutical Administration and Regulations in Japan

This file contains information concerning pharmaceutical administration, regulations, and new drug development in Japan updated annually by the English RA Information Task Force, International Affairs Committee, Japan Pharmaceutical Manufacturers Association (JPMA). The contents are not abstracts of governmental rules or regulations but concise descriptions of most current practices by 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 Sciences (<http://www.nihs.go.jp/kanren/iyaku.html>).

Japan Pharmaceutical Manufacturers Association

<http://www.jpma.or.jp/english/>

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

Social Insurance Agency and the Central Labor Relations Commission ([Fig. 1. Organization of Ministry of Health, Labour, and Welfare](#)).

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

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

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

reliability of application data.

Following this reorganization, the MHLW and PMDA handle a wide range of activities from clinical studies to approval reviews, reviews throughout post-marketing stage, and pharmaceutical safety measures ([Fig. 2. Organization of Pharmaceutical and Food Safety Bureau \(PFSB\) and Pharmaceuticals and Medical Devices Agency \(PMDA\)](#)).

## 1. PHARMACEUTICAL AND FOOD SAFETY BUREAU (PFSB)

The Pharmaceutical and Food Safety Bureau (PFSB) (except for the Department of Food Safety) is one of the 11 bureaus of the MHLW. In addition to policies 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 health of the general public including policies related to blood supplies and blood products, and narcotics and stimulant drugs. This new bureau consists of a Secretary-General, Councilor in charge of drugs, five divisions, and one office\* ([Fig. 2. Organization of Pharmaceutical and Food Safety Bureau \(PFSB\) and Pharmaceuticals and Medical Devices Agency \(PMDA\)](#)). These divisions have the following functions.

### 1.1 General Affairs Division

The functions of this division are as follows:

- 1) Overall planning and coordinating activities for the Pharmaceutical and Food Safety

Bureau

- 2) Matters related to pharmacists
- 3) Supervision of the PMDA (excluding areas under the control of the Evaluation and Licensing Division and Safety Division, and Compliance and Narcotics Division)
- 4) Issues related to PFSB not governed by other divisions

### • Office of Drug Induced Damages

- 1) Matters related to the relief of damage due to adverse drug reactions handled by the PMDA
- 2) Measures for handling health injury caused by drugs, quasi-drugs, cosmetics, and medical devices (“drugs, etc.”)

### 1.2 Evaluation and Licensing Division

The functions of this division are as follows:

- 1) Technical guidance and supervision concerning the production of drugs, quasi-drugs, cosmetics, and medical devices (“drugs, etc.”)
- 2) Manufacturing/marketing business licenses and approvals to manufacture and market drugs, etc.
- 3) Reexamination and reevaluation of drugs and medical devices
- 4) Business license and approvals to market, rental, or repair medical devices (excluding areas under the control of Health Policy Bureau [“HPB”])
- 5) Issues related to the Japanese

Pharmacopoeia (JP)

- 6) Standards and specific precautions concerning drugs, etc.
- 7) Designation of orphan drugs and orphan medical devices
- 8) Enforcement of laws pertaining to poisonous and deleterious substances (excluding areas under the control of the Compliance and Narcotics Division)
- 9) Regulations related to evaluation of chemicals that might cause damage to the health of humans, animals, and plants in living environment from the standpoint of the environment and public health, as well as regulations concerning the manufacture, import, use, and other handling of such chemicals
- 10) Control of household products containing harmful substances
- 11) Establishment of tolerable daily intake (TDI) of dioxins and related compounds
- 12) Work related to the PMDA (KIKO) (limited to approval and license to manufacture and market drugs, medical devices, etc.)
- 13) Control and dissemination of Industrial standards for medical devices and other hygiene products and other industrial standards

• **Office of Medical Devices Evaluation**

- 1) Technical guidance and supervision concerning the production of medical devices
- 2) Manufacturing/marketing business licenses and approvals to manufacture

and market medical devices

- 3) Reexamination and reevaluation of drugs and medical devices
- 4) Business license and approvals to market, rental, or repair medical devices
- 5) Standards and specific precautions concerning medical devices
- 6) Designation of orphan medical devices
- 7) Work related to the PMDA (KIKO) (limited to approval and license to manufacture and market medical devices)
- 8) Control and dissemination of Industrial standards for medical devices and other hygiene products and other industrial standards

• **Office of Chemical Safety**

- 1) Enforcement of laws pertaining to poisonous and deleterious substances (excluding areas under the control of the Compliance and Narcotics Division)
- 2) Regulations related to evaluation of chemicals that might cause damage to the health of humans, animals, and plants in living environment from the standpoint of the environment and public health, as well as regulations concerning the manufacture, import, use, and other handling of such chemicals

- 3) Control of household products containing harmful substances
- 4) Establishment of tolerable daily intake (TDI) of dioxins and related compounds

### 1.3 Safety Division

The functions of this division are as follows:

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

### 1.4 Compliance and Narcotics Division

The functions of this division are as follows:

- 1) Control of poor quality or falsely labeled drugs, quasi-drugs, cosmetics, and medical devices (drugs, etc.)
- 2) Guidance and supervision related to advertising of drugs, etc.
- 3) Testing and government certification of

drugs, etc.

- 4) Matters related to pharmaceutical inspectors
- 5) Control of substances designated by the Pharmaceutical Affairs Law (PAL)
- 6) Matters related to inspectors of poisonous and deleterious substances
- 7) Control of narcotics, psychotropics, cannabis, opium, and stimulants
- 8) Duties of narcotics control officers and staff as judicial police officials
- 9) Cooperation with international criminal investigations concerning narcotics, psychotropics, cannabis, opium, and stimulants
- 10) Work related to the PMDA (KIKO) in handling matters related to on-site inspection, etc. by the PMDA

### 1.5 Blood and Blood Products Division

The functions of this division are as follows:

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

## 2. HEALTH POLICY BUREAU

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

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

### 2.1 Economic Affairs Division

The functions of this division are as follows:

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

by the national and local governments)

- 6) Issues related to hygiene inspection offices

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

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

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

### 2.2 Research and Development Division

The functions of this division are as follows:

- 1) Matters related to research and development of drugs, etc. (excluding items handed by PFSB)
- 2) Matters related to the cultivation and production of medicinal plants
- 3) Promotion, improvement, and coordination of manufacturing business of drugs, etc. (items related to research and development)
- 4) Matters related to installation and use of medical devices (excluding medical supplies, dental supplies, and hygiene-related products) (excluding items handled by the Guidance of Medical Service Division of the HPB)
- 5) Matters related to the improvement of

health care information-processing and management system

- 6) Matters related to the evaluation of medical technology (excluding those handled by other bureaus of MHLW)

- **Japan Health Sciences Foundation**

This foundation was established in 1986 by the MHW (currently MHLW) and related companies, etc. with the aim of promoting advanced technology in the field of the health sciences. It promotes joint public and private research and development on advanced and fundamental technology, undertakes surveys and studies to contribute to such promotion, assures the supply of research resources such as cells and genes, and conducts exchanges with related organizations in Japan and overseas.

### **3. NATIONAL INSTITUTE OF HEALTH SCIENCES**

In July 1997, the name of the former National Institute of Hygienic Sciences was changed to the National Institute of Health Sciences. In addition to its long-standing work related to testing and research on drugs, quasi-drugs, cosmetics, medical devices, foods, poisonous and deleterious substances, the Institute supervised the Pharmaceuticals and Medical Devices Evaluation Center to undertake the reviews required for approval to manufacture or import drugs, quasi-drugs, cosmetics and medical devices, as

well as the reexamination and the reevaluation of drugs, and medical devices. Thereafter, the Evaluation Center was incorporated into the Pharmaceuticals and Medical Devices Agency (PMDA, KIKO) in April 2004.

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

In accordance with the special corporation rationalization plan passed by the Cabinet in December 2001, and enactment of the Pharmaceuticals and Medical Devices Agency Law in December 2002, the PMDA (KIKO) was established in April 2004, through the integration of the Pharmaceutical and Medical Devices Evaluation Center in the National Institute of Health Sciences, the OPSR, and part of the Medical Devices Center, and the PMDA started handling all consultation and review work from the preclinical stage to approvals and post-marketing surveillance.

The work of the PMDA can be divided into three main categories: ADR relief work, review work and safety measures.

The PMDA consists of 24 offices and 2 groups as follows: the Audit Office, Information Technology Promotion Group, Office of Safety I, Office of Safety II, Office of GMP/QMS Inspection, Office of General Affairs, Office of Financial Management, Office of Planning and Coordination, Office of Relief Funds, Office of Regulatory Science, Office of Review Administration, Office of Review Management,

Office of Standards and Guidelines Development, Office of International Programs, Office of New Drug I, Office of New Drug II, Office of New Drug III, Office of New Drug IV, Office of New Drug V, Office of Biologics I, Office of Biologics II, Office of OTC/Generic Drugs, Office of Medical Devices I, Office of Medical Devices II, Office of Medical Devices III, and Office of Conformity Audit. [Fig. 2 Organization of the Pharmaceutical and Food Safety Bureau (PFSB) and the Pharmaceuticals and Medical Devices Agency (PMDA)]. The duties are indicated below.

Currently, the Second Medium Range Plan (2009 – 2014) is now underway and efforts are being made to shorten the review period, make reviews more efficient, promote international harmonization by strengthening ties with Western and Asian countries, and participation in global clinical trials. The Medium Range Plan includes the “International Strategic Plan” as the basic policy for the agency’s international activities and the already developed “PMDA Vision of Internationalization,” which envisions the achievement of world-class levels of review work, safety measures, and ADR relief work, maintenance and promotion of close partnership with Asian countries for the common benefit, and positive contribution to international harmonization by, for example, establishing harmonized pharmacopoeial standards.

#### 1) Drug ADR Relief Work

- Provision of medical benefits to cover healthcare expenses, disability pensions, and survivor’s pensions for individuals suffering disease or disability due to

adverse drug reactions or bioderived infections

- Provision of medical allowances for treatment of myelo-optico-neuropathy (SMON) patients and for HIV carriers and AIDS patients
- Surveys on damage caused by drugs and research on treatment, etc. of adverse drug reactions as health and welfare work
- Provision of medical allowances based on the Special Measures Law for Provision of Medical Allowances for Treatment of Hepatitis C Patients Infected by Specified Fibrinogen Concentrates or Specified Coagulation Factor XI Concentrates.

#### 2) Review Related Work

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

#### 3) Safety Measures

- Collection, analysis, and dissemination of information related to the quality, efficacy, and safety of drugs and medical devices

- Consultations with consumers and other parties concerning drugs and medical devices
- Guidance and advice for manufacturers, etc. to improve the safety of drugs and medical devices

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

#### **4.1 Office of Review Administration**

This office handles tasks related to the receipt and processing of license and other applications, drug master file (MF) registrations and modifications, clinical trial notifications, simple consultation applications on generic drugs and the issuance of manufacturing/marketing authorization letters, etc.

#### **4.2 Office of Review Management**

This office handles tasks related to the publication (disclosure) of approval review results, receipt and processing of clinical trial consultations on new drugs, basic protocols for post-marketing surveillance, and periodic safety update reports (PMS, reevaluation, GVP). The office also handles pharmaceutical affairs consultation on R&D strategy on drugs and medical devices mainly for universities, research institutes, and venture companies.

#### **4.3 Office of Standards and Guidelines Development**

This office handles tasks related to the

preparation of draft Japanese Pharmacopoeia, standards on medical devices, standards on drugs, master file systems, and generic names (JAN).

#### **4.4 Office of International Programs**

This office represents PMDA at bilateral talks with foreign regulatory agencies and plays a central role in international communication such as the sharing of public and non-public information with foreign regulatory agencies and organizations. The main services rendered are the promotion of international harmonization of regulatory standards/practices, planning of international activities, foreign public relations campaign, and expansion of human exchange. The office serves as the administrative office of PMDA at international conferences sponsored by PMDA.

#### **4.5 Office of New Drug I**

This office confirms clinical trial notifications and adverse drug reactions and conducts reviews required for approval, reexaminations, and reevaluation of gastrointestinal drugs, dermatologic drugs, hormone preparations, and metabolic disease drugs (e.g., anti-diabetic, osteoporosis, gout, and congenital metabolic disorder drugs)

#### **4.6 Office of New Drug II**

This office confirms clinical trial notifications and adverse drug reactions and conducts reviews required for approval, reexaminations and reevaluation of new cardiovascular drugs, drugs to treat Parkinson's disease, drugs to improve

cerebral circulation and metabolism, drugs to treat Alzheimer's disease, urogenital and anal drugs, combination drugs, radiopharmaceuticals, and contrast media.

#### **4.7 Office of New Drug III**

This office confirms clinical trial notifications and adverse drug reactions and conducts reviews required for approval, reexaminations, and reevaluation of new central nervous system drugs, peripheral nervous system drugs, anesthetic agents, sensory organ drugs (other than drugs for inflammatory diseases), and narcotics.

#### **4.8 Office of New Drug IV**

This office confirms clinical trial notifications and adverse drug reactions and conducts reviews required for approval, reexaminations, and reevaluation of antibacterial drugs, antiparasitic agents, antiviral agents (except for anti-HIV/AIDS agents), new respiratory tract drugs, anti-allergy drugs sensory organ drugs (limited to drugs for inflammatory diseases), and anti-HIV/AIDS agents.

#### **4.9 Office of New Drug V**

This office confirms clinical trial notifications and adverse drug reactions and conducts reviews required for approval, reexaminations, and reevaluations of antineoplastic drugs.

#### **4.10 Office of Biologics I**

In the Office of Biologics, the PMDA confirms clinical trial notifications and adverse drug reactions

and conducts reviews required for approval, reexaminations, and reevaluation of globulins, blood coagulation factor products, etc.

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

#### **4.11 Office of Biologics II**

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

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

#### **4.12 Office of OTC and Generics**

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

#### **4.13 Office of Medical Devices I**

In the Office of Medical Devices I, the PMDA confirms clinical trial notifications and adverse drug reactions and conducts reviews required for approval, reexaminations, and reevaluation of medical devices and high-level medical electronic

devices intended for use in the fields of cerebro-/cardiovascular systems, respiratory system, neurology/psychiatry, etc.

#### 4.14 Office of Medical Devices II

The office confirms clinical trial notifications and conducts reviews required for approval, reexamination, and reevaluation of medical devices intended for use in the fields of ophthalmology, otorhinolaryngology, dentistry, gastroenterology, urology, obstetrics/gynecology, orthopedic surgery, plastic and reconstructive surgery, dermatology, and laboratory testing (*in vitro* diagnostics).

#### 4.15 Office of Medical Devices III

This office performs reviews for approval applications, investigations, etc. of generic medical devices in all fields other than laboratory testing (*in vitro* diagnostics).

#### 4.16 Office of Compliance and Standards

This office reviews the documentation included with applications for approval, reexamination, or reevaluation of drugs and medical devices to assure that the studies on which the data is based comply with GLP, GCP, GPSP, study protocol, etc. both ethically and scientifically to determine if the documents have been prepared appropriately and accurately based on the study results in accordance with the Criteria for Reliability of Application Data (Article 43 of the Enforcement Regulations, Pharmaceutical Affairs Law) ("Reliability Criteria" hereinafter) and examined on

paper. Compliance of facilities performing GLP-based studies is also examined and certified.

#### 4.17 Office of Safety I

This office undertakes centralized collection and compilation of information related to the quality, efficacy, and safety of drugs and medical devices, conducts surveys and guidance on the application of such information in medical institutions, and conducts scientific analysis and evaluation of such safety information using pharmaceutical and epidemiological procedures. It also undertakes consultations and information dissemination work.

#### 4.18 Office of Safety II

This office undertakes analysis and evaluation of adverse reactions of drugs and medical devices.

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

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

Research promotion and orphan drug development promotion, which had been

conducted by the PMDA, were transferred to the institute.

## 6. PHARMACEUTICAL AFFAIRS AND FOOD SANITATION COUNCIL (PAFSC)

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

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

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

Note 1) Expert areas: Nursing, life sciences, applied biochemistry, mathematics and

statistics, law, and economics

Note 2) Categories of drugs for the Second Committee on New Drugs to review: Antiviral drugs, chemotherapeutic agents, anti-malignant tumor agents, blood products, and biological products. Those for the First Committee: Remaining therapeutic categories

Note 3) Categories of drugs to review: New non-prescription drugs which are apparently different from existing non-prescription drugs in active ingredient, strength, dosage/administration, indications, etc.

Note 4) The First and Second Committees on New Drugs meet in January, February, April, May, July, August, October, and November in principle. The Committees on Non-prescription Drugs meets in February, May, August, and November in principle.

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

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

## 7. NATIONAL INSTITUTE OF INFECTIOUS DISEASES

In April 1997, the name of the National Institute of Health was changed to the National Institute of Infectious Diseases. The institute undertakes basic and applied research, reference and

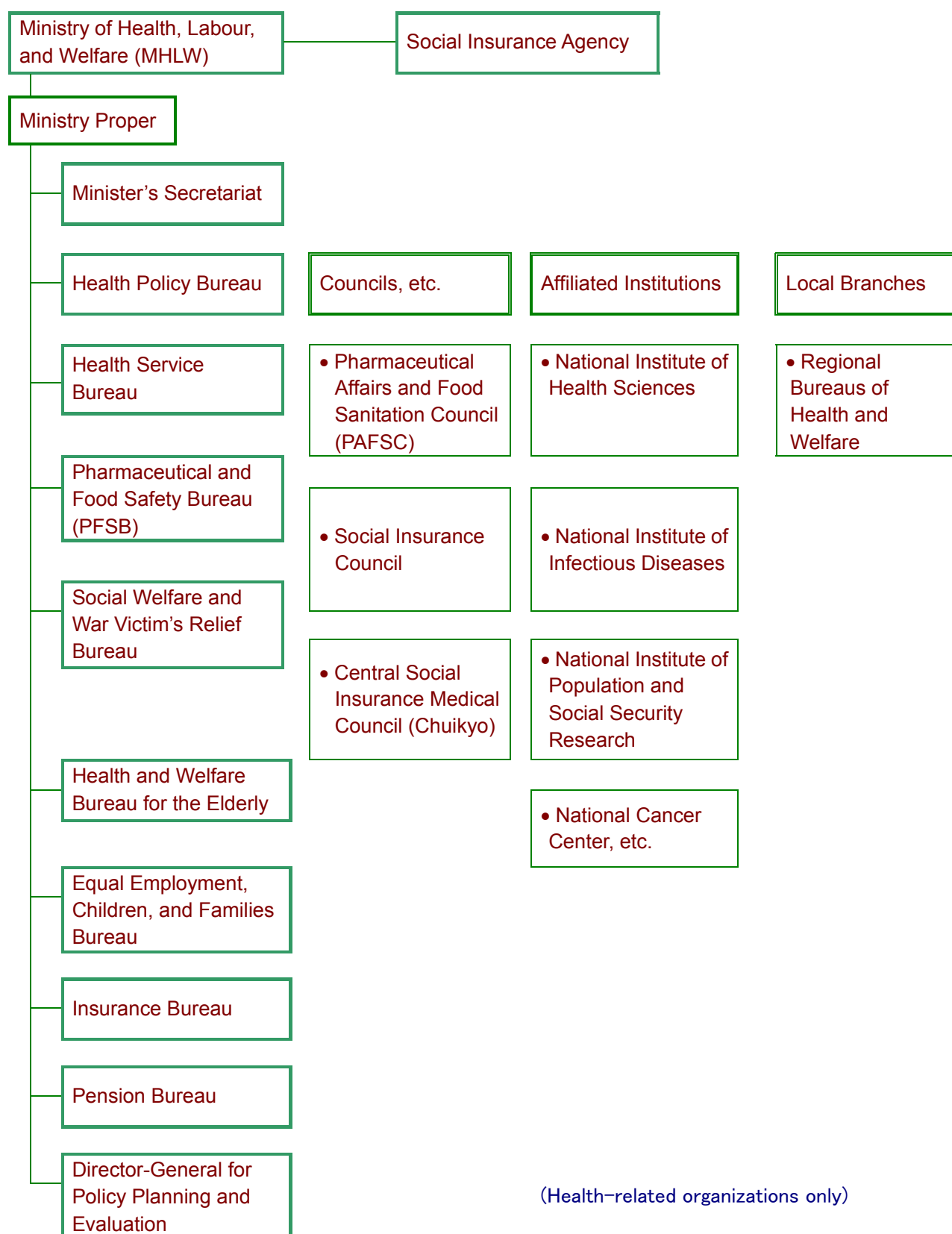
surveillance activities, and collection, analysis, and supply of information pertaining to infectious diseases, performs research on the quality control of antibiotics and other biological products, and undertakes national certification/testing and activities related to international cooperation.

- **Infectious Diseases Information Center**

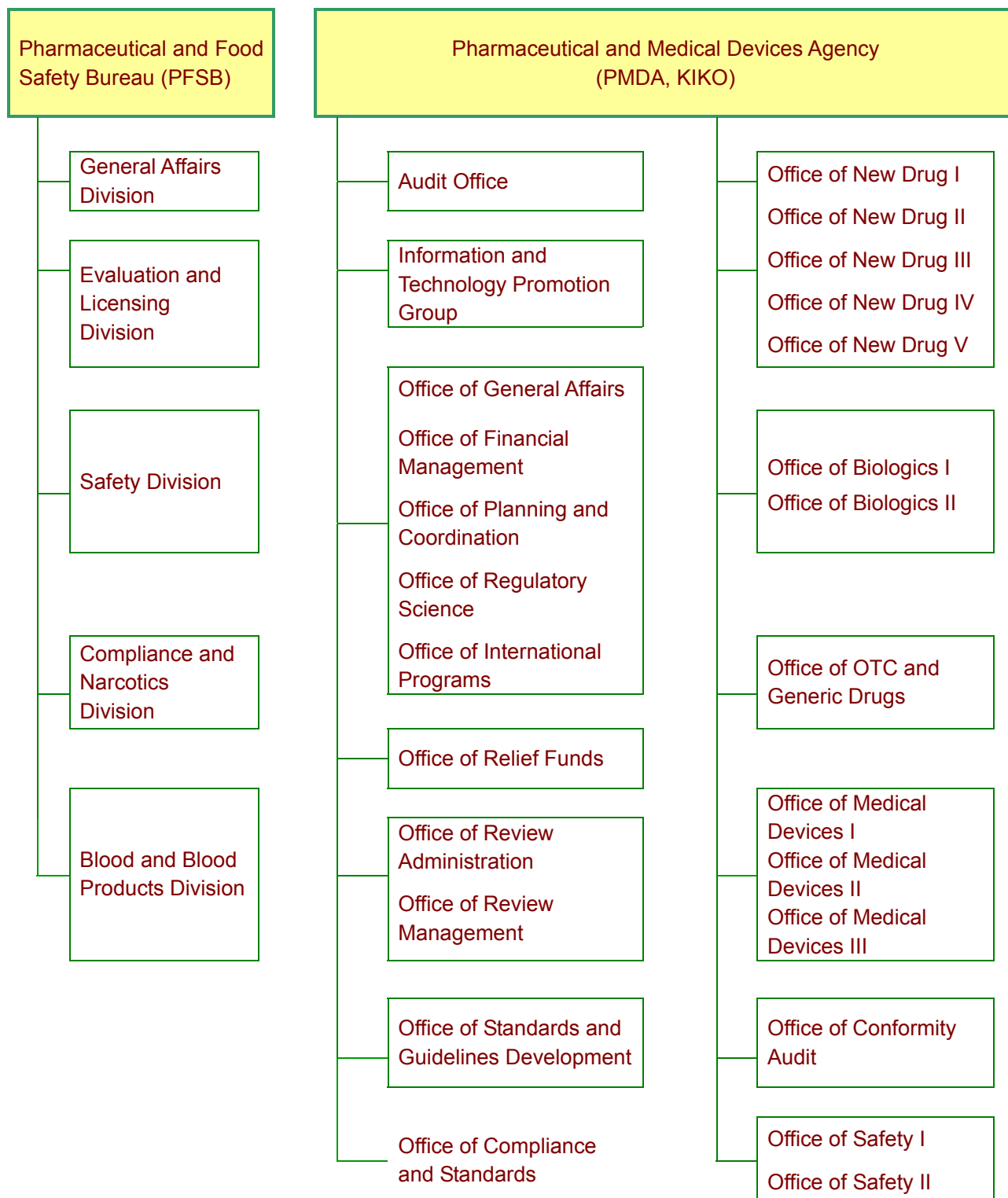
This Center was established in April 1997 to undertake surveys and research, and collect and supply information on infectious diseases, etc.

- **AIDS Research Center**

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

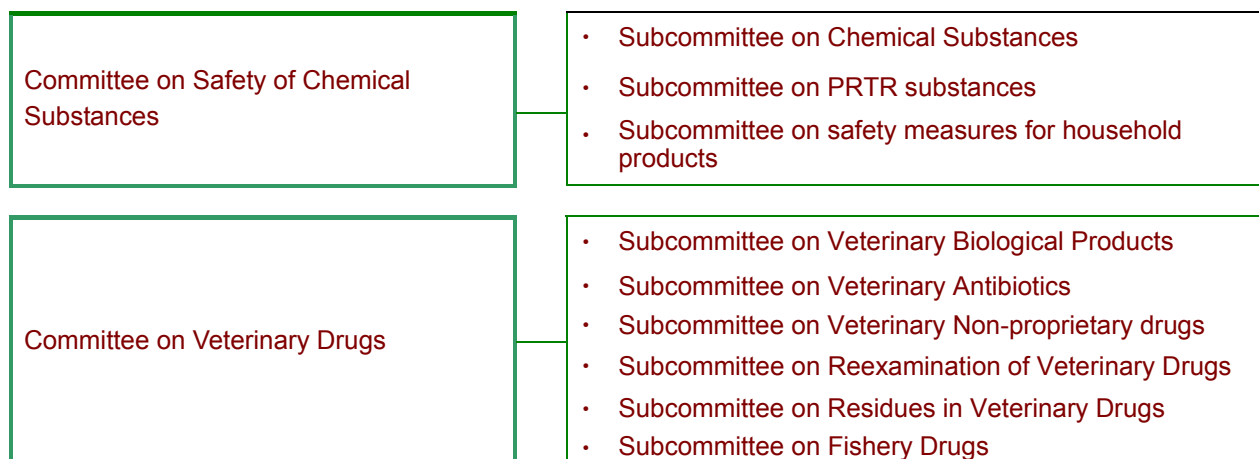


**Fig. 1 Organization of Ministry of Health, Labour, and Welfare**



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

Committee on Japanese Pharmacopoeia	
First Committee on Judgment of Sufferers from Adverse Drug Reactions and Infections	
Second Committee on Judgment of Sufferers from Adverse Drug Reactions and Infections	<ul style="list-style-type: none"> <li>• Subcommittee on Evaluation of Adverse Effects of Biological Products</li> </ul>
First Committee on New Drugs	
Second Committee on New Drugs	
Committee on Blood Products	<ul style="list-style-type: none"> <li>• Subcommittee on Safety of Blood Products</li> <li>• Subcommittee on Proper Use of Blood Products</li> </ul>
Committee on Medical Devices and <i>in vitro</i> Diagnostics	
Committee on Reevaluation of Drugs	
Committee on Handling Regulations for Biological Products	<ul style="list-style-type: none"> <li>• Subcommittee on Medicinal Products for Animals by Application of recombinant DNA Technology</li> </ul>
Committee on Non-prescription Drugs	
Committee on Cosmetics and Quasi-Drugs	
Committee on Safety of Drugs	<ul style="list-style-type: none"> <li>• Subcommittee on Transmissible Spongiform Encephalopathy</li> <li>• Subcommittee on Safety Measurements</li> </ul>
Committee on Safety of Medical Devices	<ul style="list-style-type: none"> <li>• Subcommittee on Safety Measurements</li> </ul>
Committee on Designated Substances	
Committee on Poisonous and Deleterious Substances	<ul style="list-style-type: none"> <li>• Subcommittee on Regulations for Handling Poisonous and Deleterious Substances</li> <li>• Subcommittee on Poisons and Deleterious Substances</li> </ul>



**Fig. 3 Organization of the Pharmaceutical Affairs and Food Sanitation Council (PAFSC) (17 Committees and 18 Subcommittees)**

## CHAPTER 2

# Pharmaceutical Laws and Regulations

### 1. PHARMACEUTICAL LAWS

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

For the enforcement and management of these laws, detailed regulations are prepared by the government in the form of ministerial ordinances and notices, such as the Enforcement Ordinance and the Enforcement Regulations of the Pharmaceutical Affairs Law, and notifications issued by the Director General of the Bureaus 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 that are especially essential for health care.

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

In 2002, the Pharmaceutical Affairs Law (Law No. 96, July 31, 2002) was revised

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

Thereafter, the Law for Partial Amendment of the Pharmaceutical Affairs Law (Law No. 69) to revise the OTC drug selling system and strengthen the control of illegal drugs was issued on June 14, 2006 and enforced on June 1, 2009 as planned. The amended Pharmaceutical Affairs Law has classified non-prescription drugs according to potential risks (type 1: especially

high risk, type 2: relatively high risk, and type 3: relatively low risk) and the systems of information dissemination and consultation on drugs for each classification were implemented. In addition, a notification was issued to implement registered marketing authorization holder tests to confirm the characters of registered marketing authorization holders who are engaged in the sales of type 2 and/or type 3 drugs (Notification No. 0808001 of the General Affairs Division, PFSB dated August 8, 2007). The notification was enforced on April 1, 2008.

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

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

Chapter 2: Prefectural pharmaceutical affairs councils (Article 3) (Establishment of prefectural

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pharmaceutical affairs councils)	suspension or discontinuation,
Chapter 3: Pharmacies (Article 4 - Article 11) (License standards, restrictions on designation of pharmacies, supervision of pharmacies, duty of supervisors, supply of information, etc. on pharmacy by proprietors, requirements observed by proprietors, notification of suspension or discontinuation of business, etc.)	manufacturing approvals for drugs manufactured overseas, notifications of changes in appointed manufacturer/marketing authorization holders, restrictive approvals of drugs manufactured overseas, exceptions for drugs manufactured/marketed in pharmacies, etc.)
Chapter 4: Manufacturers/marketing authorization holders and manufacturers (Article 12 - Article 23) (License standards for manufacturers/marketing authorization holders, licenses for manufacturers, surveys by the PMDA, accreditation of foreign manufacturers, manufacturing/marketing approvals, approval reviews performed by the PMDA (KIKO), restrictive approvals, reexamination, reevaluation, transfers, notification of manufacture/marketing, receipt of manufacture/marketing notifications by the PMDA, drug master files, registration by the PMDA, appointment of marketing supervisors-general, items requiring compliance by manufacturers/marketing authorization holders, notifications of	Chapter 4-2: Third-party certification bodies (Article 23-2 - Article 23-19) (Certification of manufacturing/marketing of designated controlled medical devices, appointment of manufacturer/marketing authorization holders by overseas manufacturers of designated controlled medical devices, cancellation of certification, submission of reports, registration, standards for registration, disclosure of registration, duties for reviews of criteria conformity certification, operational standards manual, etc.).
	Chapter 5: Retail sellers of drugs and retail sellers of medical devices
	Section 1 Retail sellers of drugs (Article 24 - Article 38) (License for selling drugs at stores, license for selling drugs by household distribution, restrictions on drugs sold by household distribution, license for wholesale distribution, and categories

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of non-prescription drugs, etc.)

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

Chapter 6: Standards and government certification for drugs (Article 41 - Article 43) (Japanese Pharmacopoeia and other standards, etc.)

Chapter 7: Handling of drugs

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

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

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

etc.)

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

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

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

Chapter 8-2: Exceptions for biological products (Article 69 - Article 77) (Manufacturing supervisors, items included on immediate containers, package inserts, etc., prohibition of selling and manufacture, explanation of specified biological products by appointed health professionals, regular reports on infectious diseases, preparation and retention of records on biological products, guidance and advice, complication and examination of information on regular reports on infectious diseases by the PMDA).

Chapter 9: Supervision (Article 69 - Article 76-3) (On-site inspections, on-site inspections by the PMDA, emergency

orders, disposal, test orders, orders for improvement, orders for replacement of marketing supervisors-general, supervision of household distributors, cancellations of approvals and licenses, approvals to market drugs manufactured overseas, restrictive approvals and accreditation of overseas manufacturers, procedures for refusal of renewal of licenses, exceptions for hearings, pharmaceutical affairs inspectors)

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

Chapter 9-3: Designation of orphan drugs and orphan medical devices (Article 77-2 - Article 77-2-6) (Designation, securing funds, tax relief measures, notification of suspension of research and development, cancellation of designations)

Chapter 10: Miscellaneous provisions (Article 77-3 – Article 83-5) (Supply, etc. of information, promotion and

enlightenment of proper use of drugs, etc., prevention of hazards, reporting of adverse reactions, reporting of recall, reporting, etc. to PAFSC, compilation and examination by the PMDA of data from adverse reaction reports, preparation and retention of records on specially designated medical devices, guidance and advice, fees, conditions for licenses, etc., application exemptions, etc., handling of clinical trial, review of clinical trial applications by the PMDA, duties of prefectural governments, duties of the Minister in emergencies, classification of clerical work of government agencies, delegation of authority, interim measures, drugs for animals, prohibition of manufacture/import of drugs for animals, prohibition of use, regulations on the use of drugs for animals and regulations on the use of other drugs)

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

### **3. OUTLINE OF PHARMACEUTICAL REGULATIONS**

Various regulations apply to the development, manufacture, import, marketing, and proper use of drugs and medical devices in the form of the

Pharmaceutical Affairs Law, cabinet orders, MHLW ordinances, etc. An outline of the main regulations affecting pharmaceuticals is presented here.

### 3.1 Definition of Drugs

Drugs subject to the regulations in the Pharmaceutical Affairs Law are defined as follows in Article 2, Paragraph 1 of the Pharmaceutical Affairs Law. The term "drugs" 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 not equipment or instruments.

The specifications used to judge whether or not a substance ingested orally corresponds to a drug were specified in Notification No. 476 of the PAB, MHW dated June 1, 1971, but the "Specifications on the Range of Drugs" were revised (Notification No. 0331009 of the Pharmaceutical and Food Safety

Bureau (PFSB), MHLW dated March 31, 2004).

### 3.2 Classification of Drugs

Drugs (medicinal products) ("iyakuhin" in Japanese) can be classified as follows based on the regulatory provisions in the Pharmaceutical Affairs Law, etc.

#### 1) Classification according to use and supply

##### (1) Prescription drugs

Drugs intended for use by a physician or dentist or under the prescription or instructions of a physician or a dentist

##### (2) Non-prescription (OTC) drugs

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

- \* The Law for Partial Amendment of the Pharmaceutical Affairs Law (Law No. 69 enforced in 2009) issued on June 14, 2006 to define non-prescription (OTC) drugs as the drugs not having very strong intended actions (indications) in humans and those to be selected by users based on information provided by pharmacists or other medical personnel and to classify them in

three types based on the degree of risk: Type 1 (highly risky), Type 2 (moderately risky) and Type 3 (relative low risky) (enforced on April 1, 2007).

## 2) Classification according to handling regulations related to safety

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

- (1) Poisonous substances (Article 44 of the Law).
- (2) Deleterious substances (Article 44 of the Law).
- (3) Drugs requiring a prescription (Article 49 of the Law).
- (4) Habit-forming drugs (Article 50 of the Law).
- (5) Drugs for specially designated diseases (Article 67- of the Law).
- (6) Drugs manufactured in pharmacies (Article 22 of the Pharmaceutical Affairs Law)
- (7) Narcotics (Narcotics and Psychotropics Control Law).
- (8) Psychotropic drugs (Narcotics and Psychotropics Control Law).
- (9) Opium and powdered opium (Opium

Law).

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

## 3) Biological products and specified biological products

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

- (1) Biological products
 

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

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

Biological products and specified biological products are specified by the Minister of Health, Labour and Welfare in its Ordinance No. 209 issued in 2003 and Notification No. 0520001 of the PFSB dated May 20, 2003 that came into effect on July 30, 2003.

Based on the provisions in the Law for biological products and specified biological products, the “Manufacturing Supervisors and Import and Marketing 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.

The basic technical requirements to assure the quality and safety of drugs and

medical devices processed from human-derived (autologous) cells and tissues are specified in Notification No. 0208003 of the PFSB dated February 8, 2008. On March 27, 2008, Notification No. 0327027 of the Compliance and Narcotics Division, PFSB on manufacturing control and quality control of drugs and medical devices processed from human-derived (autologous) cells and tissues was issued. The basic technical requirements to assure the quality and safety of drugs and medical devices processed from human-derived (homologous) cells and tissues are specified in Notification No. 0912006 of the PFSB dated September 12, 2008.

It is specified in the notifications that safety- and quality-related issues on drugs, etc. processed from cells and tissues are to be discussed with PMDA through regulatory strategy consulting from the early stage of research and development (Notification of No. 0630-(2) of PFSB entitled “Modifications of Handling of Medicinal Products and Medical Devices Utilizing Cells and Tissues to Comply with Implementation of Regulatory Strategy Consultation” dated June 30, 2011). Procedures for requesting and holding regulatory strategy consultation are available in Notification No. 0630007 of PMDA entitled “Implementation of Regulatory Strategy Consultation on Medicinal Products and Medical Devices dated June 30, 2011.

### 3.3 Licenses for Marketing Businesses and Manufacturing Businesses

#### 1) Licenses for marketing businesses

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

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

The licensing requirements for drug marketing businesses include the appointment of a general marketing compliance officer, who is a pharmacist, and

compliance with Good Quality Practice (GQP) for quality control and Good Vigilance Practice (GVP) for postmarketing safety surveillance. Marketing business license is valid for a period of 5 years after every renewal.

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

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

#### 2) Manufacturing business licenses

Persons wishing to establish a business for the manufacture of drugs, quasi-drugs, cosmetics, or medical devices must obtain a manufacturing business license in accordance with the manufacturing category as specified by MHLW ordinance.

### 3.4 Marketing Approvals

Formal approvals and licenses are required for individual formulations of drugs in order to market the drugs in Japan. Formal approval and/or licenses must be

obtained prior to market launch from the Minister of the MHLW or prefectural governor by submitting data and documents for required review on the ingredient(s) and strength, dosage and administration, indications, adverse reactions, etc. .

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

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

### **3.5 Good Manufacturing Practice (GMP)**

GMP specifies that compliance with the Regulations for Buildings and Equipment of Pharmacies, etc. that specify standards for structures and equipment in manufacturing plants for each manufacturing category without relation to the products manufactured is a requirement for a manufacturing business license. Compliance with the GMP ordinance that specifies standards for

structures and equipment required for the product concerned as well as standards for manufacturing control and quality control for each manufactured product is a condition for approval of the drug concerned (refer to Chapter 3).

In consideration of the characteristics of clinical trials including the early exploratory stage, the GMP for investigational products was amended on July 9, 2008 to make it possible to assure the quality of the investigational product at each stage of the clinical trial (Notification No. 0709002 of the PFSB). Thereafter, Q&A on the GMP for Investigational Products was published (Office Communication of the Inspection and Guidance Division, Narcotics Division, PFSB, MHLW dated July 2, 2009 and “Q&A on GMP for Investigational Products”).

Investigational Product GMP Certificates are also issued for investigational products (Office Communication of the Inspection and Guidance Division, Narcotics Division, PFSB, MHLW dated March 30, 2009).

### **3.6 Drug Master File (MF)**

With the amendment of the Pharmaceutical Affairs Law enforced on April 2005, approvals for drug substances that had been necessary in the past were no longer required (except for products listed in the Japanese Pharmacopoeia) and it is possible to omit documentation on drug substances

attached to applications if the marketing authorization holder presents a certificate in writing of drug master file (MF) registration. The MF system aims at protecting intellectual property of relevant information and facilitating review work by allowing a registrant (master file registrant) other than an applicant to separately submit information on quality and the manufacturing method at the time of approval reviews of drug substances to be used in drug products (Notification No. 0210004 of the Evaluation and Licensing Division, PFSB dated February 10, 2005). MF registration is optional.

When an overseas drug substance manufacturer submits an MF registration application, it is necessary to appoint a drug substance manager to handle the activities of the MF registrant in Japan.

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

When an application to change of the MF is submitted, the marketing authorization holder must submit a partial change application or a slight modification notification for the MF depending on the contents of the

change. However, when a change or changes are slight, the marketing authorization holder is not required to submit a partial change application or a slight modification notification of approved items. In both cases, MF registrants must notify the marketing authorization holder or the manufacturing approval holder of the change(s).

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

### **3.7 Accreditation of Overseas Manufacturers**

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

The specifications for accreditation are the same as those for manufacturing licenses for

domestic manufacturers.

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

<http://www.pmda.go.jp/operations/shonin/info/foreign.html> (in Japanese)

- (1) Applicants for accreditation of overseas manufacturers and their agents
  - When the applicant is a corporation, the representative (director with representative authority) makes the application.
  - The marketing authorization holder, etc. who acts as the agent for the application files the application after confirming from the applicant the type of corporation of the applicant, name, address, and agent. The name and contact information for the agent is entered in the Remarks section of the application form. The note “Application by an authorized manufacturer” should also be entered in the form, if an application is filed by an authorized manufacturer (e.g., a manufacture representing foreign marketing authorization holder for drug, etc, in question). An application by an

agent should be made by the authorized manufacturer, as a rule; however, there are other cases of application not involving authorized manufacturer (Notification No. 1008-(1) of PMDA dated October 8, 2010).

- (2) Timing of applications for accreditation of overseas manufacturers  
The application should be submitted by the time of the marketing approval application. When accreditation is not obtained beforehand, “under application” should be entered in the marketing approval application form (Marketing approval can not be obtained without accreditation approval).
- (3) Outline of the structure and facilities of the manufacturing plant required for accreditation of overseas manufacturers and attached documentation
  - The outline of the structure and facilities of the manufacturing plant should be based on that in the manufacturing business license application in Japan. A list of the structures and facilities must be included.
  - When Japanese can not be used as the language in the attached documentation under special

circumstances, a foreign language can be used, but a Japanese translation must be attached in such cases. If the foreign language is not English, certification of the translator must be attached.

- A medical certificate from a physician must be submitted when the applicant is a corporation of the executives involved in the business, namely the executive with representative authority and executives involved in the business without representative authority, and a table showing the duties of the executives must be attached. When it is difficult to submit medical certificates for physicians for unavoidable reasons in countries where the overseas manufacturer has received authorization, it is possible to submit documents verifying that the executives involved do not correspond to the provisions of Article 5, Item 3(d) (excluding the part related to adult wards) and (e) in place of the medical certificates for physicians.

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

When a GMP compliance survey is performed simultaneously with the accreditation, the structures and

facilities are required for accreditation to be confirmed in the GMP compliance survey, as a rule.

### 3.8 Drug Retail Seller Licensing

A license must be obtained from the Prefectural Governor or other specified officials for marketing or otherwise providing of drugs. Licenses for drug retailers have been classified as follows based on amendment of the Pharmaceutical Affairs Law enacted on June 14, 2006 (Law No. 69: enforced from June 1, 2009). :

- (1) Pharmacies
- (2) Store-based drug sellers
- (3) Drug sellers by household distribution
- (4) Drug sellers by wholesale distribution
- \* For store-based drug sellers and drug sellers by household distribution, qualifications (prefectural examination) for newly registered sellers have been established in addition to the those for pharmacists. These sellers can market drugs except for type 1 drugs.

### 3.9 Quality Standards and Government Certification

The Japanese Pharmacopoeia, Japanese Pharmaceutical Codex, Japanese

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

### 3.10 Labeling and Package Inserts

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

All ingredients used as excipients must be included in the package inserts of prescription and non-prescription drugs. Entries in the package inserts of biological products are specified in Notification No. 0515005 of the PFSB dated May 15, 2003 and labeling on the immediate container or packaging of biological products is specified in Notification No. 0515017 of the PFSB dated May 15, 2003. These specifications came into effect from July 30, 2003.

According to the Pharmaceutical Affairs Law amended on April 1, 2005, a new regulatory category for prescription drug labeling “Caution: Use only with a prescription from a physician” and a labeling item for manufacturer/marketing business instead of manufacturer or importer were added (refer to Chapter 5).

The Law for Partial Amendment of the

Pharmaceutical Affairs Law issued on June 14, 2006 (Law No. 69 enforced in 2009) requires the manufacturer of non-prescription drugs to prescribe in labeling matters specified in the Law in accordance of the level of potential risks.

To prevent medical accidents due to misunderstandings and assure traceability, implementation of barcode labeling for prescription drugs (excluding *in vitro* diagnostics) (Notification No. 0915001 of the Safety Division, PFSB dated September 15, 2006) and preparation of medication guides for patients are being promoted so that the patient understands the prescription drug correctly and serious adverse drug reactions can be discovered at an early stage (Notification No. 0228001 of the Safety Division, PFSB and No. 0228002 of the Compliance and Narcotics Division, PFSB dated February 28, 2006).

### 3.11 Restrictions and Prohibition of Advertising

The following restrictions on advertising are enforced to ensure proper use of drugs: prohibition of advertising of prescription drugs aimed at the general consumer, advertising of the name, manufacturing method and/or indications of a drug before approval, and false or exaggerated statements (Notification No. 1339 of the PAB dated October 9, 1980).

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

### 3.12 Good Laboratory Practice (GLP)

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

The GLP ordinance was partially revised by MHLW Ordinance No. 114 entitled “MHLW Ordinance to Partially Amend the MHLW Ordinance on Standards for Implementation of Nonclinical Studies on Safety of Drugs” and the amendment was enacted on August 15, 2008. On June 20, 2008, Notification No. 0620059 of the PMDA entitled “Establishment of Guidelines for Drug GLP and Medical Device GLP On-site

Inspections” was issued (refer to Section 3.1.4).

### 3.13 Good Clinical Practice (GCP)

“Clinical trials” refer to studies with the objective of collecting data on clinical trial results from among the data attached to drug approval application forms. In Japan, clinical trials are conducted in accordance with the GCP which was implemented to assure scientific quality and reliability of clinical study data. This GCP was replaced by the Standards for the Conduct of Clinical Studies (so-called “New GCP”; Ordinance No. 28, GCP dated March 27, 1997) based on the ICH-GCP Guidelines (E6) (see Chapter 3 for details).

Thereafter, the GCP ordinance was partially revised, and the current GCP is a modification of the Ordinance to Amend the Ordinance on Standards of Clinical Trials of Drugs (Notification No. 24 of MHLW issued in 2008) (partially enforced on April 1, 2009) and Ordinance No. 163 dated November 28, 2008. Major points of modification were concerned with the delivery of study drug, ADR reporting, and institutional review boards.

The new GCP was enacted on October 4, 1998. However, the Study Group on the Efficient Conduct of Clinical Trials indicated the need for standard operating procedures (SOP) for the proper conduct of clinical

studies, and certain improvements were made thereafter. The latest notification on the implementation of the current GCP was issued as Notification No. 2024-(1) of PFSB on October 24, 2011 and enacted on April 1, 2012. Major points of modification were review of records certifying quality control of laboratory testing at clinical laboratories, inclusion of trial-related documents and data at CROs in GCP compliance review, and abbreviated writing of clinical protocol.

The compliance with GCP regulations is also required for clinical trials with microdoses (Notification No. 0603001 of PFSB/ELD entitled “the Guidance for Conducting Microdose Clinical Studies” dated June 3, 2008) and those using pharmacogenomics (Notification No. 0930007 of PFSB entitled “the Use of Pharmacogenomics in Clinical Trials of Medicinal Products” dated September 30, 2008) (refer to Section 3.2.8 in Chapter 3).

#### History of major changes in GCP ordinance:

- 2003

Along with the revision of the Pharmaceutical Affairs Law in July 2002, a new system was established to permit physicians and medical institutions to perform clinical studies for future approval applications (so-called investigator-initiated clinical trials). It has become possible to conduct clinical studies on unapproved drugs

obtained by physicians and medical institutions, such as clinical studies on off-label applications (MHLW Ordinance No. 106 dated June 12, 2003 implemented on July 30, 2003).

#### History of major changes in GCP practices:

- 1999

The following notifications were issued: 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 (No. 65 of the Inspection and Guidance Division, PMSB dated June 30, 1999) and Ways to Reduce the Financial Burden on Study Centers, Including National Hospitals and National Universities (No. 196 of the Medical Professions Division, Health Policy Bureau dated July 2, 1999 and No. 20 of the Medical Education Division, Higher Education Bureau, Ministry of Education, Culture, Sports, Science and Technology dated July 2, 1999).

- 2000

A GCP study group summarized outcomes of their discussions on the topics of the acceptance of monitoring and audits at medical institutions and guidance on standard operating procedures for promoting GCP as Notification No. 889 issued by the Evaluation and Licensing Division, PMSB on

July 24, 2000.

- 2002

The Report of the site management organization (SMO) Study Group on Utilization of SMO was published in November 2002.

- 2005

The Council on Efficient Conduct of Clinical Trials was established to evaluate and find ways to efficiently conduct clinical trials assuring reliability of the conduct of clinical trials and safety of study subjects and discussed procedures necessary for proper conduct of investigator-initiated clinical trials and for improvement of quality and performance of institutional review board (IRB). On September 19, 2007, a report was compiled by the MHLW Council of Ideal Registration-Directed Clinical Trials. Based on this report, the Evaluation and Licensing Division of PFSB issued Notification No. 1002002 dated October 2, 2007 to reevaluate and rationalize the type and scope of documents necessary for the conduct of clinical trials.

- 2008

The current GCP ordinance (MHLW Ordinance No. 24, 2008) made public disclosure of IRB review results in summary format compulsory. Then, “the Registration of IRB Information (Request)” (Notification No. 930004 of the Evaluation and Licensing

Division, PFSB dated October 1, 2008) was issued to provide an environment for trial-related people to easily access IRB information and requests study centers to register IRB name, administrator’s name, location, and web site IP address at the PMDA website for public disclosure.

Information of IRBs currently available:

<http://www.pmda.go.jp/operations/shonin/info/chikenkanren.html>

### **3.14 Good Post-marketing Study Practice (GPSP)**

The GPMSP ordinance was enacted to specify the system and scope of activities of pharmaceutical companies to assure proper implementation of post-marketing surveillance of drugs and reliability of the data obtained after marketing (Ordinance No. 10 of the MHLW dated March 10, 1997). Thereafter, the GPMSP was divided into Good Vigilance Practice (GVP) and Good Post-marketing Study Practice (GPSP). The GPSP ordinance was enforced from April 1, 2005 (refer to Chapter 4).

### **3.15 Reexamination and Reevaluation**

Marketing authorization holders must perform post-marketing surveys on new drugs so that efficacy and safety can be reconfirmed by reexamination by the MHLW for a specified period after marketing

approval. All drugs, including those that have completed reexamination must undergo reevaluation to recheck their efficacy, safety, and quality in accordance with progress in medical and pharmaceutical sciences.

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

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

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

In this connection, applications for generic drugs cannot be filed until completion of the reexamination. Brand products are protected from generics during this period.

### **3.16 Adverse Drug Reaction (ADR) and Infection Reporting**

When marketing authorization holders of drugs are informed of any adverse reactions, infections, etc. as specified by MHLW ordinance for trial products or their marketed products, they must report them to the Minister within the specified period

(Notification No. 0317006 dated March 17, 2005).

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

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

The final report of the “Study group on identification and prevention of recurrences of drug-induced hepatitis” published in March 2010 discusses problems and future prospects related to the drug adverse event reporting system, pharmacovigilance programs, and the problems of off-label drug use and use of unapproved drugs.

<http://www.mhlw.go.jp/shingi/2010/03/s0300-1.html>

### 3.17 Dissemination of Information

Marketing authorization holders of drugs or medical devices, wholesalers, marketing authorization holders or lessors of medical devices, and overseas restrictive approval holders are asked collect and examine information on efficacy, safety, and proper use of drugs and medical devices and supply such information to health professionals such as physicians and pharmacists.

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

With the enactment of the Law Concerning Access to Information Held by Administrative Organizations on April 1, 2000, anyone has the right to request disclosure of documents retained by national government organizations. This law covers disclosure of documents retained by government organizations except those concerning non-disclosable information such as information on individuals, information on corporations, etc. This was partially amended by Cabinet Order No. 371, December 21, 2005.

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

The criteria for disclosure and

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

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

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

Approval application documentation from pharmaceutical companies is not accessible as a rule before approval but becomes accessible after approval. However, even after the approval is granted, where there is a risk that, by being made public, the rights, competitive standing, or other legitimate interests of the corporation, etc. are harmed, the information (such as that on the manufacturing method, specifications/test methods, comments/discussion of the applicant, etc.) are not disclosed. Attached application data or Module 3 (“Quality-Related Documentation” section), Module 4 (“Nonclinical Study Reports” section), and Module 5 (“Clinical Study Reports” section) are not accessible.

Later, the criteria for disclosure of Adverse Drug Reaction Report Forms were revised by Notification No. 4 of the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ) dated January 6, 2004. Notification No. 0330011 of the PMDA dated March 30, 2011 specifies points to consider in the disclosure of information related to new drug approval reviews.

### 3.19 Patent System

The patent term is 20 years from the time of application as a rule. However, if the patent can not be implemented because of laws and regulations to ensure safety of drugs, etc. the patent term can be extended

for a maximum of 5 years. The extension is for the period that the patented invention cannot be used, such as the period from the date of the start of clinical trials or date of patent registration, whichever is later, until one day prior to the date on which the patentee receives approval for the drug.

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

Generic drugs will not be approved until the substance (application) patent has expired. Brand products are protected from generics during this period. However, in the past if some of the indications or dosage and administration of brand products were patented, partial approvals were not granted

because of patent protection, but with Notification No. 0605014 of the Evaluation and Licensing Division, PFSB dated June 5, 2009, partial approvals of indications or dosage and administration not covered by the patent are permitted.

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

English website:  
<http://www.jpo.go.jp/index.htm>

### 3.20 Drug Abuse Control

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

June 26, the final day of the International Narcotics Conference held in 1987, was

designated as “International Drug Abuse Eradication Day.” At a special United Nations meeting on narcotics in 1998, the “Declaration on Guidance to Prevent Drug Abuse” was adopted.

The problem of drug abuse, including narcotics, stimulants, and hemp, has spread worldwide at present and it is one of the most serious social problems affecting the human race not only in terms of survival but also as a threat to safe and stable societies and nations. Japan is now facing a serious situation of stimulant abuse with feelings of resistance and alarm concerning drug abuse waning among young people such as middle and high school students.

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

Measures for the regulation of designated drugs (drugs with a high probability of such actions as excitation of the central nervous system that present a risk to public health and hygiene) have been added to the Pharmaceutical Affairs Law as

countermeasures against illegal drugs. Basically, the manufacture, import, and advertising of designated drugs for purposes other than healthcare is prohibited. On February 28, 2007, the Guidelines on Monitoring of Import of Designated Drugs were issued (Notification No. 0228009 of the PFSB).

## 4. MARKETING APPROVALS

### 4.1 Drug Marketing Approvals

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

quality control standards. Marketing approval is granted to products meeting these standards. This approval system is the essential basis for ensuring good quality, efficacy, and safety of drugs and related products, which is the principal objective of the Pharmaceutical Affairs Law.

### 4.2 Marketing Approval Reviews

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

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

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

meeting.

It is necessary to submit a “list of persons involved in compilation of attached data” and a “list of competitive products and companies” in relation to persons who participated in clinical studies submitted as application data immediately after application submission, prior to the expert meeting, and prior to meeting of the Committee on Drugs).

The evaluation process followed by the PMDA is as follows (see the PMDA website). From March 19, 2009, the applicant can confirm the status of review progress for each product applied for with the manager of the PMDA review team.

<http://www.pmda.go.jp/operations/shonin/outline.html#3> (Japanese)

- (1) Interview (presentation, inquiries, and replies)
- (2) Team review
- (3) Inquiries and replies
- (4) Application for GMP inspection (about 6 months before the meeting of the Committee on Drugs)
- (5) Review report (1)
- (6) Expert meeting (includes at least three clinical specialists as experts)
- (7) General review conference (main agenda items and names of participating experts made available 2 weeks prior to meeting; presentation) (Almost never held at

present)

- (8) Follow-up expert meeting
- (9) Review report (2)
- (10) Report to the Evaluation and Licensing Division, PFSB

The PAFSC is then consulted for discussions by the related committees and the Pharmaceutical Affairs Committee as required on the basis of the review report. After the report of the PAFSC report is obtained and it is confirmed that the standards are met in a separate GMP compliance review, the Minister grants the new drug manufacturing/marketing approval ([Fig. 5. Flowchart of Approval Review](#)).

“Information Concerning New Drug Approval” prepared from the review data is placed on the website of the PMDA so that accurate information concerning the quality, efficacy, and safety obtained during the approval review process is supplied to medical institutions, etc.

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

When active ingredients, dosage, administration route, and indications are the same as those of approved drugs (so-called “generic drugs”), a review by the PMDA is

undertaken after reviews on drug equivalence and compliance, and approval is granted.

A basic notification concerning drug approval reviews was issued on April 8, 1999 and came into force for approval reviews of drugs from April 1, 2000. This basic notification was partially revised on March 31, 2005 and the application categories were more strictly defined. In April 2009, (7) “biosimilars products” (or “follow-on biologics”) was added to the application categories for prescription drugs. The current categories are as follows:

- (1) Prescription drugs with new active ingredients
- (2) New combination prescription drugs
- (3) Prescription drugs with new administration routes
- (4) Prescription drugs with new indications
- (5) Prescription drugs with new dosage forms
- (6) Prescription drugs with new doses
- (7) Similar biological drugs
- (8) Prescription drugs with additional dosage forms
- (9) Prescription combination drugs with similar formulations
- (10) Other prescription drugs

With the agreement reached on the common technical document (CTD) guidelines of the International Conference on

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

These guidelines consist of five parts: Module 1 (Regulatory Information Such as Application Forms and Information Concerning Attached Documentation), Module 2 (Data Summary), Module 3 (Data on Quality), Module 4 (Nonclinical Study Reports), and Module 5 (Clinical Study Reports). Modules 2 to 5 should be prepared on the basis of the CTD guidelines. Part 1 consists of documents requested by each regulatory authority. Detailed standards are shown in the Appendix.

Electronic specifications for the CTD (eCTD) have been prepared and have been applied to application data submitted electronically since April 1, 2005 (Notification Nos. 0527004, 0825001, and 0707-(3) [partially revised] of the Evaluation and Licensing Division, PFSB dated May 27, 2004, August 25, 2008, and July 7, 2009, respectively).

In addition to the 1 year standard approval review time of the MHLW for approval of new drugs from April 1, 2000 (dated March 28, 2000) (excluding the time taken by applicants to prepare responses, etc.), the time allotted

to the applicant is also 1 year so that the time from the application to marketing approval is a maximum of 2 years. The applicant is requested by the MHLW to withdraw the application in case a longer time is required for responding to inquiries or conducting additional studies (Notification No. 0604001 of the Evaluation and Licensing Division, PFSB dated June 4, 2004).

In June 2010, "Points to consider in applications for shortening the PMDA review period for new drugs" was issued. This document includes points to consider on the applicants side to achieve the target PMDA review periods of 12 months for ordinary reviews and 9 months for priority reviews by 2013 (Office Communication of the Evaluation and Licensing Division and Compliance and Narcotics Division, PFSB, MHLW dated June 9, 2010).

On April 17, 2008, "Points to Consider for Reviewers Related to New Drug Approval Review Work" was issued. This showed the basic conditions related to new drug review activities in the PMDA and was intended to clarify the main points to consider in reviews and to assure uniform awareness of PMDA reviewers concerning review work.

Japanese website:

<http://www.pmda.go.jp/topics/h200417kohyo.html>

English website:

<http://www.pmda.go.jp/english/services/reviews/others.html>

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

##### **1) Priority review system**

Drug approval reviews are normally processed in the order that the application forms are received, but for drugs designated as orphan drugs and other drugs considered to be especially important from a medical standpoint such as new drugs to treat serious diseases, a decision must be made whether or not to specify an overall evaluation of (1) the seriousness of the targeted disease and (2) the clinical usefulness, as stipulated in Article 14-(7) of the Pharmaceutical Affairs Law. With this system, applications for specified drugs are reviewed on a priority basis (Notification No. 0901-(1) of the Evaluation and Licensing Division, PFSB entitled "Handling of Priority Review" dated February 27, 2004).

##### **(1) Priority review criteria**

##### **(A) Seriousness of indicated diseases**

- (i) Diseases with important effects on patient's survival (fatal diseases)
- (ii) Progressive and irreversible diseases with marked effects on daily life

- (iii) Others
- (B) Overall assessment of therapeutic usefulness
  - (i) There is no existing method of treatment, prophylaxis, or diagnosis.
  - (ii) Therapeutic usefulness with respect to existing treatment
    - a) Standpoint of efficacy
    - b) Standpoint of safety
    - c) Reduction of physical and mental burden on the patient
- (2) Designation of drug products for priority reviews

When drugs are designated for priority reviews, opinions of experts on such designations are compiled by the PMDA immediately after the application and reported to the MHLW. Based on this report, the Evaluation and Licensing Division decides whether or not to apply the priority review. The Evaluation and Licensing Division notifies this decision to the applicant and the PMDA. The Evaluation and Licensing Division reports this application to the next meeting of the review committee concerned of the PAFSC and obtains their approval.

Products for priority review are given priority at each stage of the review process as much as possible. When products subject to priority review are approved as new drugs, this fact is made public.

## 2) Review of products designated for priority face-to-face advice

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

## 4.4 Restrictive Approval System

The drugs to which this system applies

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

#### 4.5 Orphan Drugs

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

Drugs designated as orphan drugs are entitled to certain priority measures such as financial aid, tax relief on research expenses, guidance and advice, priority review, and extension of the reexamination period from the conventional 6 years to a maximum of 10 years for drugs and from 4 years to a maximum of 8 years for medical devices.

#### 4.6 Drugs for Pediatric Use

Drugs used in pediatric clinics are often considered as “therapeutic orphans” throughout the world because they are difficult to develop and are not provided with sufficient information. This also applies in Japan and very few drug products are indicated for pediatric use. The number of clinical trials performed in children is not sufficient, the number of products that can be used for children is insufficient, and information contained in package insert (dosage, efficacy, safety, etc.) in relation to applications in children is also insufficient. Therefore, “off-label use” of drugs basically intended for adults, use of in-hospital products without adequately verified stability, and use of drugs for pediatric use obtained by individual import are common.

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

1324 of the PMSB dated December 27, 2000).

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

The Study Group on Unapproved Drugs was founded in December 2004 to perform reliable clinical studies on drugs not approved in Japan for which efficacy was established and approvals granted in the West in order to assure prompt approvals in Japan. Periodic surveys and scientific evaluations of requests of academic societies

and patients are undertaken, often involving drugs for pediatric use. In March 2006, the Study Group on Pediatric Drug Treatment was established to collect and evaluate evidence on the efficacy and safety of pediatric drug treatment, to conduct surveys on prescriptions for drugs for pediatric use and to provide information to health professionals for the environmental improvement to adequate pediatric drug treatment. Thereafter, both study groups were developmentally reorganized into a new "Study group to investigate unapproved drugs and off-label use of drugs urgently required for healthcare" in February 2010. The committee started wide-ranging discussions on off-label drugs including unapproved drugs and pediatric drugs.

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

Since May 2010, a "List of drugs for which developing companies are being recruited or requests for development made" has been issued based on the results of discussions by

the “Study group to investigate unapproved drugs and off-label use of drugs urgently required for healthcare.” (The latest version of the list is available at the the following site).

<http://www.mhlw.go.jp/shingi/2010/05/s0521-5.html>

#### **4.7 Biosimilar products**

For biological products, it is difficult to prove the equivalence of active ingredients with those of existing drugs unlike with chemically synthesized drugs, but with the advances made in technology, biosimilars (or follow-on biologics) have been developed in recent years as products with equivalence to and the same quality as existing biological products. WHO and major countries have established new legal systems and specified technological policies. In March 2009, policies for the assurance of the quality, safety and efficacy of biosimilar products (Notification No. 0304007 of the Evaluation and Licensing Division, PFSB dated March 4, 2009) were formulated. “Biosimilar products” were established as a new application category for prescription drugs (Notification No. 0304004 of the Evaluation and Licensing Division, PFSB dated March 4, 2009). Documents on points to consider in approval applications (Notification No. 0304015 of the Evaluation and Licensing Division, PFSB dated March 4, 2009) and

handling of non-proprietary and brand names (Notification No. 0304011 of the Evaluation and Licensing Division, PFSB dated March 4, 2009) were also issued. In March 2010, “Questions and answers on policies to verify the quality, efficacy, and safety of biosimilar products” was issued (Office Communication of the Evaluation and Licensing Division, PFSB dated March 31, 2010).

#### **4.8 Codevelopment**

The objective of codevelopment is to reduce the risk of 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 that when the codevelopment group performed a clinical trial, group members had to be joint sponsors of the trial, but currently other members in the group can use data in applications from clinical trials performed by

any member of the group.

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

#### 4.9 Transfer of Marketing Approvals

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

#### 4.10 Approval Applications for Drugs Manufactured Overseas

Pharmaceutical manufacturers outside Japan can apply directly under their own name for marketing approval if they perform the studies regarding quality, efficacy, and safety required for the drugs they intend to export to Japan and undertake the necessary procedures ([Fig. 6. Procedure for Manufacturing and Marketing of Drugs for Overseas Manufacturers in Japan](#)).

In such cases, the overseas manufacturer

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

#### 4.11 Issuing of GMP Certificates for Exported Drugs and Investigational Products by MHLW

The notification on issuing export certificates for drugs and medical devices was partially revised and items related to issuance of certificates for cosmetics and package inserts of drugs were deleted (Notification No. 170 of the PMSB dated March 6, 2001). Currently, the MHLW issues the following certificates upon request: business licenses for marketing and manufacturing of drugs, etc., marketing approvals for drugs, etc., attached documentation for new drug marketing applications, GLP compliance for drugs, notifications of clinical trial for investigational products, certifications of pharmaceutical formulations, and statements of approval and licensing status of pharmaceutical products ([Table 2. Divisions of the Pharmaceutical and Food Safety Bureau in Charge of](#)

**Certification Work).** (Regulations related to the import of bovine spongiform encephalitis (BSE) from China were abolished by Notification No. 0926003 of the PFSB dated September 26, 2007.) The Ministry would like to use formats specified by the WHO; however, the government may also issue certificates in conventional forms when necessary. Export certificates on drugs, quasi-drugs, etc, are issued using the specified format via the PMDA. Certificates for the items related to compliance of drug manufacturing plants with GMP can be obtained by applying directly to the Compliance and Narcotics Division, PFSB of the MHLW.

Investigational product GMP certificates are provided to countries that have concluded bilateral agreements on GMP with Japan. In other countries, such certificates are not provided at present and the possibility of providing them continues to be investigated.

Investigational product GMP certificates are issued for countries that have concluded bilateral agreements on GMP with Japan. When such certificates are issued, compliance of investigational product manufacturing facilities with the investigational product GMP notification must be confirmed on site by the PMDA (Office Communication of the Inspection and Guidance Division, Narcotics Division, PFSB,

MHLW dated March 30, 2009).

#### **4.12 Issuing Certificates Based on the WHO Certification System**

Certificates of drugs for export have been revised in accordance with WHO guidelines. Certificates for drugs approved by the MHLW were formerly issued for each item but since January 1998, certificates including the approval and licensing status, GMP compliance, and product information are issued using two forms, one for certification of pharmaceutical products (C(o)PP) and one for statements of approval and licensing status of pharmaceutical products based on the new WHO certification system. The issuance of this certificate is stipulated in Notification No. 0128-(1) of the PFSB dated January 28, 2011 entitled “Issuance of certificates for drugs, quasi drugs and medical devices for export.” This gives details including forms for certificates etc. on certificates on drugs for export (Table 2).

The Office Communications entitled “Q&A on Handling Notifications for Drugs for Export” was issued on November 11, 2008.

<http://www.pmda.go.jp/operations/shonin/info/export.html> (Japanese)

## 5. JAPANESE PHARMACOPOEIA AND OTHER STANDARDS

### 5.1 Japanese Pharmacopoeia (JP)

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

Since it was first published in June 1886, the JP has been revised several times. The Pharmaceutical Affairs Law specifies that the JP must be subjected to a complete revision at least once every 10 years, and such revisions have actually appeared every 5 years since the 9th revision in April 1976 ([Fig. 7. Flowchart of Drug Listing in Japanese Pharmacopoeia](#)). In addition, the JP has been partially revised before the complete revision even 5 years since the 11th Edition.

Japanese :

<http://www.std.pmda.go.jp/jpPUB/index.html>

English :

[http://www.std.pmda.go.jp/jpPUB/index\\_e.html](http://www.std.pmda.go.jp/jpPUB/index_e.html)

The PAFSC held a meeting of its Subcommittee on the Japanese Pharmacopoeia to cope with recent progress

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

Basic compilation policies for the 17th edition of the JP (Office communication dated September 13, 2011)

#### (1) Basic policies

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

#### (2) Characteristics and the role of the JP

The JP is a publication that

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

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

### 3) Date of enforcement

The 16th edition of the JP was issued in Notice No. 65 of the MHLW dated March 24, 2011 and was enforced from April 1, 2011.

### (4) Selection of products for entry in the JP

Items selected for entry in the JP must be those important in healthcare that must be entered as soon as possible after marketing

based on the necessity of the drug in medical practice, wide application, and experience of use.

### (5) The compilation review organization for the JP

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

The technical research committees of the Osaka Pharmaceutical Manufacturers Association and Pharmaceutical Manufacturers Association of Tokyo,

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

<http://www.pmda.go.jp/kyokuhou.html>

## 5.2 Standards Based on Article 42 of the Pharmaceutical Affairs Law

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

- Radiopharmaceutical Standards
- Minimum Requirements for Biological Products
- Minimum Requirements for Blood Grouping Antibodies
- Standards for Biological Materials

- Standards for *in vitro* Diagnostics designated by the Minister according to Article 42-(1) of the Pharmaceutical Affairs Law

## 5.3 Standards for Biological Materials

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

Notice No. 262 issued by the MHLW on

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

- Standards for raw materials of ruminant origin
  - (1) The spine, skull, trigeminal ganglion, and dorsal root ganglion of ruminants have been added to the list of materials prohibited for use as raw materials in drugs, medical devices, quasi-drugs, and cosmetics (hereafter drugs, medical devices, etc.).
  - (2) In conjunction with the confirmation of a cow infected with BSE in the United States in December 2003, the United States was removed from the list of countries of origin of raw materials originating from cows and other ruminants that can be used as raw materials for drugs, medical devices, etc.
  - (3) Gelatin and collagen used in drugs, medical devices, etc., which are manufactured from raw materials derived from skin, have been removed from the list of regulated items from countries of origin with confirmed cases of BSE.

Based on Notice No. 310 of the MHLW dated September 28, 2007, Chile was

removed from the list of countries of origin of raw materials originating from cows and other ruminants. Based on Notice No. 343 of the MHLW dated July 1, 2009, the use of raw materials of ruminant origin with Canada as the country of origin was approved to be used within the same range as that of materials from the United States as the country of origin.

Most recently, regulatory handling in application review of raw materials used in the preparation of master cell banks or master seed banks that do not comply with the specifications in the standards for raw materials of biological origin are specified in Office Communication of the Evaluation and Licensing Division, PFSB dated March 27, 2009.

#### 5.4 Quality Standards Based on Notifications

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

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

### 5.5 Government Batch Test

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

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

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

## 6. PHARMACEUTICAL SUPERVISION

### 6.1 Pharmaceutical Supervision

Based on the provisions of the Pharmaceutical Affairs Law, the Minister of the MHLW, prefectural governors, or other may appoint "pharmaceutical inspectors" in connection with the rationalization of pharmaceutical manufacture, import, labeling, advertisements or marketing. This pharmaceutical inspection system covers falsely labeled drugs, drugs of poor quality, drugs that have not been approved or licensed, and false or exaggerated advertising. Pharmaceutical inspectors perform on-site inspections as needed, and

when violations are discovered, the inspectors may issue various orders including administrative measures. The main measures are as follows:

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

### 6.2 Product Recalls

On March 8, 2000, a notification clarifying the "recall" of drug products and medical devices was issued.

The notification emphasizes the importance of "complete" recalls by the manufacturer/marketing authorization holder, and specifies that the meaning of "recall" is to retrieve drug products from the market or to "repair" medical devices. Also, the notification specifies the necessity of recalls in case the drug fails to demonstrate the desired therapeutic effects in general clinical practice, even though it is safe.

### **6.3 Prevention of Medical Accidents Caused by Drugs, etc.**

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

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

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

### **6.4 Safety Measures against Bovine Spongiform Encephalitis (BSE)**

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

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

As a preventive measure in keeping with international trends to enhance safety measures for drugs and medical devices

using bovine-derived raw materials, Notification No. 041400 of the PFSB dated April 14, 2003 concerning bovine-derived raw materials was issued to require precautions related to the site of use and other factors, handling of blood products, handling of products derived from human urine and handling of approvals. Based on Notification No. 0522002 of the PFSB of 2003, "Canada" was added to countries in which BSE occurred in Attached Table 1 and "Canada" was removed from countries of low risk for BSE in Attached Table 2.

Following the confirmation of a cow infected with BSE in the United States in December 2003, the PFSB issued Notification No.0218004 dated February 18, 2004 entitled "Quality and Safety Assurance Related to Drugs, medical devices, etc., manufactured using bovine and other ruminant-derived products and bovine and other ruminant-derived spinal products from the United States" and Notification No. 0218001 of the Evaluation and Licensing Division, PFSB and Notification No. 0218003 of the Safety Division, PFSB dated February 18, 2004 entitled "Handling of Approvals with Respect to Quality and Safety Assurance Related to Drugs, Medical Devices, etc., Manufactured Using Bovine and Other Ruminant-Derived Products and Bovine and Other Ruminant-Derived Spinal Products from the United States". Notification No.

0705001 of the PFSB dated July 5, 2004 entitled "Handling of Approval Applications Concerning Quality and Ensuring Safety of Drugs and Medical Devices Manufactured Using Bovine and Other Ruminant-Derived Products and Bovine and Other Ruminant-Derived Spinal Products from the United States Associated with the Partial Revision of the Standards for Biological Materials" was issued.

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

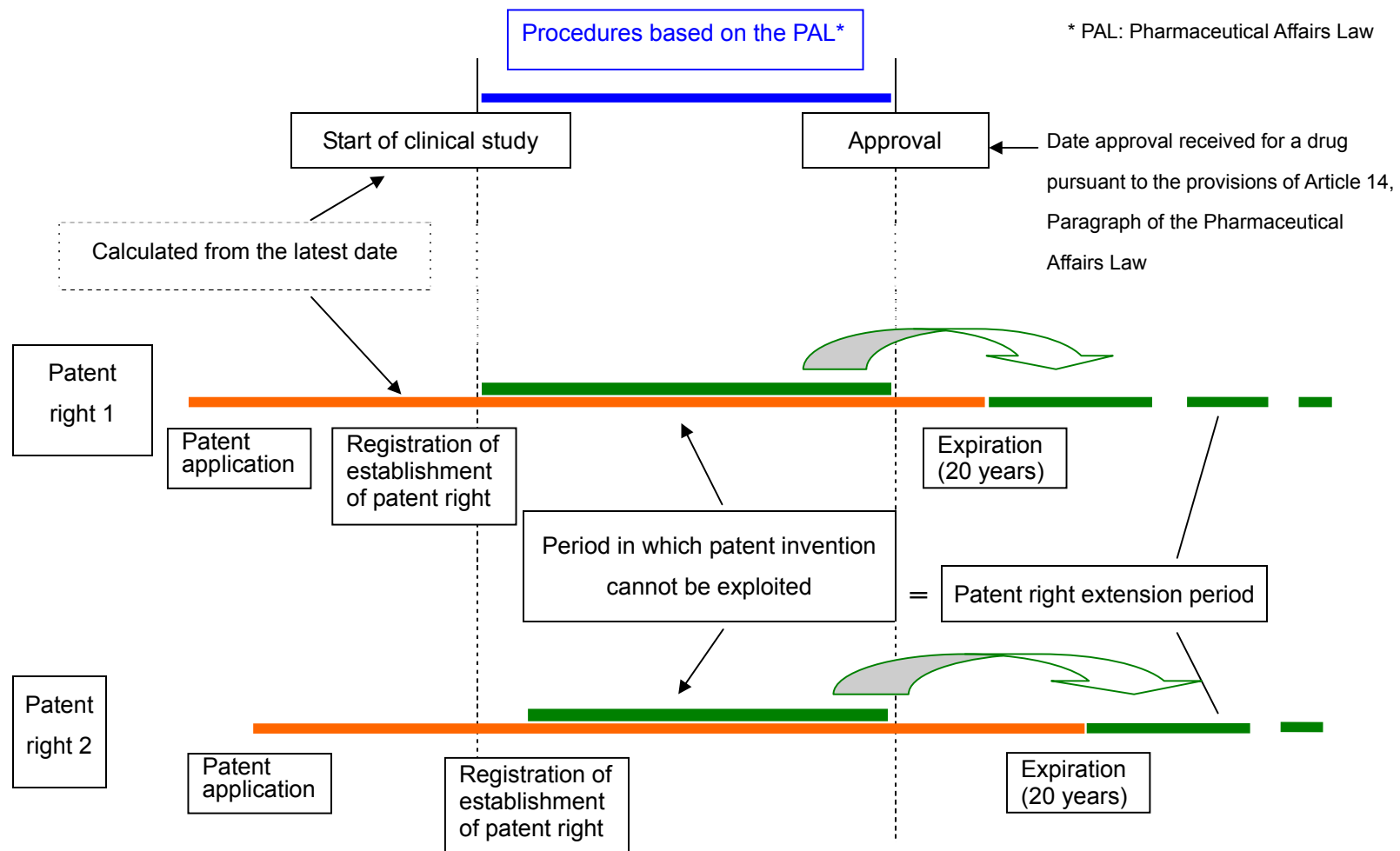
It has been considered necessary to adopt quality and safety assurance measures based on current scientific levels for drugs manufactured using raw materials of human or animal origin. Companies have been requested to undertake voluntary inspections and make adjustments in approval documentation.

Notice 262 issued by the MHLW in July 2004 partially revised the Standards for Biological Materials and Notification No. 0705001 of the PFSB dated July 5, 2004 entitled "Partial Revision of the Standards for

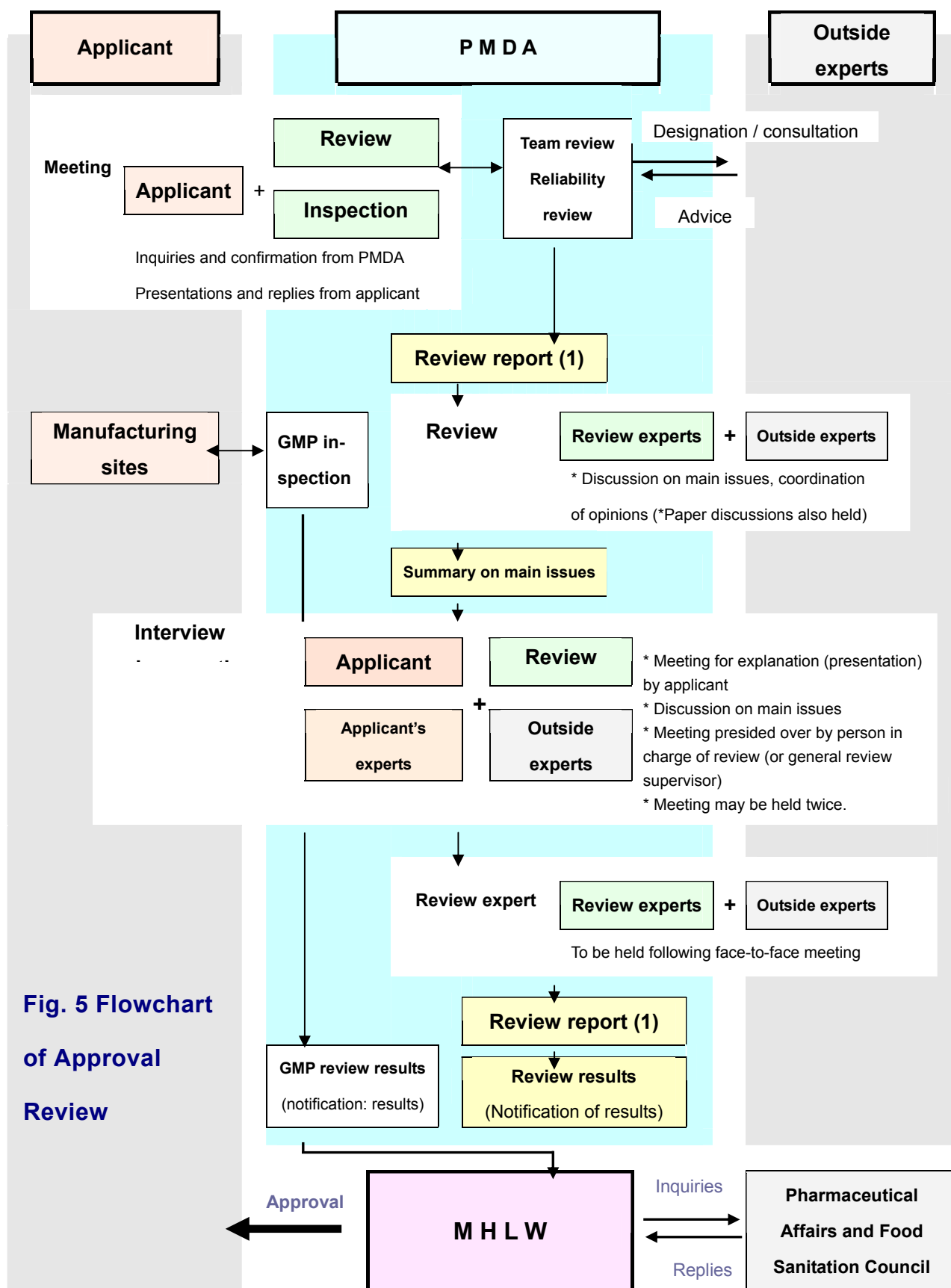
Biological Materials” was issued.

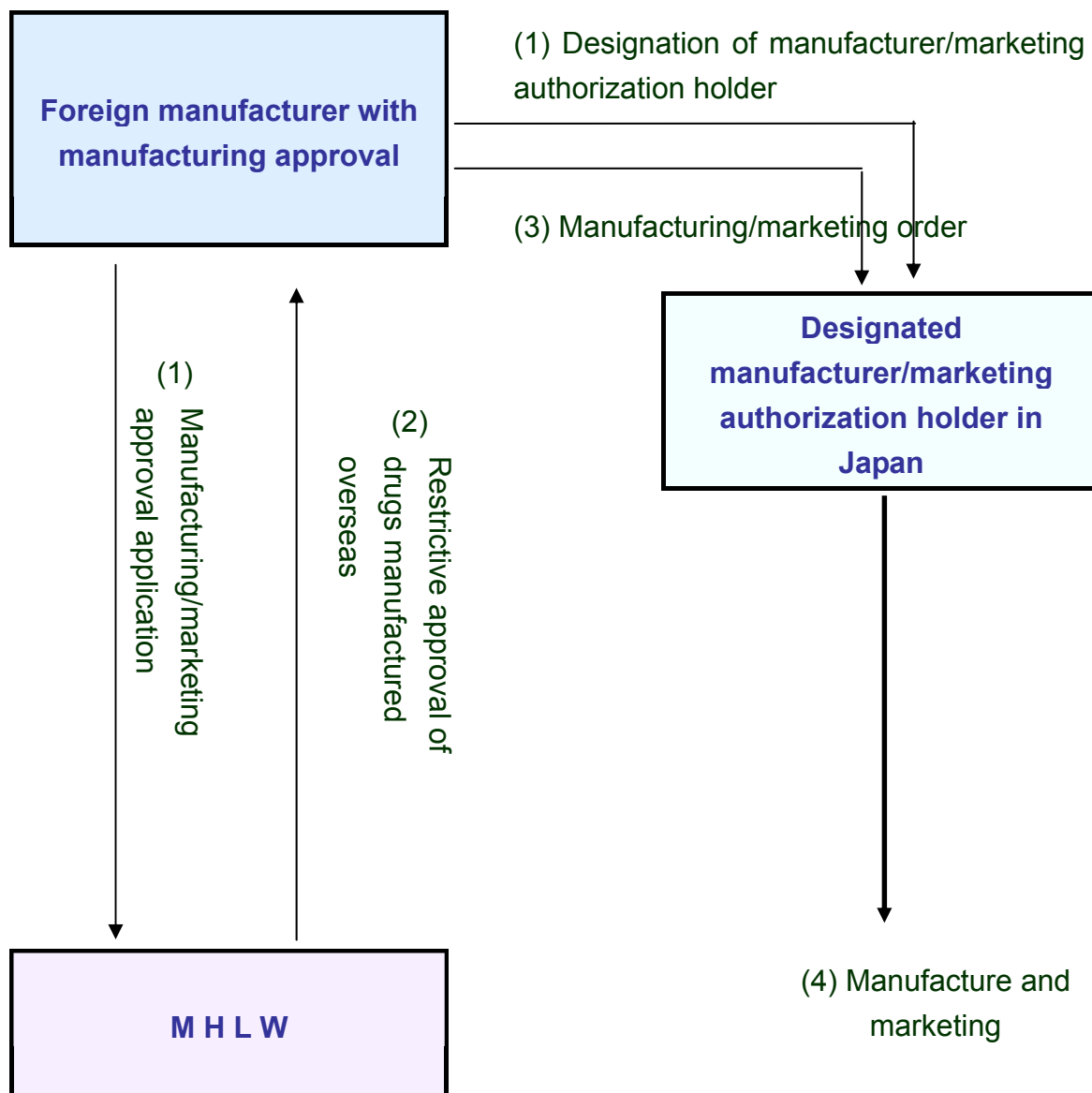
Notification No. 0325003 of the Evaluation and Licensing Division, PFSB dated March 25, 2005 entitled “Handling of TSE Data Associated with Enforcement of the Partially Amended Pharmaceutical Affairs Law” was also issued.

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



**Fig. 4 Flowchart of Patent-Life Extension**





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

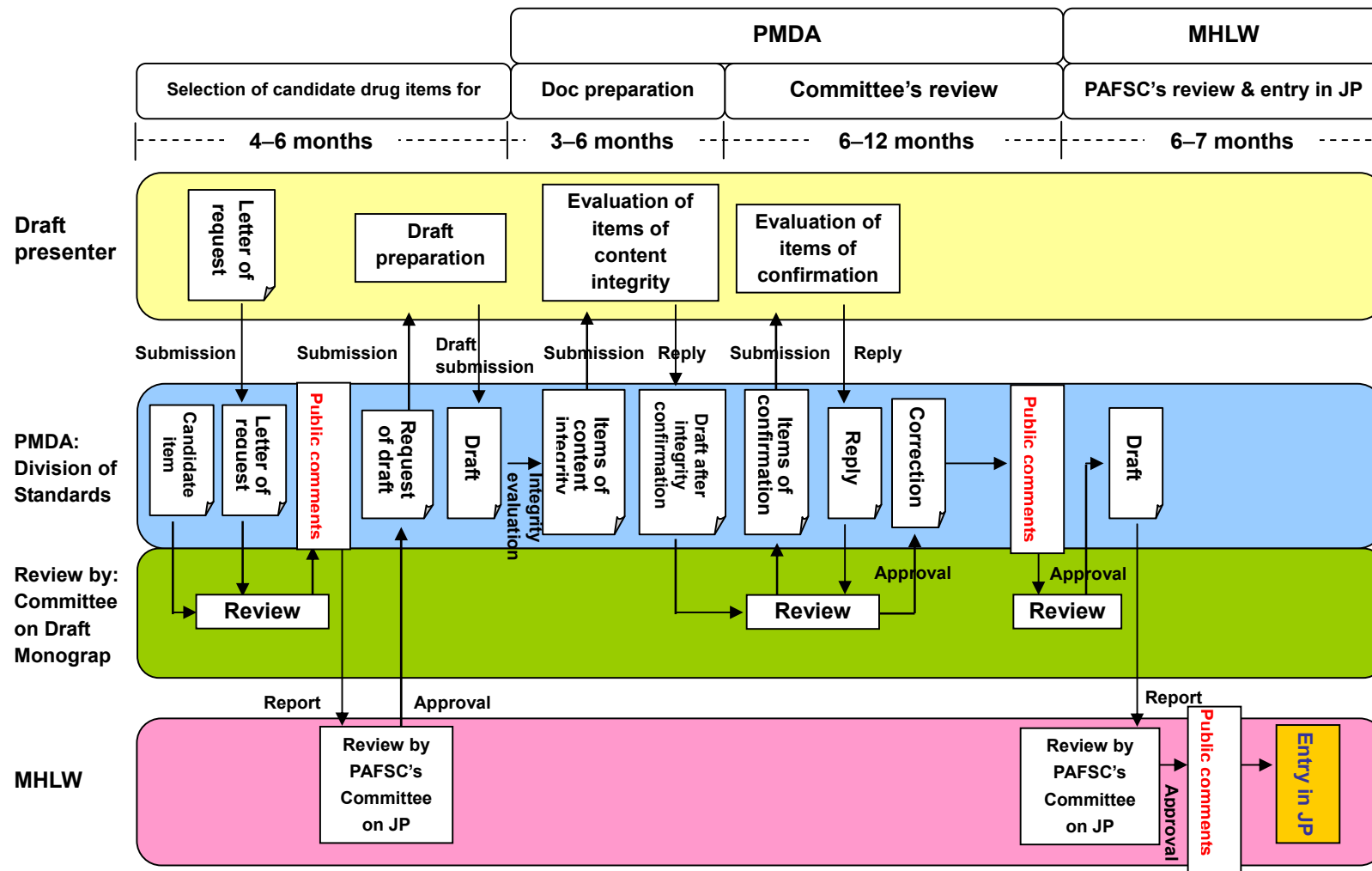


Fig. 7. Flowchart of Drug Listing in Japanese Pharmacopoeia

**Table. 1 List of Main Controlled Substances**

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

Opium and powdered opium	Opium and powdered opium obtained by concentration and processing of the liquid extract from the opium poppy. Opium and powdered opium processed as drugs are not controlled by the Opium Law but regulated as narcotics under the narcotics and psychotropics classification.
Stimulants	Stimulants are drugs specified 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.
Raw materials of stimulants	Raw materials for stimulants are specified in the Attached Table of the Stimulants Control Law” and “Government Ordinance on Specifications of Raw Materials for Stimulants.”
Clinical study drugs	Clinical study drugs are drugs used in either pre- or post-marketing clinical trials, namely investigational products or drugs or other compounds used as comparator drugs in such trials.
Investigational products for post-marketing clinical trials	Investigational products for post-marketing clinical trials are drugs or comparator drugs used in post-marketing clinical trials.
Biological products	Biological products are drugs, quasi-drugs, cosmetics, or medical devices using materials manufactured from humans or other organisms (excluding plants) as raw materials or packaging materials, which are designated by the Minister of Health, Labour and Welfare as requiring special precautions in terms of public health and hygiene.
Specified biological products	Specified biological products are biological products designated by the Minister of Health, Labour and Welfare as requiring measures to prevent the onset or spread of risk to public health and hygiene due to the biological product concerned after selling, leasing or giving.

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

Division	Item to be Certified
Evaluation and Licensing Division	<ol style="list-style-type: none"> <li>1. Items related to business licenses for manufacturing of drugs, etc.</li> <li>2. Items related to manufacturing/marketing approvals (notification) for drugs, etc.</li> <li>3. Items related to attached documentation for new drug manufacturing/marketing approval applications</li> <li>4. Items related to compliance of drugs with GLP Ordinance (Standards for Conduct of Nonclinical Studies on the Safety of Drugs)</li> <li>5. Items related to clinical trial protocol notifications for drugs</li> <li>6. Items related to certification of pharmaceutical products</li> <li>7. Items related to statements of approval and licensing status of pharmaceutical products</li> </ol>
Safety Division	<ol style="list-style-type: none"> <li>1. Items related to business licenses for manufacturing/marketing of drugs, etc. (Note: The certificate is issued by other division in case the certification is originally requested as an attachment to the application to such division.)</li> </ol>
Compliance and Narcotics Division	<ol style="list-style-type: none"> <li>1. Items related to conformity of drug manufacturing plants with GMP requirements (except for items related to certification of pharmaceutical products)</li> <li>2. Items related to conformity of drug manufacturing plants with GMP requirements for investigational products</li> </ol>

## CHAPTER 3

### Drug Development

#### 1. PROCESS FROM DEVELOPMENT TO APPROVAL

New drugs are defined as drugs with ingredients, dosage, administration route, or indications, which are clearly different from those of drugs, which have already been approved for manufacture and marketing or those listed in the JP. Applications for approval to manufacture and market new drugs must be submitted to the Ministry of Health, Labour and Welfare with results of nonclinical and clinical studies required to show the quality, efficacy, and safety of a 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 nonclinical and clinical studies. The nonclinical studies include physicochemical studies and animal studies

on pharmacology, pharmacokinetics, and toxicity. The clinical studies usually consist of Phase I, II and III studies (or human pharmacology, therapeutic exploratory, therapeutic confirmatory, and therapeutic use categories). On starting each phase of clinical studies, it is necessary to adequately confirm the safety of the drug product from the results of nonclinical studies or results of previous clinical studies.

The Pharmaceutical Affairs Law specifies that the data submitted to obtain approvals must be obtained and compiled according to the standards specified in its Article 14, Paragraph 3. Related ordinances include the Ordinance on Standards for Conduct of Clinical Trials (MHW Ordinance No. 28 dated March 27, 1997, partially revised by Ordinance No. 127 of MHLW dated October 20, 2000, Ordinance No. 106 of MHLW dated June 12, 2003, Ordinance No. 172 of MHLW dated December 21, 2004, and Ordinance No. 72 of MHLW dated March 31, 2006) (GCP); the Ordinance on Standards for Conduct of Nonclinical Studies on the Safety of Drugs (MHW Ordinance No. 21, March 26, 1997, partial amendments: Ordinance No. 127 dated October 20, 2000 and Ordinance No. 114 dated June 13, 2008) (GLP) and Standards for the Reliability of Application Data (Article 43, Enforcement Regulations, Pharmaceutical Affairs Law) which were enforced from April 1, 1997. Therefore, the

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

A flowchart from development to approval of new drugs is shown in [Fig. 7 \(Flowchart of Drug Listing in Japanese Pharmacopoeia\)](#).

## 1.2 Reviews and Guidance by the PMDA (KIKO)

The PMDA conducts advice, guidance, and reviews 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 nonclinical studies and clinical studies.

### 1) GLP reviews

The PMDA undertakes reviews of compliance with GLP, which specifies standards for the conduct of safety studies, for safety-related nonclinical studies at the request of the MHLW. These reviews are performed on the basis of the GLP compliance review guidelines

(Notification No. 23 of the PMDA dated April 1, 2004, Partial Revision No. 530 of the PMDA dated June 29, 2004, Revision No. 529 of the PMDA dated March 30, 2007, Notification No. 0620058 of the PMDA dated June 20, 2008, and Notification No. 0815008 of the PMDA dated August 15, 2008) (Refer to [3.1.4. GLP](#)).

### 2) Review of clinical trial protocol notifications

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

### 3) Face-to-face advice

The PMDA has established a consultation system for clinical study protocols to improve and reinforce the quality of clinical studies. The consultations and review work have been united under the same teams in the Review Department. With the increasing demand for clinical trial consultations, improvements have been made in the quality of consultations with respect to preparation for consultations, implementation of consultations,

<p>preparation of records, etc. as measures to meet the demands for those requesting consultations (Notification No. 0901001 of the PMDA dated September 1, 2011). Main items of the face-to-face advice (clinical trial consultations and simple consultations) handled by the PMDA are as described below. Details of the consultation items, the latest information on consultation fees, and application procedures for face-to-face consultation are available at the following websites of the PMDA. Prior consultation is also available to assure smooth face-to-face advice.</p> <p>* Consultation items and fees:  <a href="http://www.pmda.go.jp/operations/shonin/info/consult/file/8_tesuryo.pdf">http://www.pmda.go.jp/operations/shonin/info/consult/file/8_tesuryo.pdf</a></p> <p>* Application procedures:  <a href="http://www.pmda.go.jp/operations/shonin/info/consult/taimen.html">http://www.pmda.go.jp/operations/shonin/info/consult/taimen.html</a></p> <p>(1) Clinical trial consultations          (pharmaceutical affairs consultation on R&amp;D strategy [e.g., design of studies in subsequent clinical stage, data package necessary for application] of drugs including orphan drugs)</p> <p>a) Consultations on procedures</p> <p>b) Consultations on bioequivalence studies</p> <p>c) Consultations on safety</p>	<p>d) Consultations on quality</p> <p>e) Consultations before start of Phase I studies</p> <p>f) Consultations before start of early Phase II studies</p> <p>g) Consultations before start of late Phase II studies</p> <p>h) Consultations after completion of Phase II studies</p> <p>i) Consultations before application</p> <p>j) Consultations when planning clinical studies for reevaluation and reexamination</p> <p>k) Consultations on completion of clinical studies for reevaluation and reexamination</p> <p>l) Additional consultations on drugs</p> <p>(2) Other</p> <p>m) Consultations on preliminary assessment of new drugs (assessment of data concerning the following areas planned to be submitted for application in order to identify potential issues to be addressed during review):</p> <ul style="list-style-type: none"> <li>▪ Quality</li> <li>▪ Nonclinical: Toxicology</li> <li>▪ Nonclinical: Pharmacology</li> <li>▪ Nonclinical: Pharmacokinetics</li> <li>▪ Phase I trials</li> <li>▪ Phase II trials</li> </ul>
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- Phase II/III trials
- n) Consultations on pharmacogenomic biomarkers
- o) Consultations on generic drugs
- p) Consultations on generic drugs before start of clinical studies or application
- q) Consultations on preliminary assessment of medical devices and *in vitro* diagnostics
- r) Consultations on clinical trials of medical devices, *in vitro* diagnostics, and products prepared from cells and tissues
- s) Consultations on compliance with reliability standards:
- t) Consultations on R&D strategies (to discuss clinical development plan with mainly universities, research institutes, and venture companies who have found seeds throughout the R&D period from the final stage of lead compound or candidate medical device selection until the early phase of clinical development [Phase IIa])
- u) Consultations on drugs for priority review (to discuss the appropriateness of drugs, other than orphan drugs, for priority review when an applicant desires a new drug to be designated as a product for priority review. Procedures for handling

priority review are available in Notification No. 0901-(1) of the PMDA dated September 1, 2011.

- v) Prioritized face-to-face consultations (consultations on orphan drugs and especially drugs that are essential for medical treatment and review of drugs applications such as those submitted for priority review).
- w) Simple consultations (e.g., brief consultations with reviewers in charge of the approval review of generic prescription drugs, non-prescription drugs, *in vitro* diagnostics, etc. as well as the registration of drug master files)

#### 4) Compliance reviews

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

- [Paper reviews](#)

Paper reviews are performed based on the “Guidelines for Paper Compliance Review for New Drug Approval Application Data” (Notification No. 0131010 dated January 31, 2006 and partial revision No. 0331009 dated March 31, 2009 of the Evaluation and Licensing Division, PFSB) and “Implementation Procedures for Paper Reviews” (Notification No. 0330001 dated March 30, 2007, partial revision No. 0401012 dated April 1, 2009, and Notification No. 0528027 of the PMDA dated May 28, 2010) when the applicant provides the PMDA with data as evidence for approval reviews. The review assures that the approval review data has been collected and compiled in accordance with the above criteria. Methods for reviews by visits of PMDA staff to archives storing approval application data and source data (on-site paper review) have been introduced. Since August 2001, the PMDA has provided a checklist as a reference for self-compliance review by the applicant prior to paper review of application.

- [On-site reviews](#)

In these reviews, the PMDA review staff examines the data at the sites where it was collected or compiled. The guidelines for on-site GCP compliance reviews have been revised. The procedures for conducting GCP on-site inspections related to documentation attached to approval applications for drugs are shown in Notification No. 0131006 of the Evaluation and Licensing Division, PFSB dated January 31, 2006 (partial revisions: Notification No. 1228002 of the PMDA dated December 28, 2007, Notification No. 0325001 of the Evaluation and Licensing Division, PFSB dated March 25, 2009, and Notification No. 0528028 of the Evaluation and Licensing Division, PFSB dated May 28, 2010).

The reviews are generally performed in the applicant’s offices and facilities and medical institutions performing the clinical study (four facilities as a rule for new drugs; two facilities for additional indications or orphan drugs). In selection of review facilities, consideration should be given to the number of subjects in clinical trials and dates of GCP reviews performed in the past.

Appendix 4 shows the GCP on-site reviews conducted since April 1, 1997. The PMDA also provides a checklist as reference for self-inspections before on-site inspections of sponsors and medical institutions.

### 1.3 Approval Reviews

A detailed team review is performed by the review staff in the PMDA after the confirmation of reliability of submitted data in the compliance review by the PMDA (Refer to Section 4.2: Marketing Approval Reviews of Chapter 2). For the main points concerning reviews, refer to “Points to Consider for Approval Application Data for New Drugs” (Notification No. 0331009 of the Evaluation and Licensing Division, PFSB dated March 31, 2005, partially revised by Office Communication dated April 22, 2005 and by Notification No. 1020002 of the Evaluation and Licensing Division, PFSB on non-prescription drugs dated October 20, 2008). For the purposes of standardizing the criteria/procedures of review, identifying the basic attitude of reviewers toward review, and clarifying main points of review, the document entitled “Points to Be Considered by the Review Staff Involved in the Evaluation Process of New Drug” has been issued and accessible at the following PMDA websites:

<http://www.pmda.go.jp/topics/file/h200417kohyo.pdf> (Japanese)

<http://www.pmda.go.jp/english/service/pdf/points.pdf> (English)

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 and the final decision concerning approval is made by the Minister of Health, Labour and Welfare (refer to Section 4.2: Approval Reviews, Chapter 2). [Fig. 8 \(Flowchart of New Drug Development and Approval\)](#) shows general procedures followed in approval reviews of new drugs.

The current fee for approval of medicines, etc. is available at the following PMDA website:

[http://www.pmda.go.jp/operations/shonin/info/fee/file/35\\_tesuryoiyaku.pdf](http://www.pmda.go.jp/operations/shonin/info/fee/file/35_tesuryoiyaku.pdf)

The PMDA review period for new drugs is expected to be shortened through the efforts of both the regulatory authorities and the applicants, and the points to consider in the application from the standpoint of shortening the period on the applicant side are specified in the Office Communication entitled “Points to consider in shortening of the PMDA review period for new drugs” dated June 9, 2010. The main points are as follows.

- Handling of data from long-term clinical studies

Data obtained on completion of administration to all patients for at least 6 months should be appended as application data. The final report (including data on completion of administration to all patients for at least one year) and the revised draft of the CTD should be submitted at the earliest possible time as additional data. At the latest, it should be submitted by 6 months before the end of the targeted total PMDA review period.

- Handling of data from long-term stability studies  
Additional data should be submitted as a final report (including data required for setting the planned expiration period) at the latest by 6 months before the end of the total targeted PMDA review period. Additional data obtained thereafter should be submitted by the time of data submission to the Committee of Experts.
- Points to consider when using a drug master file (MF)
- Points to consider for adequate contact with the person registering the MF, verification of the MF registration conditions, and submission of information of registered MF corresponding to

Module No. 2 of the CTD without delay after filing an approval application for the product.

- Application for GMP compliance inspection  
Application for inspections of the facilities concerned and preparation for receiving inspectors at sites when the applicant judges based on contract, etc. from the department in charge of the inspection that the inspections are likely to take place.

A standard CTD format was shown by PFSB to illustrate points to be considered in the preparation of a CTD with the aim to shorten the review time for the applicant.

## **2. DATA REQUIRED FOR APPROVAL APPLICATIONS**

To reinforce the review system from April 2000 based on international conditions in global drug development, the data to be attached to approval applications for drugs is specified in the basic notification entitled “Approval Applications for Drugs” (Notification No. 481 of PMSB dated April 8, 1999 and partial revisions: Notification No. 663 of the PMSB dated June 21, 2001, No. 899 of the Evaluation and Licensing Division, PMSB dated June 21, 2001, No. 0701004 of the Evaluation and Licensing Division, PMSB dated July 1, 2003, No. 0525003 of the

Evaluation and Licensing Division, PMSB dated May 25, 2004, and Office Communication dated May 24, 2004). Detailed handling procedures are specified in “Points to Consider in Drug Approval Applications” (Notification No. 666 of the Evaluation and Licensing Division, PMSB, MHLW dated April 8, 1999). With the revision of the Pharmaceutical Affairs Law in April 2005, a notification regarding documents and data to be attached to the application form was issued for handling approval applications for manufacturing and marketing of drugs (Notification No. 0331015 of the PFSB dated March 31, 2005) (handling procedures for non-prescription drugs were partially revised by Notification No. 1020001 of the PMDA dated October 20, 2008). Notification No. 481 was cancelled, and instead, detailed procedures for application were notified by Notification No. 0331009 of the Evaluation and Licensing Division, PFSB dated March 31, 2005, entitled “Points to Consider in Submitting Applications for Approval of Manufacturing/Marketing of Medicinal Products” (partially revised by Office Communication on April 22, 2005 and on non-prescription drugs partially revised by Notification No. 1020002 of the Evaluation and Licensing Division, PFSB dated October 20, 2008).

Subsequently, an agreement was reached on the Common Technical Document (CTD)

by the ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) and a notification entitled “Handling Data Attached to Drug Approval Applications” (Notification No. 663 of the PMSB, MHLW dated June 21, 2001), which is a partial revision of the previous notification mentioned above. On the same day, another notification entitled the “Guidelines for Preparation of Data Attached to Applications for Approval to Manufacture or Import New Drugs” (Notification No. 899 of the Evaluation and Licensing Division, PMSB, dated June 21, 2001, partially revised by Notification No. 0701004 of the Evaluation and Licensing Division, PFSB, dated July 1, 2003, Notification No. 0525003 of the Evaluation and Licensing Division, PFSB dated May 25, 2004, Office Communication dated May 24, 2004, and Notification No. 0707-(3) of the Evaluation and Licensing Division, PFSB dated July 7, 2009) was issued to specify guidelines for preparation of data to be attached to approval applications based on the CTD. The data required for approval applications using CTD format is shown below. The data in Modules 2 to 5 are prepared on the basis of the CTD guidelines shown in Attachments 1 and 3 to 5 of these guidelines.

For electronic specifications of the CTD (e-CTD), “Electronic Specifications of the

Common Technical Document” (Notification No. 06404001 of the PFSB dated June 4, 2003, partially revised by Notifications No. 0527001 of the Evaluation and Licensing Division, PFSB dated May 27, 2004, No. 0527004, 0825001, and 0707-(3) dated August 25, 2008, and July 7, 2009, respectively). These specifications were enforced from October 1, 2008. Handling of submissions of electronic data and Q&A are shown in the Handling of Electronic Specifications for Common Technical Documents (Notification No. 0527004 of the Evaluation and Licensing Division, PMSB dated May 27, 2004, partially revised by Notification No. 0707-(3) of the Evaluation and Licensing Division, PMSB dated July 7, 2009), Office Communications dated March 31, 2005, April 27, 2005, October 5, 2006, December 22, 2006, July 7, 2009, and February 26, 2010. In Japan, submission of eCTD is not obligatory but it is recommended. It is no longer necessary to submit paper data for approval applications if an e-CTD is submitted as the original.

**1) Module 1: Administrative information such as application forms and prescribing information**

- (1) Module 1 table of contents (including table of contents of Module 1)

- (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], and declarations required to be attached in accordance with Notification No. 0527004 of the Evaluation and Licensing Division, PFSB dated May 27, 2004 entitled “Handling of Computer Formatting of the Common Technical Document”).
- (4) Patent status
- (5) Background of origin, discovery, and development
- (6) Data related to conditions of use in foreign countries, etc.
- (7) List of related products
- (8) Package insert (draft)
- (9) Documents concerning non-proprietary name
- (10) Data for review of designation as poisons, deleterious substances, etc.
- (11) Draft of basic protocol for post-marketing surveillance
- (12) List of attached documentation
- (13) Others
  - <1> Data related to approved drugs
  - <2> Clinical trial consultation records (copies)
  - <3> Inquiries (copies) and responses

to inquiries (copies)

<4> Other data [data submitted to the PMDA (copies), data submitted to the MHLW (copies)]

<5> Points to consider in formatting the eCTD

## 2) Module 2: Data summaries or CTD

“Gaiyo”

(1) Modules 2 to 5 (CTD) table of contents

(2) CTD introduction

(3) Quality overall summary

(4) Nonclinical overview

(5) Clinical overview

(6) Nonclinical summary (text and tables)

<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> Literature references

<6> Synopses of individual studies

## 3) Module 3: Quality

(1) Module 3 table of contents

(2) Data or reports

(3) Literature references

## 4) Module 4: Nonclinical study reports

(1) Module 4 table of contents

(2) Study reports

(3) Literature references

## 5) Module 5: Clinical study reports

(1) Module 5 table of contents

(2) Tabular listing of all clinical studies

(3) Clinical study reports

(4) Literature references

([Fig. 9. Organization of ICH Common Technical Documents](#))

### 2.1 Data to be Attached to Approval Application of Drugs

#### 2.1.1 Prescription drugs

The data required for applications for prescription drugs is shown in the basic Notification No. 481 of the PMSB dated April 8, 1999 as mentioned at the beginning of this Section 2. In line with various agreements on CTD at ICH conferences, relevant notifications were

revised accordingly (Notification Nos. 663 and 899 of the PMSB dated June 21, 2001; partial revision of No. 0701004 of the Evaluation and Licensing Division, PMSB dated July 1, 2003, No. 0525003 of the Evaluation and Licensing Division, PMSB dated May 25, 2004, Notification No. 0525003 dated May 25, 2004, and Office Communication dated May 24, 2004). Later, in accordance with the revision of Pharmaceutical Affairs Law in April 2005, a new notification on application procedures was issued (Notification No. 0331015 of the PFSB dated March 31, 2005) and biosimilar products were added as a new application category (Notification No. 0304004 of the PFSB dated March 4, 2009). Data for approval application is shown in Attached Tables 1 and 2-(1) in [Table 3 \(Data to be Submitted with an Application for Approval to Manufacture/Market: A New Prescription Drug\)](#). Data corresponding to (1) to (8), (9), (10), (10-2), and (10-4) in the application dossier are required to be prepared and submitted by the CTD format.

#### 2.1.2 Non-prescription drugs

The range of data to be submitted with applications for non-prescription drugs is specified as shown in [Table 4 \(Data to be Submitted with an Application for a](#)

[Non-prescription Drug\)](#) (partial revision in Notification No. 0331015 of the PF, dated March 31, 2005 and Notification No. 1020001 of the PFSB dated October 20, 2008). After complete enforcement of the CTD (from July 1, 2003), the present guidelines for preparation of data to be attached to approval applications can be applied to approval applications for non-prescription drugs as in the past. For the time being, data on the manufacturing method and specifications and test methods for non-prescription drugs with new active ingredients are prepared using the CTD only for reference purpose.

### 3. GUIDELINES CONCERNING DRUG APPROVAL APPLICATIONS

Guidelines outlining standard test methods and essential criteria for reference in the preparation of data for drug manufacturing and marketing 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 been internationally harmonized. 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 their study designs comply with the Japanese guidelines.

Two notifications were issued in relation to the acceptance of foreign clinical data: "Handling of Data on Clinical trials on Drugs Performed in Foreign Countries" (Notification No.739 of the PMSB dated August 11, 1998) and "Ethnic Factors to be Considered in the Acceptance of Foreign Clinical Trial Data" (Notification No. 672 of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau dated August 11, 1998 and partial revision by Office Communication dated January 4, 1999) and its Q and A (Office Communications dated February 25, 2004 and October 5, 2006). According to these notifications, when data from clinical studies performed in foreign countries are used for new drug application in Japan, the data is first checked to assure that it complies with legal requirements in Japan.

Whether or not the drug is apt to be affected by ethnic factors (intrinsic or extrinsic factors) is then evaluated. When necessary, a bridging study is performed, and when it is concluded that the clinical study outcome in a foreign population can be extrapolated to the Japanese population, the foreign data can be accepted. Since the possibility of acceptance is actually left up to the authorities concerned, it is recommended that the requirements for bridging studies be confirmed as acceptable for the regulatory agencies through consultations with PMDA.

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

Marketed drugs that have been used for unapproved indications or dosage and administration in clinical practice (off-label use) should be used appropriately by receiving marketing approval based on the Pharmaceutical Affairs Law. But in the cases the indications and dosage and administration related to off-label use are confirmed by medical and pharmaceutical knowledge in the public domain, a judgment

is made of whether or not the use can be approved without performing all or part of the clinical trials again (Notifications No. 4 of the Research and Development Division, Health Policy Bureau and No. 104 of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau dated February 1, 1999). After this notification was issued, applications based on public knowledge have been filed and approved.

(1) Cases where an official approval of indication(s) unapproved in Japan has already been granted overseas (countries with approval systems confirmed to be on the same level as the system in Japan or with corresponding systems; the same hereinafter), sufficient experience of use in medical practice is available, and data appended to the application for the regulatory authorities can be obtained.

(2) Cases where an official approval indication(s) unapproved in Japan has already been granted overseas, sufficient experience of use in medical practice is available, scientific evidence has been published in internationally reputable scientific journals, or review articles, etc. of international organizations can be obtained.

(3) Cases where there are clinical study results that can be confirmed in terms of ethics, science, and reliability by such means as contract research performed as part of public research projects.

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

### 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 required test items in reference to the specified test guidelines. For drugs with new active ingredients manufactured by chemical synthesis, refer to “Setting of Specifications and Test Methods of New Drugs” (ICH Q6A) (Notification No. 568 of the Evaluation and Licensing Division, PMSB dated May 1, 2001) For new biological products (biotechnological products/drug products derived from living organisms), refer to “Setting of Specifications and Test Methods of Biological Products (biotechnological

products/drug products derived from living organisms)" (ICH Q6B) (Notification No. 571 of the Evaluation and Licensing Division, PMSB dated May 1, 2001). These guidelines on specifications and test methods were prepared based on ICH agreements. To achieve sufficient utilization of ICH-Q6A and ICH-Q6B, it is necessary to harmonize the General Test, Processes and Apparatus of Pharmacopoeia among ICH regions, and hence the Guidelines on Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions (Notification No. 0526001 of the Evaluation and Licensing Division, PFSB dated May 26, 2009, No.1; ICH-Q4B) were issued. Based on these guidelines, when it is judged that it is possible to utilize the pharmacopoeial texts in the ICH regions, these texts can be used mutually in accordance with the conditions set in annexes.

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

- (1) Setting of Specifications and Test Methods of New Drugs (ICH Q6A) (Notification No. 568 of the Evaluation and Licensing Division, PMSB dated May 1, 2001)
- (2) Setting of Specifications and Test

Methods of Biological Products (Biotechnological Products/Drug Products Derived from Living Organisms) (ICH Q6B) (Notification No. 571 of the Evaluation and Licensing Division, PMSB dated May 1, 2001)

- (3) Text (Items) on Analytical Validation (ICH Q2A, currently Q2(R1)) (Notification No. 755 of the Evaluation and Licensing Division, PAB dated July 20, 1995)
- (4) Text (Items) on Analytical Validation (ICH Q2B, currently Q2(R1)) (Notification No. 338 of the Evaluation and Licensing Division, PAB dated October 28, 1997)
- (5) Guidelines on Impurities in Bulk Drugs with New Active Ingredients (ICH Q3A, currently Q3A(R2)) (Notification No. 877 of the Evaluation and Licensing Division, PAB dated September 25, 1995, revised in Notification No. 1216001 of the Evaluation and Licensing Division, PMSB dated December 16, 2002, partially revised by Notification No. 1204001 of the Evaluation and Licensing Division, PMSB dated December 4, 2006)
- (6) Guidelines on Impurities in Drug Preparations (ICH Q3B, currently Q3B(R2)) (Notification No. 539 of

<p>Evaluation and Licensing Division, PAB, dated June 23, 1997, revised in Notification No. 0624001 of the Evaluation and Licensing Division, PMSB dated June 24, 2003, partially revised by Notification No. 0703004 of the Evaluation and Licensing Division, PMSB dated July 3, 2006)</p> <p>(7) Guidelines on Residual Solvents in Drug Preparations (ICH Q3C, currently Q3C(R3)) (Notification No. 307 of the Evaluation and Licensing Division, PMSB dated March 30, 1998, partially revised by Notification No. 0221-(1) of the Evaluation and Licensing Division, PMSB dated February 21, 2011)</p> <p>(8) Handling of Manufacturing (Import) Approval in Association with International Harmonization of Pharmacopoeia (Notification No. 574 of the Evaluation and Licensing Division, PMSB dated May 1, 2001)</p> <p>(9) Guidelines Related to Formulation Development (ICH Q8) (Notification No. 0901001 of the Evaluation and Licensing Division, PFSB dated September 1, 2006, partially revised by Notification No. 0628-(1) of the Evaluation and Licensing Division, PMSB dated June 28, 2010).</p> <p>(10) Handling of Application of Drugs Containing a Substance with</p>	<p>Different Crystalline (Notification No. 0616-(1) of PFSB dated June 16, 2011.</p> <p>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.</p> <p>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.</p> <p>2) Guidelines for stability tests</p> <p>Standard methods for long-term stability studies, stress stability studies and accelerated stability studies for bulk drugs and preparations are specified in the Guidelines for Stability Tests Attached to Approval Applications to Manufacture or Import Drugs (Notification No. 165 of the PAB and No. 43 of the Evaluation and Licensing Division, PAB dated February 15, 1991). However, based on an ICH agreement, stability tests on drugs with new active ingredients and new combinations must be performed in accordance with the ICH Stability Test Guidelines (ICH Q1A, currently Q1A(R2))</p>
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(Notification No. 30 of the New Drugs Division, PAB dated April 21, 1994). The former guidelines for stability tests of prescription drugs with new active ingredients (Notification No. 565 of the Evaluation and Licensing Division, PMSB dated May 1, 2001) has been abolished and new stability guidelines based on ICH agreements have been established (Revision of Stability Test Guidelines (ICH Q1A(R2)), Notification No. 0603001 of the Evaluation and Licensing Division, PFSB dated June 6, 2003). Stability test guidelines were also established for approval applications in climatic zones III and IV outside the three ICH regions (EU, Japan and the US) (ICH Q1F) (Notification No. 0603007 of the Evaluation and Licensing Division, PFSB dated June 6, 2003) but they were abolished (Notification No. 0703001 of the Evaluation and Licensing Division, PFSB dated July 3, 2006) with the expansion of application of the ICHQ1A guidelines based on ICH agreement (Notification No. 0603001 of the Evaluation and Licensing Division, PMSB dated June 3, 2003). Photostability tests for drugs with new active ingredients and new combinations are performed on the basis of the Guidelines for Photostability Tests of New Bulk Drugs and New Preparations (ICH Q1B) (Notification No. 422 of the

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

Concepts concerning simplification of stability tests on a scientific basis have also been specified in Application of Bracketing and Matrixing Methods in Stability Tests on Drug Substances and Drug Products (ICH Q1D) (Notification No. 0731004 of the Evaluation and Licensing Division, PFSB dated July 31, 2002, partially revised by Office Communication dated June 3, 2003).

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

- (1) Revisions of the Guidelines for Single and Repeated Dose Toxicity Studies (ICH S4) (Notification No.88 of the Evaluation and Licensing Division, PAB dated August 10, 1993)
- (2) Guidelines for Reproductive and Developmental Toxicity Studies (ICH S5A/S5B) (Notification No.316 of the Evaluation and Licensing Division,

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

- (3) Guidance for Toxicokinetics  
(Evaluation of Systemic Exposure in Toxicity Tests) (ICH S3A)  
(Notification No.443 of the  
Evaluation and Licensing Division,  
PAB dated July 2, 1996)
- (4) Guidance for Specific Items in Genotoxicity Studies on Drugs (ICH S2A) (Notification No.444 of the  
Evaluation and Licensing Division,  
PAB dated July 2, 1996)
- (5) Guidance on Dose Selection for Carcinogenicity Tests of Drugs (ICH S1C) (Notification No. 544 of the  
Evaluation and Licensing Division,  
PAB dated August 6, 1996) and its supplement (ICH S1C(R), currently S1C(R1)) (Notification No. 551 of the  
Evaluation and Licensing Division,  
PMSB dated July 9, 1998)
- (6) Guidance on Requirements for Carcinogenicity Tests of Drugs (ICH S1A) (Notification No.315 of the  
Evaluation and Licensing Division,  
PAB dated April 14, 1997)
- (7) Timing of Preclinical Studies in Relation to Clinical Trials (ICH M3(M), currently M3(R1))

<p>(Notification Nos. 1019 and 1831 of the Evaluation and Licensing Division of PMSB dated November 13, 1998 and December 27, 2000, respectively, partially revised by Notification No. 0219-(4) of the Evaluation and Licensing Division, PMSB dated February 19, 2010)</p> <p>(8) Guidance on the Need for Carcinogenicity Studies of Pharmaceuticals (ICH S1B) (Notification Nos. 548 and 1831 of the Evaluation and Licensing Division, PMSB dated July 9, 1998)</p> <p>(9) Guidance on Carcinogenicity Tests of Pharmaceuticals (Notification No. 1607 of the Evaluation and Licensing Division, PMSB dated November 11, 1999, partially revised by Notification No. 1127001 of the Evaluation and Licensing Division, PMSB dated November 27, 2008)</p> <p>(10) Guidance on Genotoxicity Tests of Pharmaceuticals (ICH S2) (Notification No. 1604 of the Evaluation and Licensing Division, PMSB dated November 1, 1999)</p> <p>(11) Genotoxicity Tests: Standard Combination of Genotoxicity Tests of Pharmaceuticals (ICH S2B) (Notification No. 554 of the Evaluation and Licensing Division, PMSB dated July 9, 1998)</p>	<p>(12) The non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals (ICH S7B) (Notification No. 1023-(4) of the Evaluation and Licensing Division, PMSB dated October 23, 2009)</p> <p>(13) Immunotoxicity Studies for Human Pharmaceuticals (ICH S8) (Notification No. 0418001 of the Evaluation and Licensing Division, PMSB dated April 18, 2006)</p> <p>Data on the following studies that should be conducted in accordance with the above guidelines are required for the review and evaluation of a new drug application by the Ministry (<b>Table 3: Documentation that must be submitted with application for marketing approval of prescription drugs</b>):</p> <ol style="list-style-type: none"> <li>(1) Single dose toxicity studies</li> <li>(2) Repeated dose toxicity studies</li> <li>(3) Genotoxicity studies</li> <li>(4) Carcinogenicity studies</li> <li>(5) Reproductive and developmental toxicity studies</li> <li>(6) Skin irritation studies</li> <li>(7) Other toxicity studies</li> </ol> <p>Drug dependence studies were specified separately from the toxicity guidelines in the Scope of Application and the Guidelines for Animal Studies and</p>
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Clinical Observations on Drug Dependence (Notification No. 113 of the Narcotics Division, PAB dated March 14, 1975) and the Guidelines for Animal Studies and Clinical Observations on Drug Dependence (Notification No. 383 of the Narcotics Division, PAB dated June 7, 1978).

For biological products, the guideline “Nonclinical Safety Evaluation of Biotechnological Drugs” (ICH S6) (Notification No. 326 of the Evaluation and Licensing Division, PMSB dated February 22, 2000) should be referred to. For infection prophylactic vaccines, refer to the guideline “Nonclinical safety evaluation of prophylactic vaccines (Notification No. 0527-(1) of the the Evaluation and Licensing Division, PMSB dated May 27, 2010) and for anti-malignant tumor agents, refer to the guideline “Nonclinical safety evaluation of anti-malignant tumor agents (Notification No. 0604-(1) of the the Evaluation and Licensing Division, PMSB dated June 4, 2010).

#### 4) Good Laboratory Practice (GLP)

For toxicity tests conducted to confirm the safety of drugs, the reliability of the data should be assured so that the results obtained are correctly analyzed and assessed. For this purpose, all toxicity

tests conducted to support applications for new drug manufacturing and marketing approval and reexamination must be conducted in accordance with the Good Laboratory Practice Standards for Safety Studies on Drugs (GLP). (Notification No. 902 of the Evaluation and Licensing Division, PFSB dated June 21, 2001 requires safety pharmacology studies be performed in accordance with the “Guidelines on Safety Pharmacology Studies” to comply with the GLP Ordinance.)

Following the introduction of the GLP requirements in the US, 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 MHLW bureau notification were legalized as the MHW Ordinance on Standards for Implementation of nonclinical Studies on Safety of Drugs (Ordinance No.21, March 26, 1997, partially revised by Notification No. 127 of the MHLW Ordinance dated October 20, 2000) (GLP) in order to

assure greater reliability than previously of the nonclinical safety data. After partial revision by Ordinance No. 114 dated June 13, 2008, this new GLP was enforced on August 15, 2008.

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 eight chapters and 19 articles as outlined 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 caretakers

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

Chapter 8 (Article 19)

Requirements for conducting studies at more than two testing facilities

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

GLP compliance reviews conducted by the PMDA are performed on the basis of the "System of Guidelines for Reviews

Based on the Pharmaceutical GLP and Medical Device GLP” (Notification No. 23 of the PMDA date April 1, 2004; partially revised Notifications No. 530 of the PMDA dated June 29, 2004, No. 529 dated March 30, 2007, No. 0620058 dated June 20, 2008 and No. 0815008 dated August 15, 2008). GLP compliance conditions are evaluated in the following three categories by the GLP Evaluation Committee established by the PMDA based on the results of the GLP compliance review.

Class A: Compliance with GLP.

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

Class C: Noncompliance with GLP.

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

These GLP requirements also apply to data generated in other countries when they are used to support applications in

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

## 5) Guidelines for general pharmacological studies

The general policies for selection and planning of test systems to prepare data on safety pharmacology studies are specified in the Safety Pharmacology Study Guidelines (ICH-S7A) (Notification No. 902 of the Evaluation and Licensing Division, PMSB dated June 21, 2001: ICH-S7A) and it is required that safety pharmacology studies are performed in accordance with the GLP Ordinance as a rule. The objectives of the Safety

Pharmacology Study Guidelines are as follows and a research protocol that complies with these objectives should be prepared. (1) Undesirable pharmacodynamic properties of investigational products considered to be related to safety in humans must be specified; (2) adverse pharmacodynamic or pathophysiological actions of investigational products confirmed in toxicity studies or clinical studies must be evaluated; and (3) the mechanisms of pharmacodynamic adverse actions confirmed to date or posing a risk must be investigated.

Secondary pharmacology studies to understand the type and severity of pharmacological actions and to clarify the pharmacological profile of the investigational product together with primary pharmacology studies are performed with reference to the Guidelines for General Pharmacology Studies (Notification No. 4 of the New Drugs Division, PMSB dated January 29, 1991) (Notification No. 902 of the Evaluation and Licensing Division, PMSB dated June 21, 2001). For other pharmacology studies, reference should be made to Notification No. 813 of the Evaluation and Licensing Division, PMSB dated June 4, 2001 entitled "Methods of Investigating Drug Interactions" when

preparing data related to pharmacodynamic drug interactions.

#### 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. The Guidelines on Nonclinical Pharmacokinetic Studies (Notification No. 496 of the Evaluation and Licensing Division, PMSB dated June 26, 1998) were issued 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 Evaluation and Licensing Division, PAB dated July 2, 1996; ICH S3B) should be used for reference for repeated dose studies.

In cases where consideration should be given to perform pharmacokinetic evaluation of drug interactions, reference should be made to "the Guidance for

Pharmacokinetic Evaluation of Drug Interactions” (Notification No. 813 of the Evaluation and Licensing Division, PMSB dated June 4, 2001).

## 7) Guidelines for bioequivalence studies

The following guidelines have also been issued concerning bioequivalence:

- (1) Guidelines for Bioequivalence Testing of Generic Drugs (Notification No. 487 of the Evaluation and Licensing Division, PMSB dated December 22, 1997, partially revised by Notification No. 786 of the Evaluation and Licensing Division, PMSB dated May 31, 2001, and Notification No. of 1124004 the Evaluation and Licensing Division, PMSB dated November 24, 2006)
- (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, and Notification No. of 1124004 the Evaluation and Licensing Division, PMSB dated November 24, 2006)
- (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, partially revised by Notification No. 786 of the Evaluation and Licensing Division, PMSB dated May 31, 2001, and Notification No. 1124004 of the Evaluation and Licensing Division, PMSB dated November 24, 2006).
- (5) Guidelines for Bioequivalence Studies of Generic Products for Topical Dermatological Use (Notification No. 0707001 of the Evaluation and Licensing Division, PMSB dated July 7, 2003, partially revised by Notification No. 1124004 of the Evaluation and Licensing Division, PMSB dated November 24, 2006).
- (6) Guidelines for Bioequivalence Testing of New Additional Topical Dermatological Dosage Forms (Notification No. 1124001 of the Evaluation and Licensing Division, PMSB dated November 24, 2006).
- (7) Guidelines for Bioequivalence Testing of Topical Dermatological Dosage Forms with Formulation

Modifications (Notification No. 1101-1 of the Evaluation and Licensing Division, PMSB dated November 1, 2010).

### 3.2 Clinical Studies

#### 1) Basic requirements

The primary objectives of clinical studies are to evaluate therapeutic and prophylactic efficacy of investigational new drugs for target diseases or symptoms as well as their risks and possible ADRs in humans, and ultimately to assess their clinical usefulness based on a comparison of their efficacy and safety. In performing clinical studies, investigators must give scientific and ethical consideration to the subjects' human rights to minimize their risk relative to the expected benefits.

Guidance concerning drug development strategies and evaluation processes has been issued in the three ICH regions. In 1998, General Considerations for Clinical Studies (Notification No. 380 of the Evaluation and Licensing Division, PMSB dated April 21, 1998, ICH E8) was prepared as one aspect of MHLW's efforts to promote international harmonization of approval review data for new drugs.

This notification consists of the objective of the guidelines, general

principles (protection of clinical trial subjects and scientific approach in design and analysis) and development methods (points to consider for development plans and for individual clinical studies).

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

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

Clinical studies can be classified by their objectives. The basic logic behind serially conducted studies of a drug is that the results of prior studies should influence the protocols of later studies

(**Table 5. Classification of Clinical Studies According to Objectives**).

Following an ICH agreement to issue common GCP for scientific and ethical conduct of clinical studies in three regions, the MHLW Ordinance on Standards for Implementation of Clinical Studies on Drugs (GCP) (MHW Ordinance No. 28 dated March 27, 1997, partial revision by MHLW Ordinance No. 106 dated June 12, 2003, MHLW Ordinance No. 172 dated December 21, 2004, MHLW Ordinance No. 72 dated March 31, 2006, and MHLW Ordinance No. 24 dated February 29, 2008) was issued with the aims of specifying the requirements for the planning, conduct, monitoring, auditing, records, analysis, and reports of clinical studies performed to collect data to be submitted with applications for approval to manufacture and market drugs; to protect the human rights, safety, and welfare of 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 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 dated June 12, 2003). The Ministerial Ordinance No. 72 dated March 31, 2006 and the Ordinance No. 24 dated February 29, 2008 modified the management qualifications for IRB administrator, making them stricter to improve quality and performance of the IRB and allowing the hospital director to freely choose an IRB from IRBs inside or outside the institution, following recommendations of the Council on Efficient Conduct of Clinical Trials established by the MHLW.

In regard to the dissemination of ADR-related information to study centers, the Ordinance was also modified to additionally require the sponsor to transfer cases of serious ADRs not expected according to the IB periodically at 6-month intervals in addition to spontaneous reports and cases of serious ADRs expected according to the IB periodically at 6-month intervals.

## 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 the Guidelines on Timing of Nonclinical Safety Studies for Clinical Trials on Drug Products (Notification No. 1019 of the Evaluation and Licensing Division, PMSB dated November 13, 1998, partially revised on February 19, 2010: ICH

M3R(R2)).

#### (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

Products used in clinical studies should be well characterized, with information on bioavailability wherever feasible. The product 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. The standards that should be met when manufacturing investigational products were specified in the “Manufacturing Control and Quality Control Standards for Investigational Products and Standards for Buildings and Facilities of Manufacturing Plants for Investigational Products” (former Investigational Product GMP) (Notification No. 480 of the PAB dated March 31, 1997). Thereafter, this was revised in Notification No. 0709002 of the PFSB dated July 9, 2008 entitled “Manufacturing Control and Quality Control Standards for Investigational Products” (New Investigational Product GMP) to permit quality assurance of investigational products in accordance with each phase of clinical studies in consideration of the characteristics of clinical studies,

including the exploratory early clinical trials.

## 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, ICH E8), and according to this system clinical studies are classified to the following four types.

- (1) Human pharmacology studies
- (2) Therapeutic exploratory studies
- (3) Therapeutic confirmatory studies
- (4) Therapeutic use studies

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

Studies must be designed and data analyzed or evaluated according to the above clinical guideline. [Fig. 10](#) (Correlation between Development Phases and Types of Study) illustrates the close but variable correlation between the two classification systems. The distribution of the circles, open circles and

shaded circles, in the figure shows that the types of study do not automatically define the phases of development.

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

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

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

- (1) Estimation of initial safety and tolerability
- (2) Characterization of pharmacokinetics
- (3) Assessment of

pharmacodynamics

(4) Early assessment of efficacy

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

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

Phase II is usually considered to be the phase in which studies with the primary objective of exploring therapeutic efficacy in patients is initiated. The most typical Phase II study is the therapeutic exploratory study performed on a group of patients who are entered into the study according to clearly defined criteria and whose condition is monitored. An important goal for this phase is to determine the dose(s) and regimen for Phase III studies. Dose response designs should be used to assess and confirm the dose-response relation for the indication concerned. Additional objectives of Phase II clinical studies include evaluation of

study endpoints, therapeutic regimens (including concomitant medication) or target populations for further study in Phase II or III.

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

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

“Arrangements for supplying and receiving of control drugs” were established as voluntary arrangements among member companies of the JPMA in July 1981 for the smooth supply and receipt of control drugs by the companies developing new drugs and the manufacturers/marketing authorization holders of control drugs when pharmaceutical companies developing new drugs evaluate efficacy and safety of new drugs with approved drugs already on the market as controls. After

four subsequent revisions, the most recent version appeared on November 1, 2005.

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

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

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

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

**2.5) Special considerations**

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

(i) **Studies of drug metabolites**

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

(ii) **Drug interactions**

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

(iii) **Special populations**

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

Pharmacokinetic studies in patients with renal and hepatic dysfunction are important to assess the impact of the potentially altered

drug metabolism or excretion.

Other special populations are as follows:

- (1) Elderly.
- (2) Ethnic populations.
- (3) Pregnant women.
- (4) Nursing women.
- (5) Children.

(iv) **Microdose studies**

Clinical studies to obtain information on pharmacokinetics of the investigational product in humans and desired information at the preclinical stage in development candidate screening studies based on pharmacokinetic information. A dose not exceeding 1/100 of the dose expressing pharmacological effects or a dose of 100 µg/human, whichever is smaller, is administered once to healthy subjects. The range of application is mainly low molecular weight compounds.

**3) Considerations for Individual Clinical Studies**

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

study starts.

### 3.1) Objectives

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

### 3.2) Design

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

- (1) Selection of subjects.
- (2) Selection of control group.
- (3) Number of subjects.
- (4) Safety and efficacy variables.
- (5) Methods to minimize bias (randomization, blinding, and compliance).

### 3.3) Conduct

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

### 3.4) Analysis

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

### 3.5) Reporting

Clinical study reports should be appropriately prepared in accordance with the Structure and Content of Clinical Study Reports (Notification No.335 of the Evaluation and Licensing Division, PAB dated May 1, 1996: ICH E3).

## 4) Statistical analysis of clinical study results

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

The ICH guidelines, Statistical Considerations in the Design of Clinical

Trials (ICH E9) (Notification No. 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 the "Guidelines for Clinical Evaluation." The results from ICH are also introduced into Japanese regulations as ICH guidelines.

As of September 2011, the following 35 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 of Oral Contraceptives (Notification No. 10 of the First Evaluation and Registration Division, PAB dated April 21, 1987).
- (2) Guidelines for Clinical Evaluation 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 of Antihyperlipidemic Drugs (Notification No. 1 of the First Evaluation and Registration Division, PAB dated January 5, 1988)
- (4) Guidelines on Clinical Evaluation of Antianxiety Drugs (Notification No. 7 of the First Evaluation and Registration Division, PAB dated March 16, 1988).
- (5) Guidelines on Clinical Evaluation of Hypnotics (Notification No. 18 of the First Evaluation and Registration Division, PAB dated July 18, 1988).
- (6) Guidelines on Clinical Evaluation of Drugs to Treat Heart Failure (Notification No. 0329(18) of the Evaluation and Licensing Division, PFSB dated March 29, 2011).
- (7) Guidelines for Clinical Evaluation of Antibacterial Drugs (Notification No. 743 of the New Drugs Division, PMSB dated August 25, 1998).
- (8) Guidelines on Clinical Evaluation of Drugs to Treat Osteoporosis (Notification No. 742 of the Evaluation and Licensing Division, PMSB dated April 15, 1999)
- (9) Principles for Clinical Evaluation of New Antihypertensive Drugs\* (ICH E12A, currently E12) (Notification No. 0128001 of the Evaluation and Licensing Division, PFSB dated January 28, 2002)
- (10) Guidelines on Clinical Evaluation of Antiarrhythmic Drugs (Notification No. 0325035 of the Evaluation and Licensing Division, PFSB dated March 25, 2004)
- (11) Guidelines on Clinical Evaluation of Antianginal Drugs (Notification No. 0512001 of the Evaluation and Licensing Division, PFSB dated May 12, 2004)
- (12) Guidelines for Clinical Evaluation of Antimalignant Tumor Drugs (Notification No. 1101001 of the Evaluation and Licensing Division,

<p>PFSB dated November 1, 2005, partially revised by Office Communication dated November 2, 2005).</p> <p>(13) Guidelines for Clinical Evaluation of Antirheumatoid Drugs (Notification No. 0217001 of the Evaluation and Licensing Division, PFSB dated February 17, 2006).</p> <p>(14) Guidelines for Clinical Evaluation of Drugs for Overactive Bladder or Incontinence (Notification No. 0628001 of the Evaluation and Licensing Division, PFSB dated June 28, 2006).</p> <p>(15) Guidelines for Clinical Evaluation of Prophylactic Vaccines against Infections (Notification No. 0527-(5) of the Evaluation and Licensing Division, PFSB dated May 27, 2010).</p> <p>(16) Guidelines for Clinical Evaluation of Oral Hypoglycemic Agents (Notification No. 0709-(1) of the Evaluation and Licensing Division, PFSB dated July 9, 2010).</p> <p>(17) Guidelines for Clinical Evaluation of Antidepressant Drugs (Notification No. 1116-(1) of the Evaluation and Licensing Division, PFSB dated November 16, 2010).</p> <p>(18) Guidelines for Clinical Evaluation of Therapeutic Drugs for Renal Anemia</p>	<p>(Notification No. 0930-(1) of the Evaluation and Licensing Division, PFSB dated September 30, 2011).</p> <p><a href="#">[2] Guidelines for clinical evaluation in general</a></p> <p>(19) Studies in Support of Special Populations: Geriatrics (ICH E7) (Notification No. 104 of the New Drugs Division, PAB dated December 2, 1993 and Q&amp;A dated September 17, 2010).</p> <p>(20) Dose-Response Information to Support Drug Registration (ICH E4) (Notification No. 494 of the New Drugs Division, PAB dated July 25, 1994).</p> <p>(21) Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions (ICH E1) (Notification No. 592 of the Evaluation and Licensing Division, PAB dated May 24, 1995)</p> <p>(22) Structure and Content of Clinical Study Reports (ICH E3) (Notification No. 335 of the Evaluation and Licensing Division, PAB dated May 1, 1996)</p> <p>(23) General Considerations for Clinical Trials (ICH E8) (Notification No. 380 of the Evaluation and Licensing Division, PMSB dated April 21,</p>
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| <p>1998).</p> <p>(24) Ethnic Factors to be Considered in the Acceptance of Foreign Clinical Trial Data (ICH E5, currently E5(R1)) (Notification No. 672 of the Evaluation and Licensing Division, PMSB dated August 11, 1998)</p> <p>(25) Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (ICH M3(R2)) (Notification No. 1019 of the Evaluation and Licensing Division, PMSB dated November 13, 1998)</p> <p>(26) Statistical Principles for Clinical Trials (ICH E9) (Notification No. 1047 of the Evaluation and Licensing Division, PMSB dated November 30, 1998)</p> <p>(27) Clinical Investigation of Medicinal Products in the Pediatric Population (ICH E11) (Notification No. 1334 of the Evaluating and Licensing Division, PMSB dated December 15, 2000)</p> <p>(28) Choice of Control Group and Related Issues in Conducting Clinical Studies (ICH E10) (Notification No. 136 of the Evaluating and Licensing Division, PMSB dated February 27, 2001, partially revised by Office Communication dated April 10, 2001)</p> | <p>(29) Guidance for Conducting Microdose Clinical Studies (Notification No. 0603001 of the Evaluating and Licensing Division, PFSB dated June 3, 2008)</p> <p>(30) Clinical Investigation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs (ICH E14) (Notification No. 1023-(1) of the Evaluating and Licensing Division, PFSB dated October 23, 2009)</p> <p><a href="#">[3] Other guidelines</a></p> <p>(31) Research on Evaluation of Immunotherapeutic Agents for Malignant Tumors (1980).</p> <p>(32) Research on Evaluation of Blood Preparations, Especially Plasma Fraction Preparations (1984).</p> <p>(33) Research on Overall Evaluation of Interferon Preparations (1984).</p> <p>(34) Guidelines on Clinical Evaluation of Anti-inflammatory Analgesic Drugs (1985).</p> <p>(35) Guidelines on the Design and Evaluation of Sustained-release (Oral) Preparations (Notification No. 5 of the First Evaluation and Registration Division, PAB dated March 11, 1988).</p> |
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- [6\) Procedures for conduct of clinical](#)

## studies

Regarding the conduct of clinical studies to collect data to be submitted with approval applications for new drug manufacturing and marketing, the Pharmaceutical Affairs Law and the GCP (MHW Ordinance No. 28 dated March 27, 1997, partial revision by MHLW Ordinance No. 106 dated June 12, 2003, MHLW Ordinance No. 172 dated December 21, 2004, MHLW Ordinance No. 72 dated March 31, 2006, and MHLW Ordinance No. 24 dated February 29, 2008) require that the MHLW be notified of the study protocol beforehand and provide various requirements to be met by the sponsor when requesting medical institutions to perform clinical studies. Compared with the former GCP, the following points are conspicuous: a) the scope of the GCP has been extended to cover post-marketing clinical trials, b) the role and responsibilities of sponsors such as pharmaceutical companies have been clarified and strengthened, and c) medical institutions performing clinical studies are obliged to comply with the GCP. When sponsors request clinical studies they must have obtained adequate data concerning the safety, efficacy and quality from previous nonclinical studies and other human studies which support as much as possible the objectives of the

study, and the subject population, route of administration, dosage and administration, the time of exposure, and observations and evaluation items to be applied in the proposed study, as well as support for the ethical and scientific suitability of the study. All procedures must be specified in writing. Sponsors must request the study sites to inform the subjects adequately about the contents of the clinical study and obtain their written informed consent to participate in the study. The sponsor must also take the necessary measures beforehand to provide compensation for any health impairment caused by the investigational product. The range of the GCP covers not only clinical studies on patients, but also Phase I studies on healthy volunteers, bioequivalence studies on humans, studies on added indications for approved drugs and post-marketing clinical trials conducted after the drug goes on the market. In addition, investigator-initiated clinical trials are specified to be covered by the GCP by partial revision of the GCP Ordinance in 2003.

With the increase in global clinical studies in recent years, information on such studies must be entered in clinical trial protocol notices from April 1, 2008 (Notification No. 0321001 of the

Evaluation and Licensing Division, PFSD dated March 21, 2008).

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

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

Advice).

It is necessary to submit clinical trial (protocol) notifications in the following instances:

- (1) Drugs with new active ingredients
- (2) Drugs with new administration routes (excluding bioequivalence studies)
- (3) New combination drugs, drugs with new indications or new dosage and administration (excluding bioequivalence studies)
- (4) Drugs containing the same active ingredients with the originals, for which the reexamination period has not been completed yet (excluding bioequivalence studies)
- (5) Drugs considered to be biological products [excluding (1) to (4)] (excluding bioequivalence studies)
- (6) Drugs manufactured using gene recombinant technology [excluding (1) to (5)] (excluding bioequivalence studies)

The types of clinical trial protocol notifications and documents to be submitted are shown below.

- (1) Clinical trial protocol notifications (when notifications are first made for drugs with new active ingredients or new routes of administration and new combination drugs, they must be submitted at least 31 days before the

<p>planned start date of the trial stated in the contract with the medical institution performing the clinical study. Otherwise, they must be submitted at least 2 weeks before the planned date of the trial.)</p> <p>a. Document that gives the reason why the request for the clinical study was judged to be scientifically appropriate (from the 2nd notification, it should include a description of the results of new clinical studies since the previous notification and a summary of information)</p> <p>b. Clinical study protocol</p> <p>c. Explanatory materials and consent form used for obtaining informed consent</p> <p>d. Sample of the case report form (CRF) (The sample is not required if information to be contained in the CRF is explicitly stated in protocol.)</p> <p>e. Latest investigator's brochure</p> <p>(2) Notification of changes in clinical study protocols (submitted as a rule for each clinical trial protocol notification before changes in notification items)</p> <p>Data related to the changes as required:</p> <p>(3) Clinical study discontinuation</p>	<p>notification. (This notification must be submitted for each clinical trial protocol notification without delay when a clinical study is discontinued.)</p> <p>Data related to the reason for discontinuation as required (including information on study subjects collected until discontinuation):</p> <p>(4) Clinical study completion notification (This notification must be submitted for each clinical trial protocol notification without delay when a notification of completion of the clinical study is received from all medical institutions and recovery of the investigational product is completed.)</p> <p>From April 1, 2011, attachments to the clinical trial notification (including protocol revision notification, clinical trial completion notification, and clinical trial discontinuation notification) are required to be submitted in electronic format as well as in paper format (Notification No. 1227-(1) of PFSB dated December 27, 2010).</p> <p>7) <b>Safety information on Adverse Reactions and Infections during the Study</b></p> <p>Safety information obtained during the study must be reported promptly, as is specified in the ICH guidelines (ICH E2A) on Clinical Safety Data Management</p>
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(Notification No.227 of the Evaluation and Licensing Division, PAB dated March 20, 1995).

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

**A: 7-Day reports** (When either of the following events is suspected to be caused by an adverse reaction of the investigational product concerned or by an infection suspected of being caused by the investigational product concerned, and the event is not expected from the description in the investigator's brochure of the investigational product concerned: the report must be made within 7 days.)

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

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

- (a) Any of the following events suspected to be caused by an

adverse reaction of the investigational product concerned or by an infection suspected of being caused by the investigational product concerned, which is not expected from the description in the investigator's brochure of the investigational product concerned.

- Events requiring admission to a hospital for treatment or prolongation of the period of hospitalization
  - Disability
  - Cases that might result in disability
  - Other medically serious condition
  - Congenital diseases or abnormalities in the next generation
- (b) Predicted deaths or events that might result in death.
  - (c) Measures related to safety problems of the investigational product concerned, including discontinuation or manufacture and/or marketing in a foreign country.
  - (d) Research reports showing the possibility of causing cancer or other serious diseases due to adverse reactions, etc. of the investigational product concerned.

Pharmaceutical Affairs Law  
Enforcement Regulations modified in February 2008 require the sponsor to

report to the MHLW cases of serious ADRs, etc. expected according to the IB periodically at 6-month intervals.

## 8) GCP

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

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

clinical studies.

Further, the GCP was revised to expand its scope to cover clinical trials conducted by the physician or medical institution for approval application in order to manage clinical trials similarly to the current clinical trial system. The revised GCP was enacted by the Ordinance for Partial Revision of the Standards for the Conduct of Clinical Trials on Drugs (Notification No. 106 issued by the MHLW on June 12, 2003) and enforced on April 1, 2005 by the Ordinance for Partial Revision of the Standards for the Conduct of Clinical Trials on Drugs (Notification No. 172 issued by the MHLW on December 21, 2004). The GCP was further revised to improve the quality and function of the investigational review board (Ordinance for Partial Revision of the Standards for the Conduct of Clinical Trials on Drugs (Notification No. 72 issued by the MHLW on March 31, 2006).

The MHLW Council of Ideal Registration-Directed Clinical Trials discussed ways and means of institutional review boards and notification of adverse drug reactions, etc. to medical institutions performing clinical studies, etc. and compiled a report of recommendations on September 19, 2007. The report was adopted (MHLW Ordinance No. 24 of February 29, 2008) and enforced from

April 1, 2008 (partially enforced on April 1, 2009).

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). The GCP is intended to protect the human rights, maintain the safety, and improve the welfare of subjects, and to assure the scientific quality and the reliability of results of clinical studies.

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

institutions or persons performing clinical trials and sponsors of clinical trials to conduct or manage clinical trials which are both ethically and scientifically sound.

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

Among data to be submitted by persons submitting applications to receive approval in Article 3, data concerning the results of clinical studies specified in Chapter 2, Section 1 (Articles 4 to 15), Chapter 3, Section 1 (Articles 16 to 26) and Chapter 4 (Articles 27 to 55, excluding Article 29, Paragraph 1, Item 2, Article 31, Paragraph 4, Article 32, Paragraph 4 and 7, Article 33, Paragraph 3, and Article 48, Paragraph 3); and data concerning the results of clinical studies performed by persons specified in Chapter 2, Section 2 (Articles 15-2 to 15-9), Chapter 3, Section 2 (Articles 26-2 to 26-12) and Chapter 4 (Articles 27 to 55, excluding Article 29, Paragraph 1, Item 1, Article 32, Paragraphs 6 and 8, 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 medical 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. (When the institutional review board approves English labeling, investigational products used in global clinical trials may be labeled in English.)
- 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. Delivery of investigational products can be conducted via drug marketing authorization holders or other third parties if it is possible to perform reliable quality control, transport, and acceptance of the investigational product under the

responsibility of the sponsor.

- Adverse reactions that cannot be predicted from the investigator's brochure for items specified in the provisions of Article 80-2, Paragraph 6 of the Pharmaceutical Affairs Law must be reported without delay to the investigator and director of the medical institutions performing the study. When the event can be predicted, a list of patients with the event must be notified within 2 months after completion of the period every 6 months from the date of the first clinical trial protocol notification.
- 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

<p>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.</p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• Records related to the clinical trial must be retained for the specified period.</li> </ul> <p>Chapter 4: Standards for conduct of clinical trials (Articles 27 to 55)</p> <p>Provisions to be followed by the medical institutions performing clinical trials scientifically and ethically</p> <p>1) Provisions concerning the Institutional Review Boards (IRB) (Articles 27 to 34)</p> <ul style="list-style-type: none"> <li>• An Institutional Review Board (IRB), which should meet the</li> </ul>	<p>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. (However, it is not always necessary to establish an IRB in each medical institution performing the study.)</p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• The person establishing the IRB must keep records of meetings and prepare a summary and retain these documents for set periods such as 3 years after completion of the clinical study. The standard operating procedures, list of members, and summary of meeting records prepared for the IRB must be made public. On the PMDA webpage (<a href="http://www.pmda.go.jp">http://www.pmda.go.jp</a>), the name of the IRB, the name of the person establishing the IRB, the address, and webpage address must be recorded to create an environment that</li> </ul>
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<p>facilitates acquisition of study-related information by clinical study collaborators and keeps a wider public informed (Notification No. 1001013 of the PFSB dated October 1, 2008 and Office Communication dated April 2, 2009).</p> <ul style="list-style-type: none"> <li>• The director of the medical institution performing the study must heed the opinions of the IRB concerning whether it is appropriate or not to perform the clinical study in the medical institution concerned.</li> <li>• 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.</li> <li>• When it is impracticable to organize an IRB for a planned trial at each institution, alternative IRB may be selected from other IRBs inside or outside the institution in the judgment of the director of medical institution.</li> <li>• IRB may disclose information related to IRB review to enhance the level of transparency and secure quality of its review activities.</li> </ul> <p>2) Provisions related to medical</p>	<p>institutions performing clinical trials (Articles 35 to 41)</p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> <li>• 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.</li> <li>• The director of a medical institution must appoint a person or persons to carry out trial-related clerical work.</li> </ul> <p>3) Provisions related to investigators (Articles 42 to 49)</p> <ul style="list-style-type: none"> <li>• The investigator must have sufficient clinical experience to be</li> </ul>
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able to conduct the trial properly.

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

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

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

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

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

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

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

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

These GCP standards also contain provisions concerning the

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

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

Application data from clinical trials submitted to the MHLW must first undergo a GCP compliance review to

assure that it meets GCP standards. This review consists of a paper inspection and on-site inspection at the medical institution(s) performing the trial, etc. The review is intended to confirm the reliability of the data as application data. These GCP compliance reviews are performed by the PMDA at the request of the MHLW for data collected and prepared in Japan. The approval review is then undertaken by the MHLW in accordance with the results of PMDA review.

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

Practices of GCP initially stipulated in Notification No. 1001001 of PFSB dated October 1, 2008 (entitled "Implementation of the Standard Operating Procedures for the Conduct of Clinical Trials of Medicinal Products) were modified as Notification

No. 1024-(1) of PFSB dated October 24, 2011 and will be enforced from April 1, 2012 for more efficient conduct of clinical trials.

#### 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. To that end, requirements for manufacturing investigational products have been issued in 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" 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.

In light of the specificities of the investigational product, such as the use in an early exploratory development phase,

Standards for Manufacturing Control and Quality Control of Investigational Products and Standards for Buildings and Facilities of Plants Manufacturing Investigational Products ("new" Investigational Product GMP) were issued in the form of Notification No. 0709002 of the PFSB on July 9, 2008 as a replacement of the old Investigational Product GMP in order to assure the quality of investigational products depending on development phase. In addition to the protection of human subjects and reliability assurance of clinical trials, the new regulations aim to ensure not only the efficacy and safety of drug product but also adequateness of clinical studies themselves in the post-marketing phase by securing pharmaceutical consistency between the investigational product and marketed product following the final selection of research compound to be developed and by assuring the equivalence between the two products following the establishment of manufacturing method and test methods of investigational product. Q&A on the standards for manufacturing control and quality control of investigational products (Investigational Product GMP) were published in Office Communication dated July 2, 2009.

The Investigational Product GMP is applied to all investigational products

used in clinical studies conducted in accordance with the GCP ordinance. The GMP is a set of requirements to be followed by the study sponsor and investigators and also applied to investigational products manufactured at foreign facilities.

The system/procedure-related provisions of the Investigational Product GMP require the sponsor to establish investigational product manufacturing division and investigational product quality control division at each manufacturing facility. The release of investigational product from factory must be judged by personnel of the quality control division designated for individual investigational product items. The provisions require the preparation and retention of documents pertaining to ingredients/quantities, specifications, test methods, manufacturing procedures, etc. for each investigational product item and those pertaining to manufacturing hygiene control procedures, manufacturing control procedures, and manufacturing control procedures for each manufacturing facility. It is also required to prepare and retain documents standardizing manufacturing and quality control.

The GMP also contains provisions concerning the use of contract testing facilities, validation/verification, change

control, deviation control, quality test results, handling of inferior quality products, recall, self-inspections, education/training, document/record control, contracted manufacture, buildings/facilities manufacturing investigational products, etc.

The building/facility-related provisions of the Investigational Product GMP specify requirements for individual facilities 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 in the Guidelines on GMP for Drug Substances (ICH Q7A, currently Q7) (Notification No. 1200 dated November 2, 2001), which includes 20 requirements for drug substances including quality management, buildings and facilities, and validation, as approved at ICH5 held in San Diego in November 2000.

Since requests from overseas regulatory authorities to submit investigational product GMP certificates are made when a clinical study is performed overseas using an

investigational product produced in Japan for a global clinical trial, the issue of such certificates is specified in the “Supply of investigational product GMP certificates” (Office Communication dated March 30, 2009) and the procedures for requesting the issue of investigational product GMP certificates are given in the “Procedures for Issuing Investigational Product GMP Certificates” (Notification No. 0330023 dated March 30, 2009).

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

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

Since a recommendation to introduce GMP was issued by the World Health Assembly (WHA), the general meeting of the World Health Organization (WHO) in July

1969, various countries have passed laws concerning control procedures essential for the manufacture of drugs. In Japan, these are established for GMP by Regulations for Buildings and Facilities of Pharmacies, etc. with respect to hardware, and by Manufacturing Control and Quality Control for Drugs and Medical Devices with respect to software. This is because the system of approval and item licensing under the Pharmaceutical Affairs Law has been replaced by a different legal framework. However, under the revision to and enforcement of the revised Pharmaceutical Affairs Law of April 1, 2005, there has been issued a new MHLW Ordinance relating to Standards for Manufacturing Control and Quality Control for Drugs and Medical Devices (MHLW Ordinance No. 179, December 24, 2004) (“GMP regulations”), thereby integrating GMP hardware rendered necessary by the characteristics of drugs with GMP software. Specifically, Article 9 establishes basic standards for the buildings and facilities of manufacturing plants where GMP is applicable, and Article 23 establishes standards for the buildings and facilities of manufacturing plants for sterile drugs.

With respect to the former Regulations for Buildings and Facilities of Pharmacies, etc., they are revised according to the MHLW Ordinance partially revising Regulations for Buildings and Facilities of Pharmacies, etc.

(MHLW Ordinance No. 180, December 24, 2004, partial revision: MHLW Ordinance No. 73 dated April 1, 2005). Under the revision to and enforcement of the revised Pharmaceutical Affairs Law of April 1, 2005, GMP has become a requirement for manufacturing and marketing approval (Article 14-2, Paragraph 4 of the Law) and regulations for buildings and facilities have become requirements for licensing as manufacturers (Article 13-4, Paragraph 1 of the Law).

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

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

2000.

The following sections outline the GMP regulations:

#### 1) Required documentation

According to the GMP regulation, all of the operations in the plants must be divided into operations for manufacturing control and those for quality control, and various types of documentation are required, including standard operating procedures for standardization of all work conditions (drug product standards, manufacturing control standards, manufacturing hygiene control standards and quality control standards), documentation required for actual operation procedures based on these standards (manufacturing instructions and test and self-inspection protocols), records of the results of all of these operating procedures (records related to manufacture, records of manufacturing hygiene control, and records of tests and self-inspections), and records of storage and distribution. Additional documents should be compiled if they are considered necessary for proper manufacturing control and quality control. These documents must be retained for designated time periods from the date of preparation.

When damage to the health of patients or other users of biological products

(biotechnological technology-derived and of biological origin) occurs, records must be retained for the period required to clarify the cause of this damage.

## 2) Personnel organization

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

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

in the provisions of the Pharmaceutical Affairs Law. Article 5 of the GMP regulation specifies supervision of the manufacturing control manager and the quality control manager as one of the duties of product security pharmacist.

## 3) Manufacturing control

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

- To prepare and preserve manufacturing instructions.
- To manufacture products based on the manufacturing instructions.
- To prepare and preserve records related to product manufacture for each lot.
- To check packaging materials for products for each lot, and to prepare and preserve records related to the results thereof.
- To appropriately store and circulate products by lot and packaging materials by control unit, and to prepare and preserve records thereof.
- To check the cleaning of buildings and facilities, and to prepare and preserve records relating to the results thereof.

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

\* **Manufacturer, etc.:** the manufacturer or overseas manufacturer

#### 4) Quality control

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

- To collect samples required for the testing and inspection of products, etc. for each lot, and of packaging materials for each control unit, and to prepare and preserve records thereof.
- To conduct testing and inspection of the samples collected for each lot or for each control unit, and to prepare and preserve

records thereof.

- To store samples of products consisting of an amount two or more times greater than the amount required for testing and inspection for each lot under appropriate storage conditions for a period of one year longer than the expiration period or the shelf-life from the date of manufacture for the product concerned.
- To inspect and maintain on a regular schedule the facilities and implements relating to testing and inspection, and to prepare and preserve records thereof. Further to carry out appropriate calibration of measuring instruments relating to testing and inspection, and to prepare and preserve records related to the results thereof.
- To evaluate the test results of the samples collected, and to notify the manufacturing department in writing of the results thereof.  
Further, manufacturers, etc. makes use of the tests and inspections performed in the import source country, they must assure that the quality department carries out the duties set forth below:
- To confirm at on a regular schedule that that the product, etc. is manufactured in accordance with appropriate manufacturing procedures.
- To confirm on a regular schedule that the manufacturing plant of an overseas

manufacturer conforms to the standards relating to manufacturing control and quality control in that country, and to prepare and preserve records thereof.

- To confirm the records of tests and inspections carried out by the foreign manufacturer, and to prepare and preserve records thereof.

#### 5) Documents concerning procedures for validation, etc.

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

#### 6) Validation

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

- The validation plan and results must be reported in writing to the quality control unit.

The manufacturer, etc. must take appropriate measures when improvements are required in manufacturing control or quality control

based on the results of the validation.

Records of the measures taken must be prepared and retained.

#### 7) Change control

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

- To evaluate the effect on product quality due to the changes, and to obtain the consent of the quality department for implementation of changes based on the results of the evaluation.
- When implementing the changes, to take measures for amendment of the relevant documentation, education and training of personnel, and any other requisite measures.

#### 8) Deviation control

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

- To record the details of the

deviation.

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

#### 9) Information related to quality and handling quality defects

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

- To elucidate the causes of items relating to the quality information concerned, and in cases in which improvements related to manufacturing control or quality control are required, to take the requisite measures.
- To prepare and preserve a record specifying the nature of the quality information concerned, the results of the elucidation of causes, and the measures for improvement,

and to promptly and in writing notify and obtain confirmation from the quality assurance department.

- In cases in which the manufacturer, etc. has identified a quality defect or the risk thereof, to assure that the manufacturing control manager notifies quality department in writing on the basis of the standard operating procedures.

#### 10) Product recalls

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

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

#### 11) Self-inspections

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

with the standard operating procedures.

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

## 12) Education and training

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

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

- To prepare and retain records of the conduct of education and training.

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

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

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

- The manufacturer shall provide education and training on microbiology, medicine and veterinary medicine for employees engaged in manufacture or testing of biological products.

- The manufacturer shall provide education and training on the measures required to prevent contamination by microorganisms for employees engaged in work in sterile areas or in areas handling pathogenic microorganisms.

### 13) Management of documents and records

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

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

concerned plus 1 year is longer than 5 years, and with the exception of records related to education and training, for the shelf-life plus 1 year).

- The manufacturer, etc. must, when biological products are manufactured, assure that, notwithstanding the above, the documents and records specified from 1) to 12) are retained for periods from the date of their preparation as set forth below (records related to education and training, a period of 5 years). However, in the case of biological products that have been designated by the Minister of Health, Labour and Welfare, the manufacturer, etc. must assure that that a previously designated person store them for the period designated by the Minister.
- With respect to biological products or cell or tissue products, for a period of 5 years (except in cases where the shelf-life of the product concerned plus 1 year is longer than 5 years, for a period equal to the shelf-life plus 1 year).
- In the case of specified biological products or biological products manufactured using human blood

as the raw material, for a period equal to the shelf-life plus 30 years.

- In the case of biological products or cell or tissue products (except as set forth above), a period equal to the shelf-life plus 10 years).

#### 4.1 GMP Compliance Reviews

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

##### Evaluation rank criteria

- A: (Compliance): Manufacturing is performed properly.
- B: (Slightly defective): There is little effect on drug quality but improvement necessary for complete compliance with control regulations.
- C: (Moderately defective): Effect on drug quality can not be ruled out and improvement necessary for compliance with control regulations.
- D: (Seriously defective): Clear violation of control regulations

First, a review is conducted for each product using the following criteria for GMP compliance as to each article in the control regulations and building and facility

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

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

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

In such cases, the applicant must submit a concrete plan of improvements. When improvements are completed, a report on the improvement must be submitted. When the improvements have been confirmed, the rating of the corresponding item is changed to "Compliance."

The results of reviews or assessments at each of the above stages are compiled, and a report of the GMP compliance review is prepared for the plant in the application concerned. When the initial GMP compliance review results of a product

correspond to "General compliance" or "Improvement required," the subsequent course is entered in the GMP compliance review report.

#### 4.2 Mutual Recognition of GMP

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

28, 2004).

#### 4.3 Regulations for Imported Drug Management and Quality Control

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

These regulations included matters to be agreed upon with the manufacturer in foreign country by the importer in accordance with the agreement. The importer must confirm that the drug to be imported is manufactured under appropriate manufacturing control and quality control, and must import, store, and distribute drugs and conduct testing in accordance with standards, etc.

When a mutual agreement for GMP approvals has been concluded between the

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

## 5. OTHERS

### 5.1 Biotechnological Products

In December 1986, the Guidelines for Manufacturing Drugs by Recombinant DNA Technology were published by the MHW (Notification No. 1051 of the PAB dated December 11, 1986, partially revised by Notification Nos. 434 and 769 of the PMSB dated May 21, 1987 and August 18, 1995). 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. Thereafter, based on the Law for Securing Multiplicity of Living Organisms under the Use Control of Genetically-Engineered Living Organisms (so-called "Cartagena Law") (Law No. 97 dated June 18, 2003), the Ministerial Ordinance on Measures to Prevent Spread of Industrial Use among Secondary Uses of Genetically-Engineered Living Organisms (Ordinance No. 1 of the Ministry of Finance, MHLW, Ministry of Agriculture, Forestry and Fisheries, Ministry of Economy, Trade and Industry and Ministry of Environment dated January 29, 2004; partially revised in Ordinance No. 2 dated June 6, 2006) was enforced on February 19, 2004, and these policies were abolished.

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

Division, PAB dated March 30, 1984.

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

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

Another notification issued concerning biological products is the Guidelines to Assure the Quality and Safety of Drugs for Gene Therapy (Notification No. 1062 of PAB dated November 15, 1995), which was partially revised by Notification Nos. 0329004 and of 1228004 PMSB dated March 29, 2002 and December 28, 2004, respectively.

## **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 Pharmaceutical Affairs and Food Sanitation Council established “Basic Concepts for Handling and Use of Drugs and Devices Utilizing Cells or Tissues” (December 1, 2000) and the “Guidelines for Assurance of Quality and Safety of Drugs and Devices Processed from Cells and Tissues of Human Origin” (December 1, 2000) (Notification No. 1314 of the PMSB dated December 26, 2000). In addition, various notifications have been issued, manufacturers have been requested to undertake self-inspection and coordinate application documents, and safety measures have been specified. For ingredients of bovine origin in particular, notifications have been issued as required in accordance with worldwide risk conditions and measures to assure quality and safety have been strengthened (refer to “Safety Measures for Bovine Spongiform Encephalopathy [BSE]” in Section 6.4, Chapter 2). Biological products and specified biological products were newly defined in the revised Pharmaceutical Affairs

Law dated July 31, 2002 and measures to assure safety when there is a risk of infection have been designated.

### **5.3 Biosimilar Products**

With the advances made in biotechnological products, the development of similar biotechnological products (biosimilar products or follow-on biologics) equivalent to and the same quality as existing biotechnological products is being promoted overseas. Based on such technological advances, a Health Sciences Council Research Project entitled “Research on Quality, Efficacy, and Safety Evaluation Methods for Biosimilars” was established with funding from MHLW, and “Policies on Assurance of Quality, Efficacy, and Safety of Biosimilars” were formulated (Notification No. 0304007 of the Evaluation and Licensing Division, PMSB dated March 4, 2009). Biosimilars are defined as drugs developed by different marketing authorization holders as drugs with the same quality, efficacy, and safety as biotechnological products already approved as drugs with new active ingredients in Japan. “Biosimilar” does not mean that the drug has exactly the same quality with the original biotechnological product, but that they are highly similar in quality and characteristics and even if there are differences in quality and characteristics, the differences can be scientifically judged

not leading to any unintended effects on the efficacy and safety profiles of the final product. To prove the comparability, appropriate studies are necessary based on the concepts in the ICH Q5E guidelines “Comparability of Biotechnological/ Biological Products Subject to Changes in their Manufacturing Process.” It is also necessary to evaluate the comparability of biosimilars using clinical studies.

Q&A on “Policies on assurance of quality, efficacy, and safety of biosimilars” were published in an Office Communication dated July 21, 2009. Views of the regulatory authorities on timing, definitions of equivalent products, evaluations of comparability, development of formulations and test methods, and safety evaluations for biosimilar applications are included.

### **5.4 Public Disclosure of Information on New Drug Development**

A notification concerning publication of information on new drug approvals was issued (No. 1651 of the Evaluation and Licensing Division, PMSB dated November 11, 1999), and New Drug Approval Information Packages containing summary reviews prepared by the MHLW and nonclinical and clinical data submitted by the applicant have been published. Thereafter, the methods of submitting data for application were changed as specified in “Disclosure of

Information Concerning Approval Reviews of New Drugs” (Notification No. 0529003 of the Evaluation and Licensing Division, PMDA dated May 29, 2002). Basic procedures for submission and disclosure have also been specified (Notification No. 0422001 of the Evaluating and Licensing Division, PFSB dated April 22, 2005, Notification No. 042204 of the PMDA dated April 22, 2005, and Notification No. 1126005 of the Licensing and Evaluation Division of PFSB dated November 26, 2007).

Information on approval reviews for new drugs is provided on the following websites:

Japanese:

[http://www.info.pmda.go.jp/info/syounin\\_index.html](http://www.info.pmda.go.jp/info/syounin_index.html)

English (part of product items):

<http://www.pmda.go.jp/english/service/review.html>

“A Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases” was issued on January 6, 2005 as a joint communiqué by four organizations: International Federation of Pharmaceutical Manufacturers Associations (IFPMA), Pharmaceutical Research and Manufacturers of America (PhRMA), European Federation of Pharmaceutical Industry Associations (EFPIA) and Japan Pharmaceutical Manufacturers Association (JPMA). The

communiqué declared that registration for all clinical trials except exploratory studies must be disclosed and information on the results of all studies (except exploratory studies) on drugs approved or marketed in at least one foreign country must be disclosed.

Based on this declaration, the Ministry of Education, Culture, Sports, Science and Technology in Japan initiated the UMIN Clinical Trial Registration System (UMIN-CTR; <http://www.umin.ac.jp/ctr/index-j.htm>) and the MHLW publishes information concerning nonclinical trials via “Clinical trial information” (<http://www.japic.or.jp/index.html>), a database for registration and disclosure of clinical trial information through cooperation with the Japan Pharmaceutical Information Center and JPMA.

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

In a system unique to Japan, information on institutional review boards is made public voluntarily (Notification No 1001013 of the Evaluation and Licensing Division, PMSB dated October 1, 2008 and Office Communication dated April 2, 2009).

## **5.5 ICH (International Conference on**

### Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use)

ICH policies are drafted by a steering committee consisting of members from six groups, namely regulatory authorities and pharmaceutical industry organizations in the EU, Japan, and the United States. Members include the Food and Drug Administration (FDA), Pharmaceutical Research and Manufacturers of America (PhRMA), the European Medicines Agency (EC/EMA or EMA as from December 2009), 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), Canadian 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 expert working groups consisting of specialists, representing the six groups and government officials on each topic.

The harmonization in five steps is known as the ICH process.

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

guidelines

Step 2: Approval of draft ICH guidelines by the steering committee.

Collection of opinions on draft guidelines in each country

Step 3: Revision of guidelines based on the collected opinions

Step 4: Establishment of ICH guidelines by the steering committee

Step 5: Adoption of these guidelines in the domestic regulatory

As of September 2011, over 60 guidelines have been approved (Step 4 or 5) based on ICH activities. As shown in **Fig. 11** (ICH Topics and Guidelines—Progress of Harmonization).

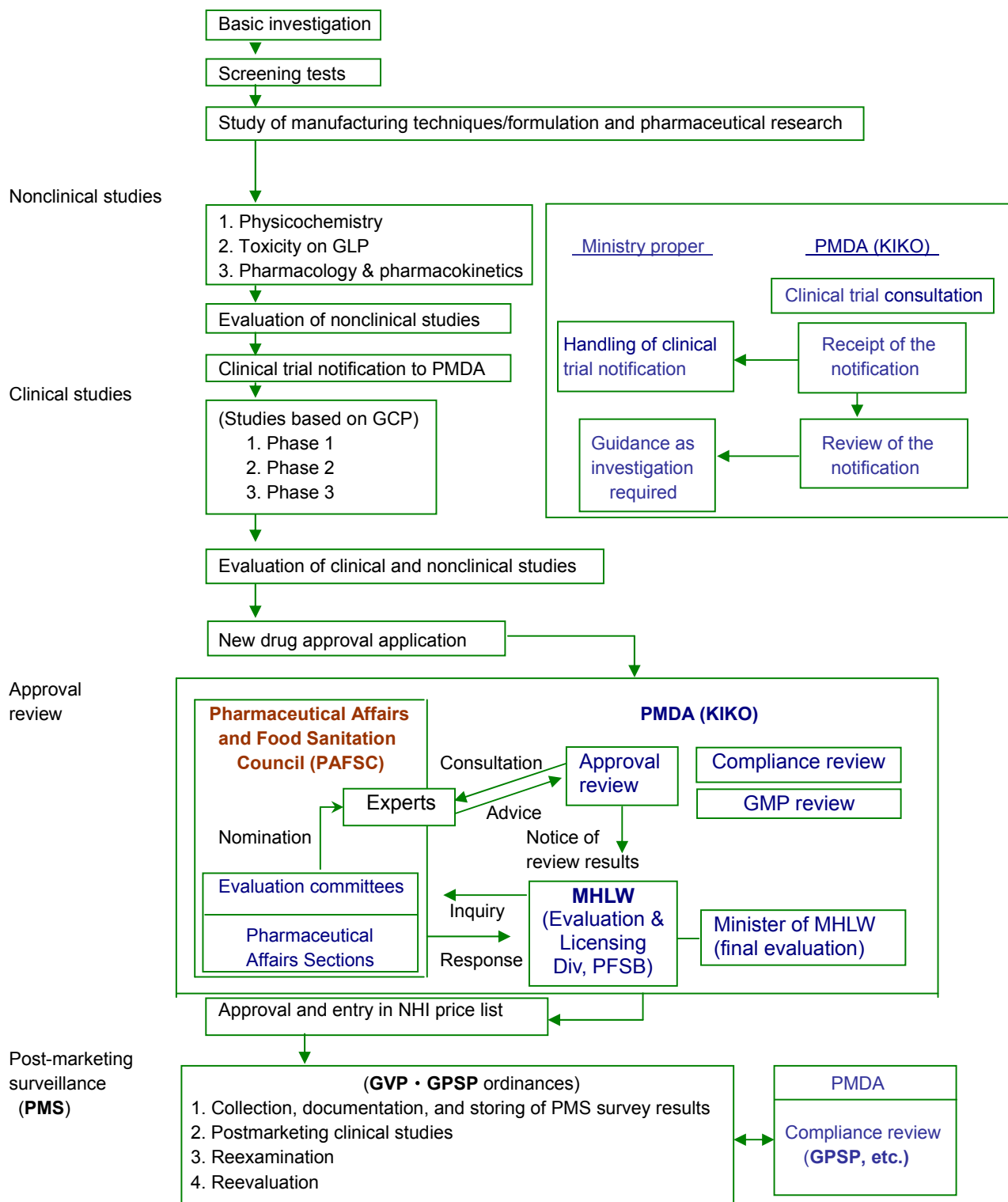
Visit the following websites for details of ICH guidelines.

Relevant website (Japanese):

[http://www.pmda.go.jp/ich/ich\\_index.html](http://www.pmda.go.jp/ich/ich_index.html)

(English):

<http://www.ich.org/cache/compo/276-254-1.html>



**Fig. 8 Flowchart of New Drug Development and Approval**

**Table 3 Data to be Submitted with an Application for Approval to Manufacture/Market a New Prescription Drug (Attached Table 2-1 in PFSB Notification No. 0304004 dated March 4, 2009)**

	A 1 2 3	B 1 2 3	C 1 2 3	D 1 2 3	E 1 2 3 4 5 6	F 1 2 3 4 5 6 7	G
(1) Prescription drugs with new active ingredients	○ ○ ○	○ ○ ○	○ ○ ○	○ ○ △	○ ○ ○ ○ × △	○ ○ ○ △ ○ △ △	○
(2) New combination prescription drugs	○ ○ ○	× ○ ○	○ ○ ○	○ △ △	○ ○ ○ ○ × △	○ ○ × × × △ ×	○
(3) Prescription drugs with new administration routes	○ ○ ○	× ○ ○	○ ○ ○	○ △ △	○ ○ ○ ○ × △	○ ○ × △ ○ △ △	○
(4) Prescription drugs with new indications	○ ○ ○	× × ×	× × ×	○ × ×	△ △ △ △ × △	× × × × × × ×	○
(5) Prescription drugs with new dosage forms	○ ○ ○	× ○ ○	○ ○ ○	× × ×	○ ○ ○ ○ × △	× × × × × × ×	○
(6) Prescription drugs with new doses	○ ○ ○	× × ×	× × ×	○ × ×	○ ○ ○ ○ × △	× × × × × × ×	○
(7) Similar biological drugs	○ ○ ○	○ ○ ○	○ △ △	○ × ×	△ △ △ △ × △	△ ○ × × × △ △	○
(8) Prescription drugs with additional dosage forms (during reexamination period)	○ ○ ○	× ○ ○	△ △ ○	× × ×	× × × × ○ ×	× × × × × × ×	×
(8-②) Same with (8) (not during reexamination period)							
(9) Combination prescription drugs with similar formulations (during reexamination period)	○ ○ ○	× ○ ○	○ ○ ○	△ △ ×	× × × × × ×	○ △ × × × △ ×	○
(9-②) Same with (9) (not during re-examination period)							
(10) Other prescription drugs (during reexamination period)							
(10-②) Same with (10) (changes in manufacturing method of biological products, etc.)							
(10-③) Same with (10) (not during reexamination period)	× × ×	× △ ○	× × ○	× × ×	× × × × ○ ×	× × × × × × ×	×
(10-④) Same with (10-③) (changes in manufacturing method of biological products, etc.)							

○: Date required

×: Data not required

△: Data required depending on individual cases

**(Table 3) Drug classification system**

(1) "Prescription drugs with new active ingredients" refer to drugs that have ingredients never before been used as active ingredients in drugs that have already been approved for manufacture/marketing or are specified in the Japanese Pharmacopoeia ("approved drugs, etc." hereinafter).
(2) "New combination prescription drugs" refer to drugs with different active ingredients or combining ratios from those of combination drugs specified in the Japanese Pharmacopoeia or combination drugs that have already been approved for manufacture/marketing as prescription drugs. However, combination prescription drugs with similar formulations specified in (8) and drugs such as digestive enzyme combination drugs and mild acting poultices that are judged not to be new from an overall evaluation are excluded.
(3) "Prescription drugs with new administration routes" refer to drugs that have the same active ingredients as approved drugs, etc. but have different routes of administration (oral, subcutaneous, intramuscular, intravenous, percutaneous, per-rectal, transvaginal, eye drops, nasal drops, inhalation, etc.).
(4) "Prescription drugs with new indications" refer to drugs that have the same active ingredients and routes of administration as approved drugs, etc. but have different indications.
(5) "Prescription drugs with new dosage forms" refer to drugs that have the same active ingredients, routes of administration and indications as approved drugs, etc. but have new dosage forms with different administration, etc. because of pharmaceutical changes such as sustained release. However, drugs with additional dosage forms specified in (7) are excluded.
(6) "Prescription drugs with new doses" refer to drugs that have the same active ingredients and routes of administration as approved drugs, etc. but have different doses.
(7) "Biosimilar products" refer to biotechnological products equivalent to existing (approved) biotechnological products in quality
(8) "Prescription drugs with additional dosage forms" refer to drugs that have the same active ingredients, routes of administration, indications and dosage and administration as approved drugs, etc., but have different dosage forms or contents.
(9) "Combination prescription drugs with similar formulations" refer to prescription drugs with active ingredients and combining ratios that are judged to be similar to those of combination drugs specified in the Japanese Pharmacopoeia or combination drugs that have already been approved for manufacture/marketing as prescription drugs.
(10) "Other prescription drugs" refer to biological products such as vaccines and blood products entered in the Biological Product Standards; recombinant DNA drugs, cell culture drugs and other drugs applying biotechnology or drugs derived from living organisms.

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

**Table 4 Data to be Submitted with an Application for a Non-prescription Drug  
(Attached Table 2-2 in PFSB Notification No.1020001 dated October 20, 2008)**

	A 1 2 3	B 1 2 3	C 1 2 3	D 1 2 3	E 1 2 3 4 5 6	F 1 2 3 4 5 6 7	G
(1) Non-prescription drugs with new active ingredients	○ ○ ○	○ ○ ○	○ ○ ○	○ ○ Δ	○ ○ ○ ○ × Δ	○ ○ ○ Δ ○ Δ Δ	○
(2) Non-prescription drugs with new administration routes	○ ○ ○	× ○ ○	○ ○ ○	○ Δ Δ	○ ○ ○ ○ × Δ	○ ○ × Δ ○ Δ Δ	○
(3)-① Non-prescription drugs with new indications	○ ○ ○	× × ×	× × ×	○ × ×	Δ Δ Δ Δ × Δ	× × × × × × ×	○
(3)-② Non-prescription drugs with new dosage forms	○ ○ ○	× ○ ○	○ ○ ○	× × ×	○ ○ ○ ○ × Δ	× × × × × × ×	○
(3)-③ Non-prescription drugs with new doses	○ ○ ○	× × ×	× × ×	× × ×	○ ○ ○ ○ × Δ	× × × × × × ×	○
(4) Non-prescription drugs with new active ingredients for non-prescription drugs	○ ○ ○	× × ○	Δ × Δ <sup>*2</sup>	× × ×	Δ × × × × ×	Δ Δ × × × Δ Δ	○
(5)-① Non-prescription drugs with new administration routes for non-prescription drugs	○ ○ ○	× × ○	Δ × Δ <sup>*2</sup>	× × ×	Δ × × × × ×	Δ Δ × × × Δ Δ	○
(5)-② Non-prescription drugs with new indications for non-prescription drugs	○ ○ ○	× × ×	× × ×	× × ×	Δ × × × × ×	× × × × × × ×	○
(5)-③ Non-prescription drug with New formulation non-prescription drug	○ ○ ○	× × ○	Δ × Δ <sup>*2</sup>	× × ×	Δ × × × × ×	× × × × × × ×	○
(5)-④ Non-prescription drugs with new doses for non-prescription drugs	○ ○ ○	× × ×	× × ×	× × ×	Δ × × × × ×	× × × × × × ×	○
(6) New non-prescription combination drugs	○ ○ ○	× × ○	Δ × Δ <sup>*2</sup>	× × ×	Δ × × × × ×	Δ Δ × × × Δ ×	○
(7)-① Non-prescription combination drugs with similar formulations	× × ○	× × ○	Δ × Δ <sup>*2</sup>	× × ×	Δ × × × × ×	Δ Δ × × × × ×	×
(7)-② Non-prescription combination drugs with similar dosage forms	× × ○	× × ○	Δ × Δ <sup>*2</sup>	× × ×	Δ × × × × ×	× × × × × × ×	×
(8) Other non-prescription drugs (drugs with approval standards, etc)	× × ○ <sup>*1</sup>	× × ○	Δ × Δ <sup>*2</sup>	× × ×	× × × × × ×	× × × × × × ×	×

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

<sup>\*1</sup> A drug product that conforms to approval standards may be applied by submitting a comparison table of the standards and active ingredient(s) and its amount(s). A non-drug product must be documented with the basis of formulation development, efficacy, safety, and other necessary characteristics.

<sup>\*2</sup> Long-term stability data are necessary if stability for more than 3 years is not ensured by accelerated stability tests. If the product is confirmed to be stable for at least 1 year based on ongoing long-term stability tests, the application itself is acceptable. The final report of the long-term tests must be submitted until approval.

**(Table 4) Drug classification system**

(4) “Non-prescription drugs with new active ingredients for non-prescription drugs” refer to non-prescription drugs other than drugs with new active ingredients and contain ingredients not used as active ingredients in approved non-prescription drugs.
<p>(5)-① “Non-prescription drugs with new administration routes for non-prescription drugs” refer to non-prescription drugs other than drugs with new routes of administration and contain the same active ingredients as approved non-prescription drugs but have different routes of administration.</p> <p>(5)-② “Non-prescription drugs with new indications for non-prescription drugs” refer to non-prescription drugs other than drugs with new indications and have the same active ingredients and routes of administration as approved non-prescription drugs but have different indications.</p> <p>“Non-prescription drugs with new dosage forms for non-prescription drugs” refer to non-prescription drugs other than drugs with new dosage forms and have the same active ingredients, routes of administration and indications as approved non-prescription drugs but have dosage forms with different administration, etc. because of pharmaceutical changes such as sustained release.</p>
(6) “New non-prescription combination drugs” refer to drugs with ingredients the same as active ingredients of approved non-prescription drugs that have different combinations of active ingredients than those of approved non-prescription drugs that are non-prescription drugs other than non-prescription drugs judged to have similar combinations of active ingredients. Basically, the drugs in No. 1. (1)-(1) a) to f) in Notification No. 0331053 of the Pharmaceutical and Food Safety Bureau dated March 31 2008 are equivalent to new non-prescription combination drugs.
<p>(7)-① “Non-prescription combination drugs with similar formulations” refers to drugs with ingredients the same as active ingredients of approved non-prescription drugs that are non-prescription drugs with similar combinations of active ingredients as approved non-prescription drugs.</p> <p>(7)-② “Non-prescription drugs with similar dosage forms” refer to non-prescription drugs with the same active ingredients, routes of administration and indications as approved non-prescription drugs but with different dosage forms, but they are not equivalent to drugs in (5)-(3) among non-prescription drugs with different dosage forms.</p>
(8) “Other non-prescription drugs” refers to non-prescription drugs that are not equivalent to the drugs in (1) to (7).

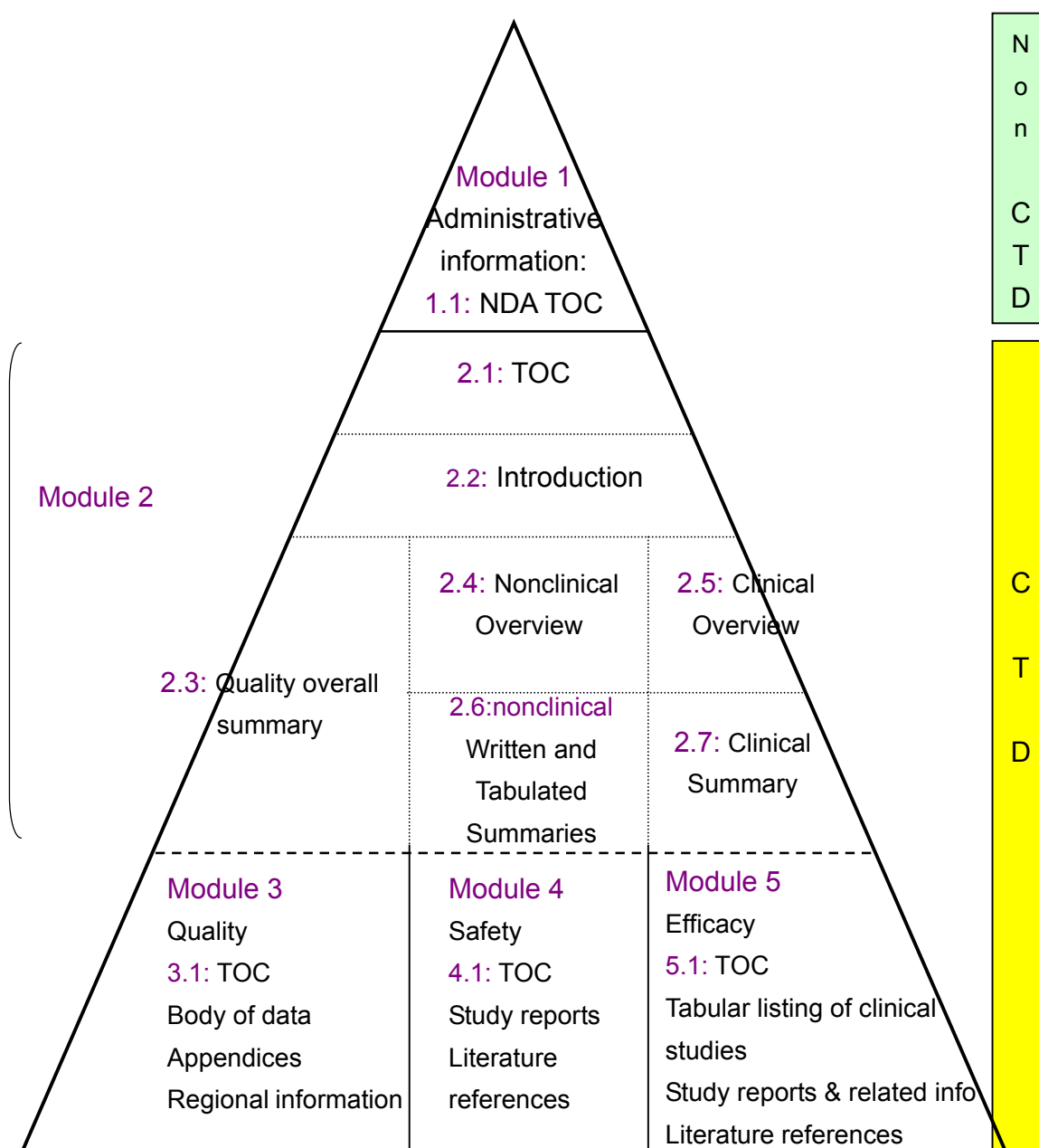
a. Origin or background of discovery, conditions of use in foreign countries	1. Origin or background of discovery 2. Conditions of use in foreign countries 3. Special characteristics, comparisons with other drugs, etc.
b. Manufacturing methods, standards and test methods	1. Chemical structure and physicochemical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

**Table 5 Classification of Clinical Studies According to Objectives**

Type of study	Objective of study	Study examples
Human pharmacology	<ul style="list-style-type: none"><li>• Assess tolerance</li><li>• Define/describe PK<sup>1)</sup> and PD<sup>2)</sup></li><li>• Explore drug metabolism and drug interactions</li><li>• Estimate activity</li></ul>	<ul style="list-style-type: none"><li>• Dose-tolerance studies</li><li>• Single and multiple dose PK and/or PD studies</li><li>• Drug interaction studies</li><li>• ADME studies</li></ul>
Therapeutic exploratory	<ul style="list-style-type: none"><li>• Explore use for the targeted indication</li><li>• Dose-response exploration studies</li><li>• Provide basis for confirmatory study design, endpoints, methodologies</li></ul>	<ul style="list-style-type: none"><li>• Earliest studies of relatively short duration in well-defined narrow patient populations, using surrogate or pharmacological endpoints or clinical measures</li></ul>
Therapeutic confirmatory	<ul style="list-style-type: none"><li>• Demonstrate/confirm efficacy</li><li>• Establish safety profile</li><li>• Provide an adequate basis for assessing the benefit/risk relationship to support licensing</li></ul>	<ul style="list-style-type: none"><li>• Adequate, and well controlled studies to establish efficacy</li><li>• Clinical safety studies</li><li>• Large simple studies</li></ul>
Therapeutic use	<ul style="list-style-type: none"><li>• Refine understanding of benefit/risk relationship in general or special populations and/or environments</li><li>• Identify less common adverse reactions</li><li>• Refine dosing recommendation</li></ul>	<ul style="list-style-type: none"><li>• Comparative effectiveness studies</li><li>• Studies of mortality/morbidity outcomes</li><li>• Large simple studies</li><li>• Pharmacoeconomic studies</li></ul>

1) Pharmacokinetics

2) Pharmacodynamics



**Fig. 9 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. Compliance 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>





	Q4B (Annex 14)		Bacterial endotoxins test
Step 2*	Q11		Development of active pharmaceutical ingredients
Step 1*	Q3D		Guideline for metal impurities

	Safety		
	Code	Previous code	Topics
Step 5*	S1A S1B S1C (R2) S2A S2B S3A S3B S4 S5 (R2) S6 S7A S7B S8 S9	S1C, S1C (R)       S4, S4A S5A, S5B	Need for carcinogenicity studies Testing of carcinogenicity of pharmaceuticals Dose selection for carcinogenicity studies Genotoxicity: Mutation assays Genotoxicity: Standard battery of genotoxicity tests Toxicokinetics: Assessment of systemic exposure in toxicity studies Pharmacokinetics: Repeated-dose tissue distribution Single- and repeated-dose toxicity studies Reproduction studies of medicinal products Safety evaluation of biological products Safety pharmacology studies The non-clinical evaluation of QT interval prolongation potential Immunotoxicology studies Non-clinical evaluation of anticancer drugs
Step 4*	S6 (R1) S2 (R1)		Safety evaluation of biological products (Annex) Genotoxicity (review of guideline)
Step 3*			
Step 2*			
Step 1*	S10		Guidance on photosafety testing

**Step 1:** Selection/analysis of topics to be studied. Establishment of expert working groups, and preparation of draft guidelines  
**Step 2:** Approval of draft ICH guidelines by the steering committee.  
Collection of opinions on draft guidelines in each country  
**Step 3:** Revision of guidelines based on the collected opinions  
**Step 4:** Establishment of ICH guidelines by the steering committee  
**Step 5:** Adoption of these guidelines in the domestic regulatory  
With the new codification revisions to an ICH Guideline are shown as (R1), (R2), (R3) depending on the number of revisions, revisions, and additions. The codes of Guidelines in implementation are not changed.

Source: <http://www.ich.org/>

	Efficacy			Multidisciplinary		
	Code	Previous code	Topics	Code	Previous code	Topics
Step 5*	E1		The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life threatening condition	M1		Medical dictionary for regulatory activities (MedDRA)
	E2A		Clinical safety data management: Definitions and standards for expedited reporting in the clinical phase	M2		Electronic standards for transmission of regulatory information
	E2B (R2)	E2B (M)	Data elements for transmission of individual case safety reports			Electronic form of application (v. 3.2.2)
	E2C (R1)	E2C	Clinical safety data management: Periodic safety update reports	M2 (e-CTD)		
	E2D		Post-approval safety data management			
	E2E		Pharmacovigilance planning (PVP)	M3 (R2)		
	E3		Structure and content of clinical study reports			
	E4		Dose-response information to support drug registration			
	E5 (R1)	E5	Ethnic factors in the acceptability of foreign clinical data			
	E6 (R1)	E6	Guidance for good clinical practice			
	E7		Studies in support of special populations: Geriatrics			
	E8		General considerations for clinical trials			
	E9		Statistical principles for clinical trials			
	E10		Choice of control group and related issues in clinical trials			
	E11		Clinical investigation of medicinal products in the pediatric population			
	E12	E12A	Principles for clinical evaluation of new antihypertensive drugs			
	E14		The clinical evaluation of QT interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs			
	E15		Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data, and sample coding categories			
	E16		Genomic biomarkers related to drug response: Context, structure and format of qualification submissions			
Step 4*	E2F		Development of safety update report			
Step 3*	E2B (R3)		Data elements for transmission of individual case safety reports	M5		Data elements and standards for drug dictionaries
Step 1*	E2C (R2)		Clinical safety data management: Revision of PSUR	M7		Genotoxic impurities
				M8 (e-CTD)		Organization of e-CTD

**Fig. 11. ICH topics and guidelines—Progress of harmonization**

## 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 and to establish proper methods of use of drugs consists of three systems: the ADR collecting and reporting system, the reexamination system, and the reevaluation system ([Fig. 12. Pharmaceutical Post-marketing Surveillance System](#)).

The re-examination system for new drugs was introduced in the 1979 amendment of the Pharmaceutical Affairs Law, and 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 Ordinance No. 151 of MHW dated December 27, 2000, and “Early Post-marketing Surveillance” for new drugs was newly established to reinforce safety measures in an early phase of marketing (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.

Periodic reporting of safety information on new drugs, etc. was agreed at the ICH in January 1996, and the periodic safety update report (PSUR) system was introduced by Notification No. 32 of the Safety Division, Pharmaceutical and Medical Safety Bureau dated March 27, 1997 and the Guidelines on Methods for Surveillance of Results of Use of Prescription Drugs (Notification No. 34 of the Safety Division, Pharmaceutical and Medical Safety Bureau dated March 27, 1997) were specified. However, because of an increase in post-marketing ADRs not observed in the clinical trial stage of drug development and implementation of safety measures, regulations on safety measured for drugs (Notification No. 25 of the Safety Division, Pharmaceutical and Medical Safety Bureau) and entries in case report forms for ADRs and infections were specified in March 11, 1998. Furthermore, a new guideline,

Implementation of Early Post-marketing Surveillance for Prescription Drugs (Notification No. 0324001, the Safety Division, PFSB dated March 24, 2006) to further strengthen the safety monitoring of medical products ([Fig. 13. Post-marketing Collection and Reporting of Pharmaceutical Safety Information](#)).

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

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

171 issued by MHLW on December 20, 2004). The MHLW Ordinance on GPMSP was abolished.

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

## 1. GVP

Good Vigilance Practice (GVP)

establishes standards for post-marketing safety management related to the collection, evaluation, and assessment of proper use information on the establishment of appropriate safety-related organizations and systems as one of licensing requirements for the marketing authorization holder, development and implementation of relevant SOPs, marketed drugs, etc., and to the implementation of measures for safety assurance.

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

#### (1) Purpose (Article 1)

This Ministerial Ordinance establishes the standards established by the MHLW Ordinance related to post-marketing safety management set forth in Article 12-2, Paragraph 2 of the Pharmaceutical Affairs Law.

#### (2) Definitions of terms (Article 2)

- [1] Safety management information refers to material relating to the quality, efficacy or safety of drugs etc., and any other information required for the proper use of drugs, etc.
- [2] Quality assurance activities refers to any activity related to post-marketing quality control concerned with requisite measures based on the

collection and study of safety management information, or on the results.

- [3] Early post-marketing surveillance refers to any safety assurance activities that are performed within a period of 6 months following commencement of marketing by the marketing authorization holder of a drug in order to promote proper use of the drug in medical treatment, and to quickly identify the occurrence of serious adverse drug reactions, etc. It is specified as a condition of approval.
- [4] Person in charge of drug information and person in charge of medical device information refer to persons whose main duties consist of collecting and providing safety assurance information through visits to health care professionals in order to contribute to the proper use of drugs or medical devices.

Articles 3 to 12 are specified for the first type of marketing authorization holder (marketing authorization holders of prescription drugs and highly controlled medical devices).

#### (3) Duties of general marketing compliance officer (Article 3)

The general marketing compliance

officer must undertake the following duties.

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

#### (4) Organizations and personnel involved in safety assurance (Article 4)

- [1] A department (safety management department) meeting the following requirements must be established to handle all duties related to safety assurance.
  - This department is under the supervision of the general manufacturing/marketing supervisor
  - This department must employ adequately qualified and competent personnel who are able to undertake safety assurance activities properly and smoothly.

- This department should be independent of all divisions responsible for marketing drugs and other departments that would hinder proper and smooth safety assurance activities.
- [2] A safety management supervisor meeting the following requirements must be appointed.
  - The safety management supervisor is the supervisor of the safety management department.
  - This supervisor must have been engaged for at least 3 years in safety assurance work or related work.
  - This supervisor must have the ability to properly and smoothly undertake safety assurance activities.
  - This supervisor must not belong to any division responsible for marketing drugs, etc.
- [3] When all or part of the safety assurance activities are undertaken by persons other than the safety management supervisor, a supervisor of the work concerned (safety management implementation supervisor) must be appointed.

(5) Standard operating procedures for post-marketing surveillance (Article 5)

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

- Procedures for collection of safety management information
- Procedures for drafting of safety assurance measures based on examination of safety management information and the results thereof
- Procedures for implementation of safety assurance measures
- Procedures for reporting from safety management supervisors to general marketing compliance officer
- Procedures for early post-marketing surveillance
- Procedures for in-house inspections
- Procedures for education and training
- Procedures for retention of records
- Procedures for contacts with quality assurance supervisors and other supervisors engaged in work related to marketing of prescription drugs and highly controlled medical devices

- Other procedures necessary for properly and smoothly implementing safety assurance measures of post-marketing surveillance

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

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

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

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

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

- Overall supervision of safety assurance work

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

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

- [1] The following safety management information shall be collected by the safety management supervisor and safety management implementation supervisor and records shall be prepared thereof.
- Information from health professionals
  - Information on reports presented at scientific meetings, reports from the literature and other research reports
  - Information from the Ministry of Health, Labour and Welfare, other government institutions, prefectural governments and organizations
  - Information from foreign governments and overseas organizations

- Information from other pharmaceutical manufacturers/marketing authorization holders
- Other safety management information

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

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

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

- [1] The safety management supervisor shall perform the following duties.
- Examine the collected safety management information without delay and record the results thereof.
  - Supply all safety information that the quality assurance supervisor must be familiar with in writing without delay to the quality assurance supervisor.
  - When it is confirmed necessary from an examination of safety management information, measures shall be drafted to

<p>discard, recall or suspend marketing of the product, revise package inserts, supply information to health professionals by persons in charge of drug or medical device information, reports to the Minister of Health, Labour and Welfare and other safety assurance measures.</p> <ul style="list-style-type: none"> <li>• Drafts of safety assurance measures shall be reported in writing to the general marketing compliance officer and copies shall be retained.</li> </ul> <p>[2] When the safety management supervisor has the safety management implementation supervisor examine safety management information, he or she shall issue instructions in writing and retain a copy. Records of the examination performed by the safety management implementation supervisor shall be prepared and reported in writing. The safety management supervisor shall retain these results.</p> <p>(9) Implementation of safety assurance measures (Article 9)</p> <p>[1] The general marketing compliance officer must undertake the following</p>	<p>duties.</p> <ul style="list-style-type: none"> <li>• Appropriately evaluate drafts of safety assurance measures, decide the safety assurance measures to be taken and prepare and retain records thereof.</li> <li>• When safety management supervisors undertake safety assurance measures, instructions shall be issued in writing and retained</li> <li>• When safety management implementation supervisors undertake safety assurance measures, instructions shall be issued in writing and the safety management implementation supervisor shall retain copies. The safety management implementation supervisor shall prepare records and make reports in writing. Copies shall be given to the safety management supervisor.</li> </ul> <p>[2] The following duties must be undertaken by the safety management supervisor.</p> <ul style="list-style-type: none"> <li>• Safety assurance measures shall be undertaken based on instructions from the general marketing compliance officer and records thereof shall be</li> </ul>
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- prepared and retained.
- When safety assurance measures are undertaken by safety management implementation supervisors, instructions shall be issued in writing and copies shall be retained. Records shall be prepared, reported in writing and retained.
  - The results of implementation of safety assurance measures shall be reported in writing to the general marketing compliance officer, and a copy shall be retained.
  - Copies of reports from the safety management implementation supervisor shall be retained.
- [3] Evaluation of drafts of safety assurance measures for which post-marketing safety management standard operating procedures have been specified beforehand, deciding on safety assurance measures to be taken, and preparation and retention of records can be undertaken by the safety management supervisor in place of the general manufacturing/marketing supervisor.

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

- [1] A protocol (early post-marketing surveillance protocol) containing the following items must be prepared each time early post-marketing surveillance is performed.
- Objective of the early post-marketing surveillance
  - Method of early post-marketing surveillance
  - Period of early post-marketing surveillance
  - Other necessary items
- [2] When the early post-marketing surveillance protocol is prepared or revised, the early post-marketing surveillance protocol must be dated and retained.
- [3] The general marketing compliance officer shall make available early post-marketing surveillance protocol in the office performing the work and also must make available copies in other offices performing surveillance work.
- [4] The safety management supervisor shall confirm that early post-marketing surveillance is being performed appropriately and smoothly and records of such confirmation shall be prepared and retained. He or she shall also

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| <p>revise the early post-marketing surveillance protocol as required.</p> <p>[5] When early post-marketing surveillance is performed by the safety management implementation supervisor, the safety management implementation supervisor shall prepare records and report in writing to the safety management supervisor, and the safety management supervisor shall retain such reports.</p> <p><b>(11) In-house inspections (Article 11)</b></p> <p>[1] in-house inspections of duties related to post-marketing safety management shall be performed on a regular schedule by a person appointed beforehand.</p> <p>[2] When the person appointed beforehand in (1) is the safety management supervisor, the safety management supervisor shall prepare and retain records of in-house inspections.</p> <p>[3] When the person appointed beforehand in (1) is a person other than the safety management supervisor, that person shall prepare records of in-house inspections and report in writing to the safety management supervisor. The safety management supervisor shall</p> | <p>retain these reports.</p> <p>[4] The safety management supervisor shall report the results of the in-house inspection in writing to the general marketing compliance officer and shall retain a copy of the report.</p> <p>[5] The general marketing compliance officer shall examine the necessity of improvements in post-marketing safety management based on the results of in-house inspections and when improvements are necessary, the general marketing compliance officer shall undertake the specified measures and prepare records thereof. The safety management supervisor shall retain these records.</p> <p><b>(12) Education and training (Article 12)</b></p> <p>[1] The general marketing compliance officer shall prepare and retain education and training protocols for employees engaged in duties related to post-marketing safety management</p> <p>[2] Education and training shall be performed as planned by a person appointed beforehand.</p> <p>[3] When the person appointed beforehand in (2) is the safety management supervisor, the safety management supervisor shall</p> |
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- prepare and retain records of education and training.
- [4] When the person appointed beforehand in (2) is a person other than the safety management supervisor, that person shall prepare records of education and training and report in writing to the safety management supervisor. The safety management supervisor shall retain these reports.
- [5] The safety management supervisor shall report the results of the education and training in writing to the general marketing compliance officer and shall retain a copy of the report.

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

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

- [1] Establishment of a safety management division is not specified.
- [2] No qualifications for safety management supervisors are

specified.

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

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

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

- [1] (1) to (3) in Article 13 above.
- [2] Standard operating procedures for post-marketing safety management are not specified.
- [3] Collection of safety information in (7) for quasi-drugs and cosmetics is limited to research reports and other safety management information.
- [4] In-house inspections and education and training are not specified.

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

- [1] The period of retention of 5 years from the date when the records are no longer utilized. However, the period shall be 10 years for biological products, 30 years for

specified biological products, and 15 years for designated controlled medical devices and highly controlled medical devices.

Records related to in-house inspections and education and training shall be kept for 5 years from the date of preparation

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

## 2. GPSP

GPSP (Good Post-marketing Study Practice) specifies items that are to be strictly complied with in order to achieve appropriate post-marketing surveillance and studies conducted by marketing authorization holders, and to assure the reliability of data submitted when applying for reexamination or re-evaluation.

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

### (1) Purpose (Article 1)

This Ministerial Ordinance sets forth the items that must be strictly complied with by marketing authorization holders of drugs in conducting post-marketing

surveillance and studies.

This GPSP applies to inspections, etc. of documents and data related to reexamination and reevaluation of prescription drugs. For post-marketing clinical studies forming part of post-marketing surveillance, GCP is also applicable, in addition to GPSP.

### (2) Definitions of terms (Article 2)

- [1] Post-marketing surveys, etc. refers to drug use-results surveys or post-marketing clinical studies that the marketing authorization holder of drugs conducts in order to collect, screen, confirm or verify information relating to the quality, efficacy and safety of drugs.
- [2] Among post-marketing surveys, drug use-results survey refers to a survey by the marketing authorization holder to screen or confirm information related to the incidence of each disease due to adverse drug reactions, together with the quality, efficacy and safety of drugs, without specifying the condition of the patients that use the drugs.
- [3] Among drug use result surveys, specified drug-use survey refers to a survey by the marketing authorization holder to screen or confirm information relating to the

incidence of each disease due to adverse drug reactions, together with the quality, efficacy and safety of drugs, in specified populations of patients, such as pediatric patients, elderly patients, pregnant women, patients with renal and/or hepatic disorders, and patients using the drug for long periods.

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

**(3) Standard operating procedures for post-marketing surveillance (Article 3)**

The following standard operating procedures for post-marketing surveillance shall be prepared and retained by the marketing authorization holder for the proper and smooth conduct of post-marketing surveillance. The date must be entered in the SOP manual when SOP are prepared or revised.

- [1] Procedures related to drug

use-results surveys

- [2] Procedures related to post-marketing clinical studies
- [3] Standards related to in-house inspections
- [4] Procedures related to education and training of personnel involved in post-marketing surveys, etc.
- [5] Procedures related to the outsourcing of duties in post-marketing surveys, etc.
- [6] Procedures related to the preservation of records involving duties in post-marketing surveys, etc.
- [7] Any other procedures necessary for appropriate and smooth implementation of post-marketing surveys, etc.

**(4) Supervisor of post-marketing surveys, etc. (Article 4)**

- [1] A supervisor of the marketing authorization holder must be appointed to coordinate the duties involved in post-marketing surveys, etc. (supervisor of post-marketing surveys, etc.).
- [2] The supervisor of post-marketing surveys, etc. must not be a member of a department involved in marketing.
- [3] Duties to be performed by the supervisor of post-marketing

<p>surveys, etc.:</p> <ul style="list-style-type: none"> <li>• To prepare and preserve a basic protocol for post-marketing surveys, etc. for each drug individually.</li> <li>• To set forth in writing protocols for the implementation of drug use-results surveys, protocol for post-marketing clinical studies, and any other matters necessary for conducting post-marketing surveys, etc.</li> <li>• To revise the basic protocol for post-marketing surveys, etc. as required.</li> <li>• In cases in which a basic protocol for post-marketing surveys, etc. is prepared or revised, to date and preserve it.</li> <li>• When it is considered necessary for the conduct of post-marketing surveys, etc., to provide written opinions to the marketing authorization holder, and to preserve these documents or copies thereof.</li> </ul> <p>[4] The marketing authorization holder must respect the opinions provided by the supervisor of post-marketing surveys, etc.</p> <p>[5] The marketing authorization holder must not make any statements that</p>	<p>would interfere with the supervisor of post-marketing surveys, etc. in the performance of his or her duties.</p> <p>(5) Post-marketing surveys, etc. (Article 5)</p> <p>[1] The marketing authorization holder's supervisor of post-marketing surveys, etc. must assure that the duties for implementation of post-marketing surveys, etc. are performed as set forth below:</p> <ul style="list-style-type: none"> <li>• To prepare plans, proposals and surveys for implementation of post-marketing surveys, etc.</li> <li>• To confirm that post-marketing surveys, etc. are conducted appropriately and satisfactorily in accordance with the standard operating procedures for duties for post-marketing surveys, etc. and the basic protocol on post-marketing surveys, etc.</li> <li>• To provide notification in writing of the results of post-marketing surveys, etc.</li> </ul> <p>[2] The marketing authorization holder must arrange that, for both drug use-results surveys and post-marketing clinical trials, records are prepared and preserved in order that the supervisor of post-marketing surveys, etc. understands the conditions under which the surveys or tests were conducted.</p>
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(6) Drug use-results surveys (Article 6)

- [1] The marketing authorization holder must instruct the supervisor or other designated person to conduct drug use-results surveys according to the post-marketing surveillance SOP and basic post-marketing survey protocol.
- [2] Contracts in writing must be concluded with the medical institutions competent in conducting the drug use-results survey and preserved.
- [3] Contract may be handled by electronically.
- [4] In protocols for drug use-results surveys, the purpose of the survey, scheduled number of cases, controls, survey method, survey period, items surveyed, analytical method and other necessary matters must be established.

(7) Post-marketing clinical studies (Article 7)

- [1] The marketing authorization holder must perform post-marketing studies by the post-marketing surveillance supervisor or other person designated by the marketing authorization holder based on the post-marketing surveillance SOP or basic post-marketing survey protocol.

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

(8) In-House inspections (Article 8)

- [1] The marketing authorization holder must conduct in-house inspections on a regular schedule. Items that have been audited based on GCP do not require in-house inspections. In cases in which a person other than the supervisor of post-marketing surveys, etc. conducts an in-house inspection, the supervisor of post-marketing surveys, etc. is to be notified in writing of the results of the inspection. Records of the results of the in-house inspection are prepared and preserved.
- [2] Post-marketing surveillance supervisors must report in writing the results of the self-inspections to the marketing authorization holder.
- [3] When it is found that improvements must be made in the work based on the results of the self-inspection, the necessary measures must be taken, and records of these measures must be prepared and retained.

(9) Education and training (Article 9)

The supervisor of post-marketing surveys, etc. or a person designated by the marketing authorization holder, etc.

must assure that the duties set forth below are conducted.

- [1] Planned education and training related to post-marketing surveillance must be performed by the post-marketing surveillance supervisors or other persons designated by the marketing authorization holder for persons employed in post-marketing surveillance work.
- [2] In cases in which education and training are performed by a person other than the supervisor of post-marketing surveys, etc., the supervisor of post-marketing surveys, etc., is notified in writing of the conditions of its implementation.
- [3] Records of education and training are prepared and preserved.

[\(10\) Delegation of duties of post-marketing surveys, etc. \(Article 10\)](#)

The marketing authorization holder may assign some of the duties of post-marketing surveys, etc. to persons who are capable of properly and effectively carrying out these activities.

[\(11\) Preservation of records in connection with post-marketing surveys, etc. \(Article 11\)](#)

Records of reexamination and reevaluation data must be retained for 5 years from the date that reexamination or

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

[\(12\) Standards for Compliance of Reexamination and Reevaluation Data in Connection with Post-marketing Surveillance \(Article 12\)](#)

In addition to provisions of the GCP MHLW Ordinance, the provisions of Article 3 through Article 8, Article 10, and Article 11 of this GPSP MHLW apply *mutatis mutandis* to the collection and preparation of data for reexamination and reevaluation applications in connection with post-marketing surveys, etc.

### **3. DATA COMPLIANCE SURVEYS AND COMPLIANCE SURVEYS OF MARKETING AUTHORIZATION HOLDERS BASED ON GPSP**

GPSP compliance surveys for reexamination and reevaluation application data and surveys to assess GPSP compliance status of marketing authorization holders, including verification of reliability of the collection and preparation of data submitted to the Minister of the MHLW to report adverse drug reactions and infections, are implemented in accordance with the

Guideline for Implementation of GPSP On-site Surveys (Notification No. 0330003 of the Evaluation and Licensing Division, PFSB dated March 30, 2005) established by the MHLW.

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

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

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

#### **4. ADVERSE DRUG REACTIONS AND INFECTIONS REPORTING SYSTEM**

Programs for collecting and reporting safety information on drugs such as adverse drug reactions include an adverse drug reaction reporting system undertaken by pharmaceutical companies, the drug and medical device safety information reporting system undertaken by medical personnel, and the WHO International Drug Monitoring Program whereby drug safety information is exchanged among various countries ([Fig. 14. Collection and Reporting of Pharmaceutical Safety Information](#)).

##### **4.1 Adverse Drug Reaction and Infectious Disease Reporting System by Pharmaceutical Companies**

This system, based on the Pharmaceutical Affairs Law (Article 77-(4)-2-1), requires the reporting of safety findings by pharmaceutical companies to the PMDA for information processing. In light of the medical problems such as the development of AIDS associated with the use of HIV-contaminated, unheated blood products, provisions were established in the revised Pharmaceutical Affairs Law, which came into effect in April 1997, to mandate reporting of "adverse drug reactions" and the "occurrence of infections suspected to be caused by the use of the drug concerned."

Revisions in the Enforcement Regulations

of the Pharmaceutical Affairs Law, which became effective at the same time, based on items agreed to at the International Conference on Harmonization (ICH), also have defined the scope of "serious cases" subject to reporting. In addition, regulatory information such as measures adopted in overseas to discontinue marketing of a drug due to safety concerns must now be reported.

The collection and examination of Japanese and overseas drug safety information, as well as the adoption of specific measures based on this information, must be carried out in accordance with the standard operating procedures for post-marketing safety management (GVP).

The provisions in Article 253 of the Enforcement Regulations for reporting adverse drug reactions specify reporting within 15 days and within 30 days. The type of cases requiring reporting within 15 days was specified in Notification No. 0317006 of the Pharmaceutical and Food Safety Bureau dated March 17, 2005. This change was intended to assure focused supervision of serious cases caused by adverse reactions of drugs with little post-marketing clinical experience and to coordinate reporting criteria for adverse drug reactions with international standards. A summary of these provisions is presented below.

#### (1) Reporting within 15 days

The following must be reported within 15 days from the time they are first known:

- a) The cases described below include suspected adverse reactions to the drug concerned reported both in Japan and overseas. These also include cases where the occurrence of an adverse reaction, its incidence, and/or the conditions of onset was unexpected based on the precautions in the package insert of the drug concerned (previously unknown serious cases).
  - (1) Death
  - (2) Disability
  - (3) Any events possibly leading to death or disability
  - (4) Any case that requires hospitalization for treatment or prolongs the duration of hospitalization.
  - (5) Any other serious cases involving items (1) through (4) above
  - (6) Any congenital disease or anomaly in the offspring of a treated patient.
- b) Any case involving items (1) through (6) above resulting from any unknown or known infections due to

- use of the drug concerned, including cases both in Japan and overseas.
- c) Any implementation of measures by regulatory authorities in foreign countries such as suspension of marketing of the drug.
  - d) Known deaths
  - e) Changes in onset trends of known serious adverse drug reactions that would result in or increase public health hazards.
  - f) Serious cases considered to be caused by adverse reactions of drugs with new active ingredients within 2 years from the date of approval (known or unknown).
  - g) Serious cases discovered in early post-marketing surveillance among adverse reactions of drugs other than drugs with new active ingredients for which early post-marketing surveillance is an approval condition (known or unknown).

## (2) Reporting within 30 days

The following must be reported within 30 days from the time they are first known:

- a) Any cases involving items (2) through (6) in subsection (a) of the previous section attributed to a known adverse reaction of the drug

concerned occurring in Japan (known serious cases).

- b) Research reports about the drug concerned, which demonstrate that it does not have an approved indication.

## (3) Periodic reports of unknown non-serious adverse reactions of drugs

The degree of seriousness of cases of adverse drug reactions was conventionally classified into three grades: serious, moderate and mild, but the classification has been changed to the two-stage serious and non-serious system used internationally. Cases suspected of being caused by adverse drug reactions that are unknown and non-serious must be reported periodically.

To further expedite assessments of adverse drug reactions by pharmaceutical companies, and to promote reporting of these adverse reactions in a more timely and proper manner, specific criteria for assessment of cases subject to reporting have been established by the Standards for Classification of Serious Adverse Drug Reactions (Notification No. 80 of the Safety Division, PAB dated June 29, 1992).

This seriousness classification of adverse drug reactions includes the following nine categories: liver, kidneys,

blood, hypersensitivity, respiratory tract, gastrointestinal tract, cardiovascular system, neuropsychiatry, and metabolic and electrolyte abnormalities.

The scope of “seriousness” was defined in April 1997 based on agreements at the ICH conference and details of the agreement on ICH E2D guideline were announced as the “Standards for expediting reporting of post-approval safety data” (Notification No. 0328007 of the Safety Division, PMSB dated March 28, 2005).

From October 27, 2003, three submission methods have been specified for E2B/M2: (1) via the Internet, (2) mainly FD (disk) reports together with paper reports, and (3) mainly paper reports with FD reports attached.

From January 2006, access to all cases of suspected adverse drug reactions reported by companies has been possible on the homepage of the PMDA.

[http://www.info.pmda.go.jp/iyaku\\_anzen/anzen\\_index.html](http://www.info.pmda.go.jp/iyaku_anzen/anzen_index.html)

#### **4.2 Drug and Medical Device Safety Information Reporting System by Medical Personnel**

This is a MHLW reporting system that directly collects safety information from

health professionals. Because of the need for collection of further information required for post-marketing product safety strategies, the limitation on reporting facilities was eliminated in July 1997. This system has been expanded and revised to include all medical institutions and pharmacies, and the reporting format has been simplified in order to further increase the number of reports from physicians, dentists, and pharmacists. Furthermore, the need of report as the duty of medical personnel was specified in the Pharmaceutical Affairs Law in July 2003.

\* The Pharmaceutical Affairs Law revised on June 14, 2006 (Law No. 69 to be enforced in 2009) also requests the registered marketing authorization holder to report safety information.

The information subject to reporting includes adverse reactions associated with the use of prescription medicines, over-the-counter drugs, medical devices, etc. with the exception of mild, well-known adverse events, even though a causal relationship with the drug concerned is unclear.

When drugs and related products require especially intensive investigation and collection of information, the MHLW selects medical institutions and, if necessary, performs "early post-marketing phase safety information collection program (fixed-point survey)" in collaboration with them.

#### 4.3 WHO International Drug Monitoring Program

Because of the necessity of safety measures to be implemented for drugs on an international level in view of the deformation scandal caused by thalidomide in 1961, 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.

#### 5. PERIODIC INFECTION REPORTS FOR BIOLOGICAL PRODUCTS

With the revision of the Pharmaceutical Affairs Law in July 2002, drugs manufactured from materials derived from humans or other living organisms (excluding plants) that require caution in terms of public health and hygiene are designated as biological products by the MHLW, as a lesion from

incidents of AIDS infection and Creutzfeldt-Jacob disease due to contaminated blood coagulation factors. From July 30, 2003, the system of periodic infection reports was introduced by which manufacturers of such biological products must evaluate their products based on findings obtained from the latest reports on infections caused by raw materials of the products and report the results every 6 months to the Minister (Article 68-8 of the Pharmaceutical Affairs Law).

#### 6. REEXAMINATION SYSTEM (ARTICLE 14-4 OF THE PHARMACEUTICAL AFFAIRS LAW)

The reexamination system is aimed at reconfirmation of the clinical usefulness of drugs by performing GPSP or GVP as one aspect of PMS, through collecting information on the efficacy and safety of the drug during a specified period of time after approval. This system was commenced in April 1980. Based on the revision of October 1993, the reexamination period for orphan drugs was extended to a maximum of 10 years.

There are limitations on the quantity and quality of data submitted for review at the time of approval of a new drug. Examples of such limitations include relatively small numbers of subjects in clinical studies performed prior to approval, relatively short

use data of the drug, and lack of experience using the drug under diverse conditions such as concomitant medication, complications, and age. There are limitations on confirmation of all of these aspects before approval.

It is, therefore, obligatory for manufacturing/marketing companies to perform postmarketing surveillance of their drugs after approval in order to determine if any problems have arisen with efficacy when the drug is used in actual practice, or to see if the level of efficacy has not been changed by factors such as dosage, duration of administration, complications or concomitant medication. In terms of safety, any marked increase in the incidence of ADRs and changes in the incidence of ADRs due to factors such as dosage, duration of administration, complications, or concomitant medication should be detected and assessed.

When the revised Pharmaceutical Affairs Law was enforced from April 1997, the surveillance and studies required for reexamination applications must be performed in compliance with the GPMSP, GCP or GLP depending on their objective. It is also obligatory to prepare application data in accordance with these standards. Based on the revision of the Law in April 2005, the GPMSP has been abolished and replaced with the GPSP and GVP.

## 6.1 Designation for Reexamination of Drugs

The drugs subject to reexamination include products designated by the MHLW at the time of marketing approval as drugs with, for example, active ingredients, quantities of ingredients, dosage and administration, and/or indications that are distinctly different from drugs that have already been approved (Article 14-4 of the Law).

The timing when these drugs should be reexamined is designated by the MHLW at the time of their approval as new drugs. The times that reexaminations should generally be conducted for specific products are given below.

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

- Orphan drugs

### (2) Reexamination 8 years after the date of approval:

- Drugs containing new active ingredients

### (3) Reexamination 6 years after the date of approval:

- New prescription combination drugs
- Drugs with new routes of administration

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

- Drugs with new indications
- Drugs with new dosages

The reexamination period for drugs with new active ingredients was extended from 6 years to 8 years based on Notification No. 0401001 of the PFSB dated April 1, 2007.

When pharmacoepidemiological surveys or clinical studies for setting pediatric doses performed, the study period can be prolonged before completion of the reexamination period as required (maximum reexamination period: 10 years).

## **6.2 Periodic Safety Reports (Article 63 of the Enforcement Regulations of the Law)**

On the basis of agreements at the ICH concerning periodic safety update report (PSUR) system, however, a "periodic safety report system" was enacted into law at the time of revision to the Pharmaceutical Affairs Law in April 1997.

As the base date for the reporting period of these reports, the concept of the international birth date in the PSUR system was introduced. Based on this concept, the date designated by the MHLW at the time of approval is established as the base date. The frequency of reports is every 6 months during the first 2 years from this base date. Thereafter, reports are to be submitted once each year during the remaining period of reexamination. The drugs for which these reports are applicable include prescription medicines designated for reexamination

(medical devices are subject to annual reporting as previously). In the event that a drug is marketed in a foreign country, reports must specify any adverse drug reactions that appeared in that country and information about any regulatory measures adopted. In addition, when PSUR prepared by foreign companies should be appended to the Japanese Periodic Safety Report together with the information obtained in drug use-results survey in the section "Future Safety Measures Planned on the Basis of Surveillance Results" in the Periodic Safety Report, and submitted, or the contents of the PSUR should be compiled and incorporated into the Japanese Periodic Safety Report and submitted. Either method is acceptable. A summary of the report items to be submitted includes the following:

- Period of the survey
- Number of cases surveyed
- Quantity of product shipped
- Status of implementation of drug use-results survey
- Summary of the surveillance results and analysis of the data
- Incidence of adverse drug reactions classified by type
- A list of cases in which adverse drug reactions occurred
- Measures adopted to ensure proper product use such as revisions of the precautions

- Package inserts
- Future safety measures planned on the basis of surveillance results

### 6.3 Data Required for Reexamination Applications and Reexamination Procedures

Post-marketing surveillance to acquire data required for reexamination applications, including drug use-results surveys, specified drug-use surveys, and post-marketing clinical trials, must be implemented in accordance with the GPSP. The data must also be collected and prepared in accordance with these standards (post-marketing clinical trials must be conducted also in compliance with the GCP).

Applications for reexamination must be completed within 3 months from the time of the designated base date. The data submitted and organization of this data should generally be as described below, with a focus on data from specified drug-use surveys and post-marketing clinical trials of the drug concerned in the application. In addition, for any other research data acquired after drug approval related to indications and/or safety of the drug concerned, a Periodic Safety Report submitted near the date of the reexamination application should be attached.

#### (1) Summary of data for reexamination

#### applications

The data should include a summary of the drug specified in the application; specific details up to the time of reexamination application including the changes in quantity and value of product shipped and the estimated number of patients who used the drug, the status of approval and sales overseas; summary of post-marketing surveillance; information about safety and efficacy; and references.

#### (2) Data Attached to Reexamination Applications

This data should include summary of drug use-results surveys; specified drug-use survey reports; post-marketing clinical trial reports; data from patients who have developed adverse drug reactions or infections; data from research reports; reports of specific measures adopted in Japan and overseas; and reports of serious adverse drug reactions.

#### (3) Compliance survey data

This includes data from GPSP compliance reviews as well as data from GCP and/or GLP compliance reviews as required.

**(4) Reference data**

This includes, for example, case report forms used in drug use-results surveys, package inserts at the time of reexamination application, summaries of replies, review reports, a summary of the data at the time of product approval application (for Evaluation Committees), copies of approval forms, and a copy of periodic safety report submitted closest to the reexamination application.

Reexamination is based on submission of the above application data. [Fig. 15 \(Reexamination System\)](#) is a flow diagram of this reexamination process. After the application is received, the PMDA evaluates compliance with standards such as GPSP and conducts surveys on quality, efficacy, and safety. The application is next reviewed by the Department on Drugs of the PAFSC. Then, the MHLW issues an official report of the results of the examination. The results of these examinations are classified into one of the three approval categories shown below, and any required specific measures are adopted. Article 14 Paragraph 2 of the Pharmaceutical Affairs Law specifies three reasons for refusal of approval. These include cases where (1) the indications of the drug stated in the application have not been demonstrated; (2) the drug exhibits prominent harmful effects that outweigh any

target indications, thus rendering the product not useful; and (3) the drug is judged to be markedly inappropriate with respect to public health and hygiene because of its characteristics or quality.

**\* Designated Classifications**

- [I] Approval refused (manufacturing and marketing suspended, approval revoked)
- [II] Changes in approval (modifications in approved items as directed)
- [III] Approved (as per application for reexamination)

**7. REEVALUATION SYSTEM (ARTICLE 14-5 OF THE PAL)**

The reevaluation of drugs is a system whereby the efficacy and safety of a drug, which has already been approved, is reconsidered on the basis of the current status of medical and pharmaceutical sciences. This system was initiated in December 1971 on the basis of administrative guidance. From January 1985, reevaluations were based on the Pharmaceutical Affairs Law, and the new reevaluation system came into effect from May 1988.

**New Reevaluation System:**

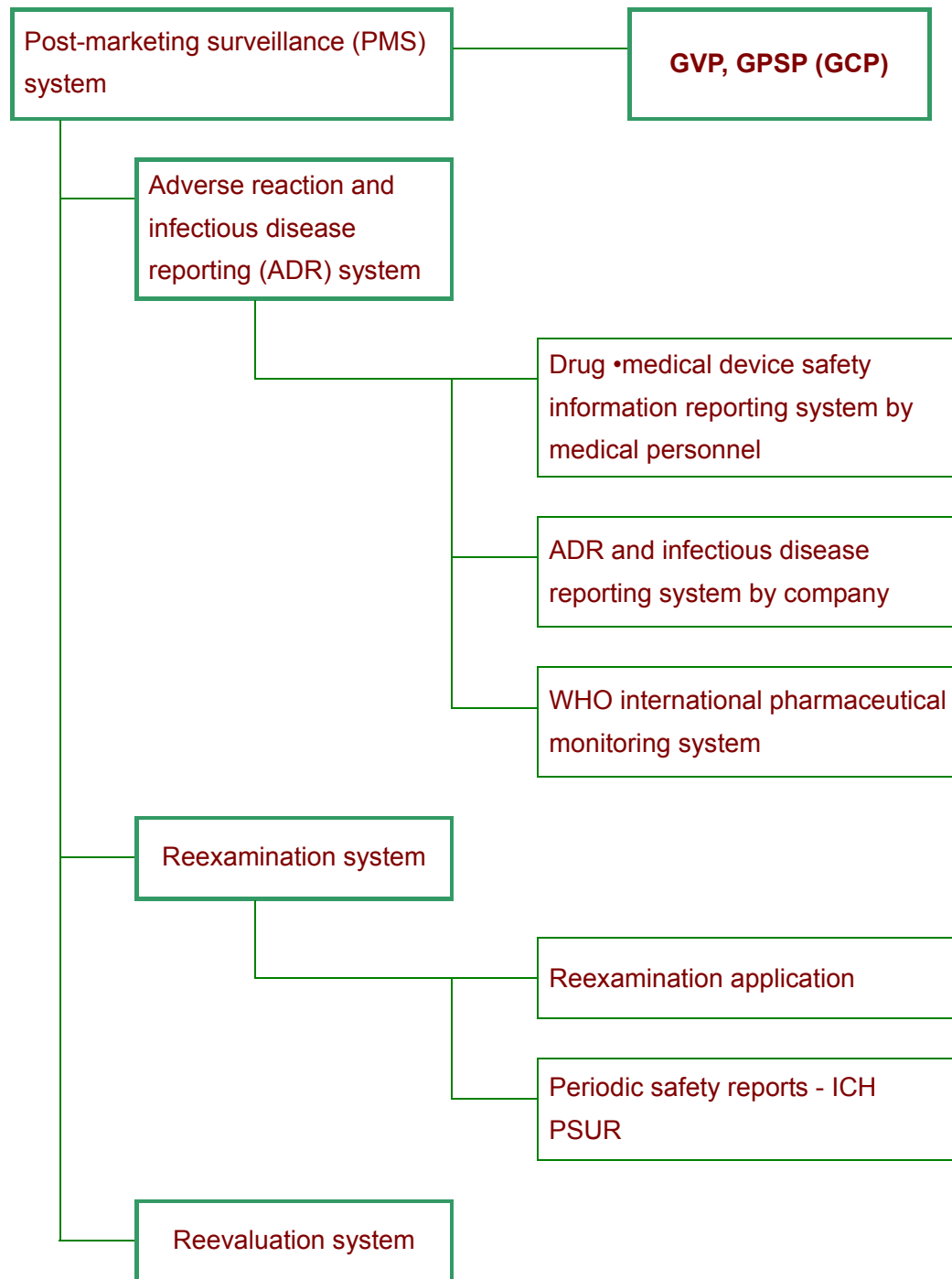
This new reevaluation system aimed at reevaluations of the efficacy and safety of all prescription drugs was started in May 1988. These reevaluations are at first performed by means of a review by the PAFSC. When the Council's decision requires further literature surveys by the manufacturers, they are required to perform such surveys according to the provisions of the Pharmaceutical Affairs Law ([Fig 16. Reevaluation System](#)).

The new reevaluations were designated from February 1990.

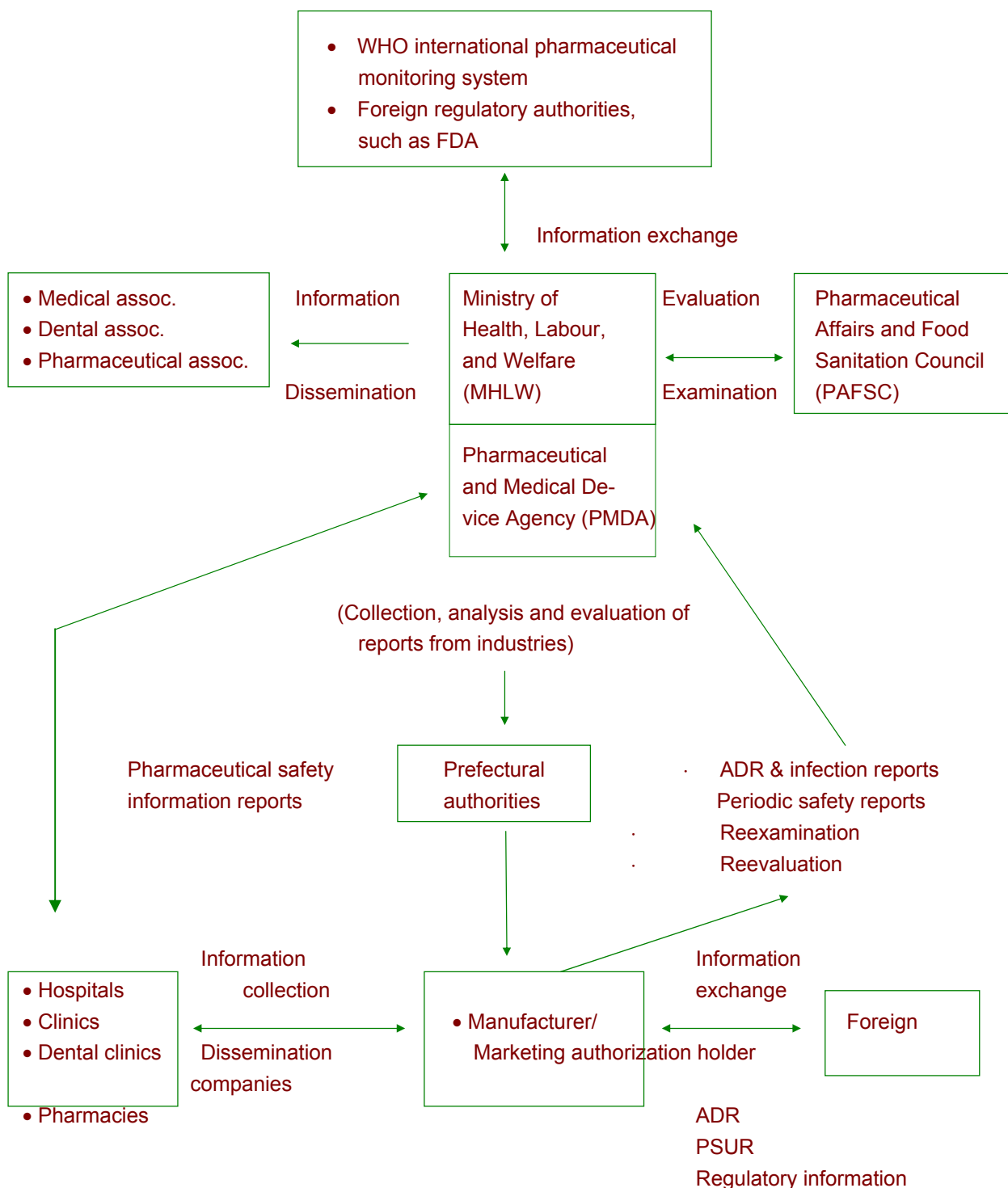
The MHLW has implemented various measures related to generic drugs. In the final report of the Council on the Pharmaceutical Sector in the 21st Century issued on May 28, 1993, it was suggested that manufacturing control and quality control must be thoroughly implemented for all products including original drugs. For this purpose the dissolution test was proposed as a routine verification method. In February 1997, "quality reevaluation" was started, and dissolution test conditions and specifications were set for original drugs that had no specified dissolution test. This step was intended to assure the quality of generic drugs by confirming their equivalence to the original products.

Thereafter, a notification entitled "Guidelines for Bioequivalence Studies on Generic Drugs" was issued in December 22, 1997 and partially revised on May 31, 2001 (Notification No. 786 of the Evaluation and Licensing Division, PFSB) and on November 24, 2006 (Notification No. 1124004 of the Evaluation and Licensing Division, PFSB) to guarantee the therapeutic equivalence of generic drugs to the original drugs.

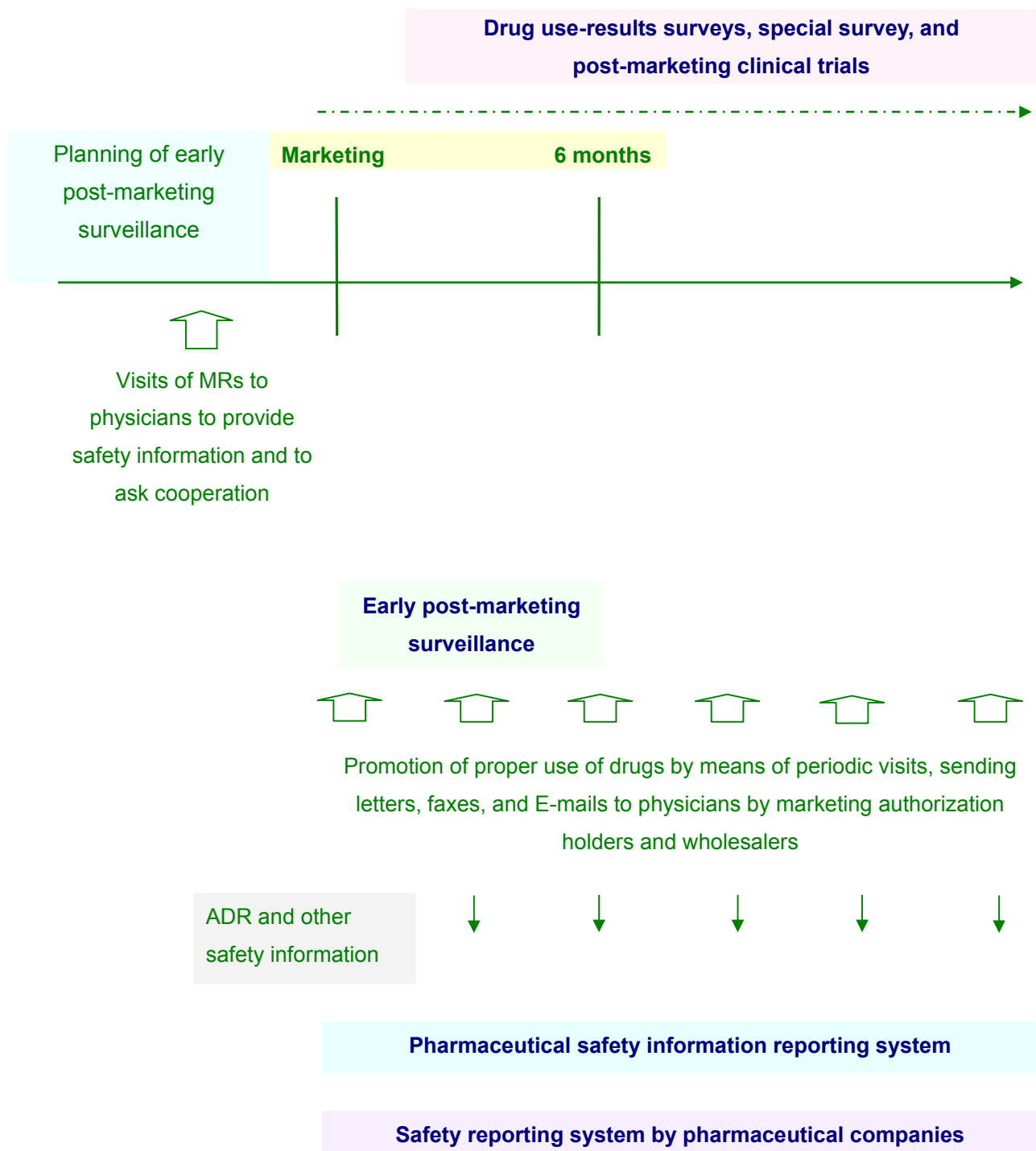
For products with dissolution tests established after completion of quality reevaluation, "official dissolution tests" were included in the third section of the Japanese Pharmaceutical Codex, which was published on March 23, 1999.



**Fig. 12 Pharmaceutical Post-marketing Surveillance System**

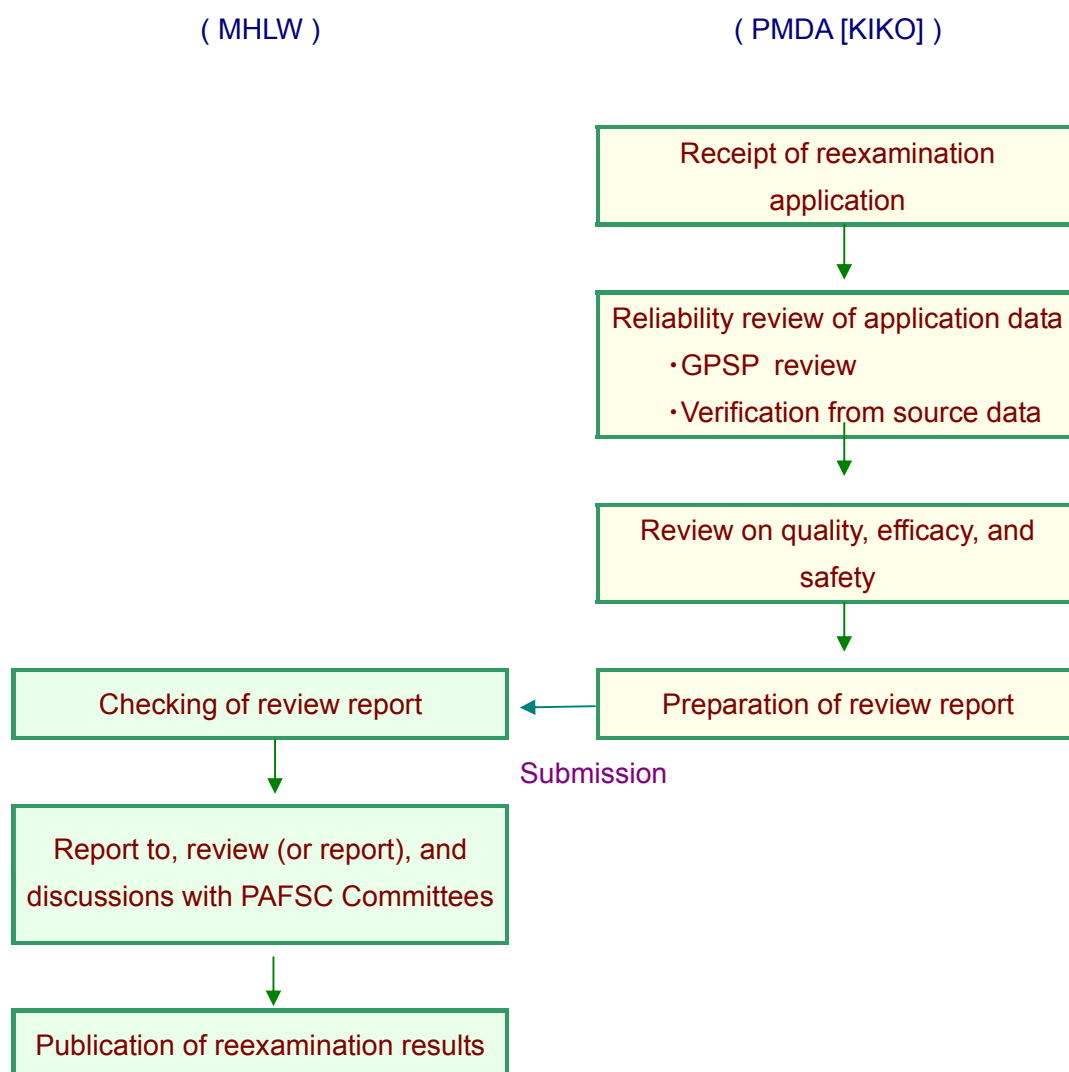


**Fig. 13 Collection and Reporting of Pharmaceutical Safety Information**

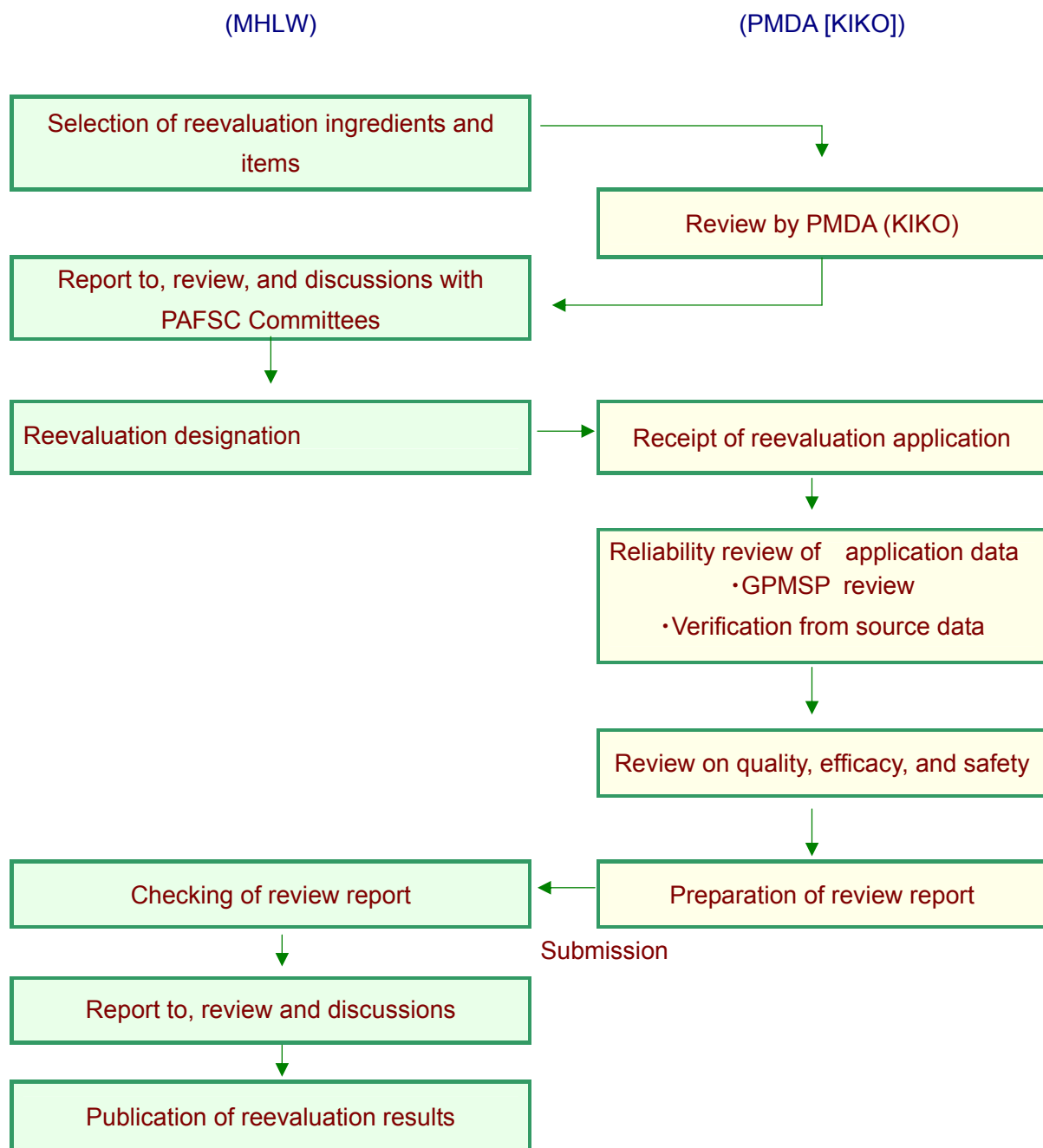


**Fig. 14 Post-marketing Collection and Reporting of Pharmaceutical Safety**

## Information



**Fig. 15 Reexamination System**



**Fig. 16 Reevaluation System**

## CHAPTER 5

### Supply and Dissemination of Drug Information

Marketing authorization holders of drugs must collect and examine information on proper use of drugs such as information on drug efficacy, safety and quality, and supply this information to medical institutions as specified in the Pharmaceutical Affairs Law. For this purpose, drug marketing authorization holders should prepare standard operating procedures based on the provisions in the GVP ordinance and endeavor to establish a comprehensive system for the supply and dissemination of information on proper and safe use of drugs.

#### 1. PACKAGE INSERTS

The most basic tool for supplying information on drugs to health professionals is package inserts, and the contents of package inserts for prescription drugs have been specified by the Pharmaceutical Affairs Law. These package inserts are public documents that pharmaceutical marketing

authorization holders are obliged to prepare for the purpose of supplying to physicians, dentists and pharmacists the information necessary to assure the safety of patients administered the drug and to promote the proper use of the drug concerned based on the provisions of the Pharmaceutical Affairs Law. The Law specifies items which must be included in the package inserts, points to consider when preparing the package inserts and items which are prohibited in package inserts. It also specifies penalties for not complying with these provisions and for including false or exaggerated information in package inserts. The MHLW has also issued notifications that provide guidelines on the actual items to be included, order of their inclusion, and preparation of package inserts, as well as guidelines on the preparation of Precautions for package inserts. Important information on adverse reactions, etc. obtained and evaluated in post-marketing surveillance on product safety must be reflected in package inserts. Because of the limitations on space and the amount of information that can be presented in package inserts, manufacturers and marketing authorization holders may prepare various types of information to supplement the package inserts.

The necessity of a complete reconsideration of package inserts was pointed out in the final report of the Council

on 21st Century Pharmaceuticals entitled "Proper Use of Drugs in Future Health Care and the Role of the Regulatory Authorities" in May 1993, and in the interim report of the Study Committee on Measures to Promote Appropriate Use of Drugs in July 1995. At about the same time, the Sorivudine incident involving a very severe adverse reaction caused by the interaction of this antiviral agent and an anticancer drug occurred, and the MHW (currently MHLW), health professionals and pharmaceutical companies considered emergency measures to assure proper supply of information on drug safety, mainly related to interactions (Notification No. 999 of PAB and Notice No. 1445 of the Japan Pharmaceutical Manufacturers Association).

To cope with this problem, the MHW (currently MHLW) established three study groups on the revision of pharmaceutical package inserts, which completed their work and submitted reports in May 1996. Based on these reports, guidelines for package inserts and for Precautions were completely revised, and the following three notifications were issued in April 1997:

- (1) Guidelines for Package Inserts for Prescription Drugs (Notification No. 606 of PAB dated April 25, 1997).
- (2) Guidelines for Package Inserts for Prescription Drugs (Notification No. 59 of the Safety Division, PAB dated April 25, 1997).

- (3) Guidelines for Precautions for Prescription Drugs (Notification No. 607 of PAB dated April 25, 1997).

The main points in these notifications are as follows:

- Package inserts have been revised to make them easier to understand and to use by health professionals.
- The purpose is to supply scientifically accurate information.

Two notifications concerning package inserts for biological products were issued in May 2003: "Entries in Package Inserts for Biological Products" (Notification No. 0515005 of the PFSB dated May 15, 2003) and the "Guidelines for Entries in Package Inserts of Biological Products" (Notification No. 0520004 of the Safety Division, PFSB dated May 20, 2003). These notifications came into effect from July 2003.

Labeling was changed with the amendment of the Pharmaceutical Affairs Law in April 2005. "Manufacturer and importer" was changed to "marketing authorization holder."

"Drug requiring a prescription" was changed to "prescription drug" based on Notifications No. 0331008 of the Compliance and Narcotics Division, PFSB dated March 31, 2005, "Handling of Labeling of Drugs in the Amended Pharmaceutical Affairs Law" and No. 0210001 of the PFSB dated February 2005 "Designation of prescription

drugs." "Caution: Use under prescription from a physician, etc." is entered.

To improve the supply of information on generic drugs, Notification No. 0324006 of the Safety Division, PFSB dated March 24, 2006 was issued. This notification specifies the entry of bioequivalence study data in the "Pharmacokinetics" section of the package insert.

## 1.1 Summary of the New Guidelines

### 1) Coordination of formats

- (1) Items considered important must be entered close to the beginning of the package inserts.
- (2) "Warnings" and "Contraindications" must be entered at the beginning of the package inserts. Package inserts with "Warnings" have a red bracket-shaped band printed in the right margin. The "Warnings" must be in red letters encased in red and "Contraindications" must be encased in red.
- (3) Overlapping entries under two or more headings should be avoided, in principle.
- (4) The size of the package insert should be within four A4 size pages, in principle.

### 2) Improved contents

- (1) The "Precautions" must follow

"Indications" and "Dosage and Administration" in that order.

- (2) The incidence of adverse reactions must be given in numerical values with appropriate classifications whenever possible.
- (3) "Adverse Reactions," "Interactions" etc. must be as clearly visible as possible using tables, etc.
- (4) The former headings "Drug Characteristics and Development Process" and "Nonclinical Studies" have been abolished, and the required information must be supplied in a scientifically accurate manner by improvement of the information given under such headings as "Clinical Pharmacology" and "Pharmacokinetics."

### 3) Addition of new headings

- (1) The new heading "Conditions for Approval" has been added.
- (2) This heading consists of a list of the dates of entry in the NHI Reimbursement Price List, initial marketing in Japan, publication of the latest reexamination and/or reevaluation results, latest approval of (additional) indications, the international birth date, etc.

## 1.2 Headings and Their Sequence in

### Package Inserts

The actual headings and the sequence in which they are entered in package inserts for prescription drugs are shown below. Refer to [Fig. 17 \(Layout of a Package Insert for a Prescription Drug \(with "Warning"\)\)](#) for the layout.

All of the headings should be included whenever possible, but when no appropriate information is available, the heading may be omitted.

For details of the contents of the headings in package inserts, refer to the three MHW notifications mentioned above (Notifications No. 606 and 607 of the PAB and Notification No. 59 of the Safety Division, PAB) and notifications related to biological products (Notification No. 0515005 of the PFSB and Notification No. 0520004 of the Safety Division, PFSB). For changes in entries in package inserts with the enforcement of the amended Pharmaceutical Affairs Law in April 2005, refer to Notification No. 133 of the Japan Pharmaceutical Manufacturers Association (JPMA) dated March 4, 2005 and Notification No. 0324006 of the Safety Division, PFSB dated March 24, 2006 concerning supply of information on generic drugs.

#### \* Headings and their Sequence in Package Inserts

1) Date of preparation and/or

revision(s) of the package insert

2) Standard Commodity Classification No. of Japan, etc.

- Standard Commodity Classification No. of Japan (SCCJ)
- Approval number
- Date of listing in the national health insurance (NHI) reimbursement price list
- Date of initial marketing in Japan
- Date(s) of latest reexamination
- Date(s) of latest reevaluation
- Date(s) of latest approval of additional indication(s)
- International birth date
- Storage, etc. (storage, expiration date, shelf-life, etc.)

3) Therapeutic category

4) Regulatory classification (specified biological product, biological product, poisonous substance, deleterious substance, habit-forming drug, prescription drug, etc.)

5) Name(s) [brand name, non-proprietary name, Japanese Accepted Name (JAN), etc.]

- ◆ At the beginning of the package insert

Precautions concerning specified biological products (encased in black)

6) Warning(s) (in red letters encased in

- red)
- 7) Contraindications (in black letters encased in red)
    - (1) Contraindications
    - (2) Relative contraindications
  - 8) Composition and description
    - (1) Composition
    - (2) Product description
  - 9) Indication(s)
    - (1) Indication(s)
    - (2) Precautions related to Indications
  - 10) Dosage and administration
    - (1) Dosage and administration
    - (2) Precautions related to dosage and administration
  - 11) Precautions (refer to Notifications No. 606 of PAB, No. 59 of the Safety Division, PAB, No. 607 of PAB, No. 0515005 of PFSB, and No. 0520004 of the Safety Division, PFSB) (refer to Sections 1.3 and 1.5)
  - 12) Pharmacokinetics
  - 13) Clinical studies
  - 14) Clinical pharmacology
  - 15) Physicochemistry (active ingredient)
  - 16) Precautions for handling
  - 17) Conditions for approval
  - 18) Packaging
  - 19) References and reference requests
    - ◆ Information of drugs with limited

administration periods

- 20) Manufactured and/or marketed by:  
(name and address)

### 1.3 Precautions

The Precautions are prepared voluntarily by the manufacturer of the drug concerned or under the guidance of the MHLW based on the guidelines in the MHLW notifications listed previously. Information obtained from post-marketing drug use results (clinical experience) surveys, and foreign and domestic case reports and research reports is collected and evaluated, and the Precautions are revised to incorporate the latest data as required. Revisions based on the results of reexaminations and/or reevaluations are undertaken as required.

The headings\* used in the Precautions are as follows. Refer to the following MHW notifications: (1) No. 606 of PAB, (2) No. 59 of the Safety Division, PAB and (3) No. 607 of PAB, and notifications related to biological products (Notification No. 0515005 of the PFSB and Notification No. 0520004 of the Safety Division, PFSB) for details concerning the contents of Precautions.

#### \* Headings used with precautions

- 1) "Warning" (in red letters and encased in red at the beginning of "Precautions")
- 2) "Contraindications" (in black letters

<p>and encased in red following "Warning" in principle. However, at the beginning of the Precautions when there is no "Warning")</p> <p>(1) Contraindications ("This product is contraindicated in the following patients.")</p> <p>(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.")</p> <p>3) Precautions related to indications (In the event of such precautions, they are entered under the heading "Precautions" following "Indications" in the package insert.</p> <p>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.</p> <p>5) Careful administration ("<i>This product should be administered with care to the following patients.</i>")</p> <p>6) Important precautions</p> <p>7) Drug interactions</p> <p>(1) Contraindications for coadministration ("<i>This product should not be coadministered</i></p>	<p><i>with the following drugs.</i>") (in black letters and encased in red, with simple explanation provided under "Contraindications" above.)</p> <p>(2) Precautions for coadministration</p> <p>The MHW issued an office communication stressing that the Drug Interaction section must be based on the most recent scientific findings [office communication dated December 25, 2000 as a supplement of Notification No. 607 of PAB, MHW].</p> <p>8) Adverse reactions (incidence shown in numerical values whenever possible)</p> <p>* A key to the frequency of adverse reactions should be provided at the beginning.</p> <p>(1) Clinically significant adverse reactions</p> <p>(2) Other adverse reactions</p> <p>9) Use in the elderly</p> <p>10) Use during pregnancy, delivery, or lactation</p> <p>11) Pediatric use (low birth weight infants, newborns, infants, small children, children)</p> <div data-bbox="874 1850 1369 1899"> <p>Reference: Age classification for</p> </div>
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**pediatric use (basic standards)**

- Children: under 15 years of age
- Small children: under 7 years of age
- Infants: under 1 year of age
- Newborns (neonates): under 4 weeks of age
- Low birth weight infants (premature infants): body weight of less than 2,500 g (according to the WHO recommendation)

- 12) Effects on laboratory tests
- 13) Overdosage
- 14) Precautions concerning use
- 15) Other precautions (toxicity obtained in animal studies requiring particular caution, etc.)

#### 1.4 Labeling of Excipients

When excipients such as stabilizers, preservatives, and vehicles are used in products listed in the Japan Pharmacopoeia (JP), in the Minimum Requirements for Biological Products or in the Radiopharmaceutical Standards, the names and quantities of these excipients must be included in the relevant package inserts or on the containers or wrappers.

Since safety problems considered to be caused by excipients have appeared, the names and quantities of excipients specified

in Notification No. 853 of the PAB dated October 10, 1988 must be included in the relevant package inserts or, if necessary, on the containers or wrappers of all prescription drugs since October 1988.

The labeling of excipients in non-prescription drugs is the same as that for prescription drugs based on a voluntary agreement of the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ) (FPMAJ Notification No. 165 dated March 27, 1991; Office Communication of the Safety Division, PAB dated June 3, 1991).

All ingredients of both prescription and non-prescription drugs must be included in the package insert based on a voluntary agreement of the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ) (FPMAJ Notification No. 170 dated March 13, 2002) because of the social responsibility to disclose as much information as possible related to drugs as life-related products. For non-prescription drugs, the names of excipients, including designated ingredients entered voluntarily, must be labeled on the outer container or the equivalent (the above FPMAJ Notification No. 165 is canceled by the voluntary agreement concerned). The above Office Communication of the Safety Division, PAB dated June 3, 1991 was canceled by Notification No. 0409001 of the Safety

Division, PFSB dated April 9, 2002.

## 1.5 Entries for Biological Products

### Specified biological products

- 1) Regulatory classification  
Specified biological products
- 2) Name  
For genetic recombinants, "recombinant" is included immediately after the non-proprietary name
- 3) Beginning of the package insert (before the "Warning")
  - (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. Active measures by related companies were requested in Notification No. 0602009 of the PFSB dated June 2, 2004. Specifications were also given for brand names of combination drugs and heparin products (injections) and for handling labeling of solvents attached to injections (Notification No. 0922001 of the Evaluation and Licensing Division and the Safety Division, PFSB dated September 22, 2008).

The application fee for revising brand name was lowered in April 2005. The timing of brand name revision for prevention of medical accident is the time for NHI price listing twice a year. As a result, measures have been completed for a total of about 5,400 products as of the NHI price listing in September 2009.

## 1.7 Information on Package Inserts in English

Information on package inserts in English of some drugs prepared by marketing authorization holders in Japan has appeared on the JPMA homepage basically once a year since 2001.

<http://www.e-search.ne.jp/~jpr/>

## 2. INFORMATION TO SUPPLEMENT PACKAGE INSERTS

Because of space limitations in Japanese package inserts, the following main media are also used to provide more detailed information about pharmaceutical products.

### 2.1 Outline of Prescription Pharmaceutical Product Information

The Outline of Prescription Pharmaceutical Product Information prepared by manufacturers and marketing authorization holders is intended to provide accurate and appropriate information to health professionals to assure proper use of their drugs.

This document is prepared on the basis of the Guidelines for Preparation of Outlines of Prescription Pharmaceutical Product Information published by the Japan Pharmaceutical Manufacturers Association (JPMA) in April 2009, but the contents also follow the MHLW notification on the Guidelines for Preparation of Package Inserts. The document must also comply with the Promotion Code.

New drugs approved during or after October 2001 are marked with a logo indicating that the drug is under early post-marketing surveillance for a period of

time as specified in the labeling (refer to Chapter 4, 1. GVP).

## 2.2 Pharmaceutical Interview Forms (IF)

Pharmaceutical Interview Forms also serve to supplement package inserts. The IF basically specifies questions to be asked by pharmacists to obtain detailed information on pharmaceutical products in interviews with pharmaceutical company medical representatives (MRs). However, in order to reduce the burden on physicians and MR, the replies (detailed information) to the questions are already entered, and the IF are supplied to health professionals as material to be used in explanations and discussions concerning the product.

The Japanese Association of Hospital Pharmacists published new preparation guidelines in September 2008, and interview forms (IF) are being prepared in the new format for new drugs approved from April 2009.

## 3. SUPPLY AND DISSEMINATION OF SAFETY MANAGEMENT INFORMATION

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

Safety management information reported to the MHLW, etc. is evaluated by the PMDA after hearing opinions of experts. After the Committee on Safety of Drugs of the Council on Drugs and Food Sanitation approves the results, the necessary administrative measures based on the evaluation results are taken. These administrative measures include the following:

- Discontinuation of manufacturing or marketing of drugs, and recall of products
- Cancellation of approval
- Partial changes in approved items related to indications, dosage and administration, etc.
- Instructions for distribution of emergency safety information
- Instructions for distribution of safety flash reports (so-called blue letters)
- Revision of Precautions
- Changes in designation as controlled substances such as poisons, narcotics, or prescription drugs, or changes of regulatory category
- Instructions to companies to perform surveillance or research

Among these measures, extremely urgent and important safety-related information to warn the public and healthcare professionals of safety concerns or to restrict the use of products will be distributed as emergency

safety information, and information necessary for improving their precautions on safety concerns earlier than the conventional approach through package inserts revision will be distributed as safety flash reports.

In addition to emergency safety information and safety flash reports, other information including notices of revision of Precautions is also distributed. but this the most frequently used administrative measure.

In order to facilitate efficient revision of package inserts of drugs, a “Flowchart of standard procedures related to work on package inserts of drugs” has been specified in Office Communication of the Safety Division, PFSB dated February 10, 2010. This flowchart is posted on the webpage for supply of information on drugs and medical devices.

<http://www.info.pmda.go.jp/iyaku/file/h220210-001.pdf>

<http://www.info.pmda.go.jp/iyaku/file/h220210-002.pdf>

When the PMDA considers that an investigation of safety measures is necessary as a result of screening (primary and secondary) of data collected by the PMDA, a basic time schedule in weekly units is prepared in which the PMDA first sends an inquiry to the company, the company submits its opinions, an interview consultation is held, a meeting of experts is convened (convened

about every 5 weeks), and measures (issuing of notifications, etc.) are taken. When the company considers that it is necessary to investigate safety measures, the same type of schedule is shown starting with a revision consultation from the company, holding an interview (face-to-face) consultation, convening a meeting of experts, and taking measures ([refer to Fig. 18](#)).

The PMDA receives applications for consultation from companies for not only revision of package inserts of individual drugs but also for promotion of proper use to prevent serious adverse drug reactions, treatment safety, and other measures to improve safety of drugs. Accurate advice and guidance are given to the companies, and this contributes not only to the improvement of the safety of individual drugs but also to improvement of the system for safety measures of the company.

Refer to the following PMDA web page for consultations on revision, etc. of package inserts applied for by companies and procedures for applications for other consultations.

<http://www.pmda.go.jp/operations/anzen/info/bunsyosoudan.html>

Media and procedures for provision and dissemination of safety management information include the obligation to prepare SOPs by drug marketing authorization holders based on the specifications in the

GVP Ordinance, and provision and dissemination of information based on these SOPs.

The main information media and information dissemination procedures are described below.

### 3.1 Distribution of Emergency Safety Information (Yellow Letters)

#### 1) Preparation criteria

Emergency safety information (“yellow letter”) is prepared by the marketing authorization holder on the basis of discussion with the MHLW and PMDA following an order or instruction of the MHLW, voluntary decision by the marketing authorization holder, or other requirements in cases where it is judged necessary to take the measures (2) below in for drawing people (patients) or physician’s emergent and specialized attention to safety-related matters and drug-use restriction in situations (1) as listed below. Guidelines for the preparation of such information were specified in Notification No. 0715-(1) of the Safety Division, PFSB dated July 15, 2011 and enforced from October 1, 2011 (Notification No.160 of the Safety Division, PAB dated October 2, 1989 was abolished).

##### (1) Situations

- Situations where cases of deaths, disabilities, events that may lead

death or disability, and difficult-to-treat conditions are reported by ADR reporting systems

- New safety-related problems such as the occurrence of unknown serious ADRs that apparently outweigh expected therapeutic benefits
- Regulatory measures taken overseas to resolve and prevent emergency and significant safety issues
- Safety issues considered to remain unresolved despite the dissemination of urgent safety information (“yellow letter”) or safety flash reports (“blue letter”)

##### (2) Measures to be implemented

- Creation of “warning” box or addition of “warning notice”
- Creation or addition of contraindications
- Revision of precautions accompanying the implementation of new safety measures (e.g., laboratory tests)
- Changes in indications, dosage, method of administration, or method of use for safety-related reasons
- Regulatory measures (discontinuation or suspension of marketing or cancellation of approval) for safety-related reasons,

- accompanying a recall of a drug
- Other measures for the prevention or early detection of ADRs concerned

## 2) Format and content

Emergency safety information must be prepared in the style and format specified in the guidelines, using yellow paper, etc. for easy identification of important information by the public (patients) and medical personnel.

## 3) Methods of information dissemination

- (1) The staff (MRs) [refer to Appendix] in charge of drug information of the marketing authorization holder directly distributes the information to physicians, pharmacists, and other health professionals in medical institutions. The dissemination is required to be efficiently carried out by using multiple communication tools such as direct handout, direct mail, fax, and e-mail to achieve prompt and widespread alert for safety concerns. PMDA distributes urgent safety information, revisions to package inserts, etc. to medical personnel who have registered their e-mail address with the Agency via PMDA medi-navi.
- (2) The marketing authorization holder must transfer safety information to medical or pharmaceutical organizations and

requests them to cooperate in collecting and disseminating information through efficient communication tools such as their websites. If the marketing authorization holder knows patient groups that use the products concerned, the safety information should be distributed to such groups.

## 4) Distribution

The distribution of emergency safety information to medical institutions must be completed within 1 month of receipt of the government order, according to the plan and method of distribution. The marketing authorization holder must submit a safety information dissemination report to the Director of the Safety Division of PFSB when distribution has been completed as specified by the office.

### 3.2 Safety Flash Report (Blue Letters)

#### 1) Preparation criteria

The safety flash report ("blue letter") is prepared by the marketing authorization holder on the basis of discussion with the MHLW and PMDA following an order or instruction from the MHLW, voluntary decision by the marketing authorization holder, or other requirements in cases where it is judged necessary to take the measures specified in Section 3.1: 1-(2) above for drawing physician's urgent and

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<p>specialized attention to safety-related matters and measures necessary for optimal drug use (e.g., efficient method of notification, laboratory tests, etc.) similarly to the procedures for handling important safety information as noted above but more promptly than routine revisions of “precautions for use” with an intent to prevent the recurrence and spread of health-related harm or injury to the public. Practices for disseminating such information are specified in Notification No. 0715-(1) of the Safety Division, PFSB dated July 15, 2011.</p>	<p>PMDA distributes safety flash reports, revisions of package inserts, etc. to medical personnel who have registered their e-mail address with the Agency via PMDA medi-navi.</p>
<p>2) Format and content</p> <p>Safety flash reports must be prepared in the style and format specified in the guidelines, using blue paper, etc. Information contained in the reports may be required to be arranged for the public (patients) depending on the usage in practice.</p>	<p>(2) The marketing authorization holder must transfer safety information to medical or pharmaceutical organizations, as appropriate, and requests them to cooperate in collecting and disseminating information through efficient communication tools such as their journals. If the marketing authorization holder knows patient groups that use products concerned, safety information should be distributed to such groups, as appropriate.</p>
<p>3) Method of information dissemination</p> <p>(1) The staff (MRs) in charge of the drug information of the marketing authorization holder are to efficiently distribute the information to physicians, pharmacists, and other health professionals in medical institutions by using multiple communication tools such as direct handout, direct mail, fax, and e-mail to achieve prompt and widespread alert for safety concerns.</p>	<p>4) Distribution</p> <p>The distribution of safety flash reports to medical institutions must be completed within 1 month of receipt of the government order, according to the plan and method of distribution. The marketing authorization holder must submit a safety information dissemination report to the Director of the Safety Division of PFSB when distribution has been completed as specified by the office.</p>

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### **3.3 Distribution of Information by 'Notices of Revision of Precautions'**

#### **1) Preparation criteria**

- (1) Cases where the Director of the Safety Division of PFSB, MHLW orders or recommends revision of the Precautions or other sections of package insert based on the results of an investigation by the PMDA.
- (2) Cases where the manufacturer and marketing authorization holder voluntarily revises the Precautions (revisions are to be notified to the MHLW beforehand).

#### **2) Format and contents**

The paper must be not yellow or blue.

#### **3) Method of dissemination**

In the case of 1)-(1) above, MRs of the marketing authorization holder are to promptly distribute the notices to physicians, pharmacists, and other health professionals. PMDA distributes the notices of the Director of the Safety Division, PFSB, etc. to medical personnel who have registered their e-mail address with the Agency via PMDA medi-navi.

In the case of 1)-(2) above, the notices are to be distributed to health professionals, as required, as directed in 1)-(1) above.

#### **4) Dissemination**

The dissemination of the notices to medical institutions must be completed as soon as possible after receipt of the notification of the the Director of the Safety Division of PFSB or the decision to make a voluntary revision. Based on the instructions of the Safety Division for 1)-(1) above, the marketing authorization holder must submit a Notice of Change for items in the Precautions of the drug concerned to the PMDA.

### **3.4 Dissemination of Information for Drugs That Have Completed Reexamination or Reevaluation**

Once the reevaluation results and reexamination results are available, the marketing authorization holder of the drug concerned disseminated information by preparing a "Notice of Reevaluation Results" and "Notice of Reexamination Results" as required, which they distribute to medical institutions. The FPMAJ compiles all of the reevaluation results and publishes a "Notice of Prescription Drug Reevaluation Results" in the journals of the Japan Medical Association, Japan Dental Association, and Japan Pharmaceutical Association.

### **3.5 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 the manufacturer/marketing authorization holder, and ADR reports collected from or submitted by health professionals, the MHLW compiles commentaries and Notices of Revisions of Precautions concerning important ADRs. They are supplied in digest form as "Pharmaceuticals and Medical Devices Safety Information" to health professionals who submitted ADR reports, and also published in the media, on the PMDA Home Page (<http://www.info.pmda.go.jp/>), and in various publications such as the Journal of the Japan Medical Association and the Journal of the Japanese Association of Hospital Pharmacists. An English version is sent to WHO.

The digest was published bimonthly from June 1973 and then monthly from June 2001 (from Issue No. 167) (recently, 11 issues annually). The digest is available and regularly updated at the following website of the PMDA.

<http://www.info.pmda.go.jp/>

### **3.6 Dissemination of Information by Drug Safety Update**

The Society of Japanese Pharmacopoeia and the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ) have been jointly editing and publishing the Drug Safety Update (DSU), which includes information on ADRs of prescription drugs (revisions of the Precautions) under supervision of the MHLW since September 1992 (10 times per year) (published by the FPMAJ since Issue No. 128 dated April 2004). The journal is distributed by mail to medical institutions nationwide including approximately 10,000 hospitals, 90,000 clinics and 60,000 dental clinics, as well as about 70,000 pharmacies and dispensing facilities within one month after printing. The journal is available and regularly updated at the following website of the PMDA.

<http://www.info.pmda.go.jp/>

### **3.7 Commentaries on "Precautions" in Package Inserts of New Drugs**

Commentaries on "Precautions" in package Inserts of new drugs are prepared by the manufacturer/marketing authorization holder of drugs to provide the most basic safety information on new drugs. The manufacturer/marketing authorization holder must prepare easy-to-understand "commentaries" concerning the basis and

contents of Precautions, and their MRs distribute the commentaries to medical institutions before new drugs are used in medical practice in order to assure proper use of new drugs.

With the revisions of the guidelines for the preparation of package inserts and Precautions in April 1997, a guide for preparation of these commentaries was issued (Notification No. 88 of the Safety Division, PAB dated June 27, 1997). Thereafter, companies started to prepare commentaries on their new drugs. New drugs that are approved after October 2001 are marked with a logo indicating that the drug is subject to early post-marketing surveillance for such a period of time as specified in labeling (refer to Chapter 4, 1. GVP).

#### 4. ELECTRONIC INFORMATION DISSEMINATION

The MHLW received a report from its study group on policies to supply drug information to health professionals, etc. using the Internet and started operation of a "Drug Information System" to supply such information via the Internet at the end of May 1999 (currently PMDA Home Page, <http://www.info.pmda.go.jp/>).

The information supplied includes information regarding the proper use of

drugs, information on package inserts of prescription drugs, safety information disseminated by the MHLW, cases of suspected adverse reactions collected by the MHLW, as well as information on Dear Doctor Letters, drug guide for patients, the manual for handling disorders due to adverse drug reactions, drug approval applications, drug recalls, etc.

The marketing authorization holder is required to discuss the necessity for issuance and publication of "PMDA requests on the proper use of drugs" among official notices on the proper use of drugs, if ADRs due to drug use or those due to improper drug use do not decrease despite major revisions to labeling such as an issue or revisions of warnings and precautions. The marketing authorization holder is also required to determine the necessity of disseminating such information through print media, as appropriate.

With this system, package insert information for prescription drugs is provided in SGML (Standard Generalized Markup Language) format to facilitate downloading and processing of the information for various purposes. In addition, the MHLW provides all information in PDF (Portable Document File) format in view of the inherent convenience.

The supply of package insert information for non-prescription drugs was started from

March 2007 and supply of information on drug interview forms from May 2009.

## **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 PMSB of the MHLW issued notifications on August 12, 1999 on the type and format for non-prescriptions drugs to define items of information to be included in the +package insert, entry methods for Precautions, and information that should be included on the outer containers. The style and format of the description on the outer containers or wrappers were revised to assist the purchase of suitable drugs based on labeling and issued as a notification of PFSB on October 14, 2011. The old notification of PMSB dated August 12, 1999 was abolished accordingly.

Labeling requirements of excipients of non-prescription drugs are the same as those for prescription drugs according to a voluntary agreement of the JPMA (Notification No. 165 of the JPMA dated March 27, 1991) and Office Communication of the Safety Division, PAB dated June 3,

1991. Based on a voluntary agreement of the JPMA (Notification No. 170 of the JPMA dated March 13, 2002), all ingredients must be included in package inserts by March 31, 2004 and the names of excipients including voluntarily designated ingredients must be included on the outer container (or its equivalent).

Based on this voluntary agreement, Notification No. 165 of the JPMA was canceled and the Office Communication of the Safety Division, PAB dated June 3, 1991 was canceled by Notification No. 0409001 of the Safety Division, PFSB dated April 9, 2002.

For the background of labeling of drug excipients, refer to Section 1.4 on pharmaceutical excipients.

**Fig. 17 Layout of a Package Insert for a Prescription Drug (with “Warning”)**

Package inserts consist of specified headings in a specified order (Refer to 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.

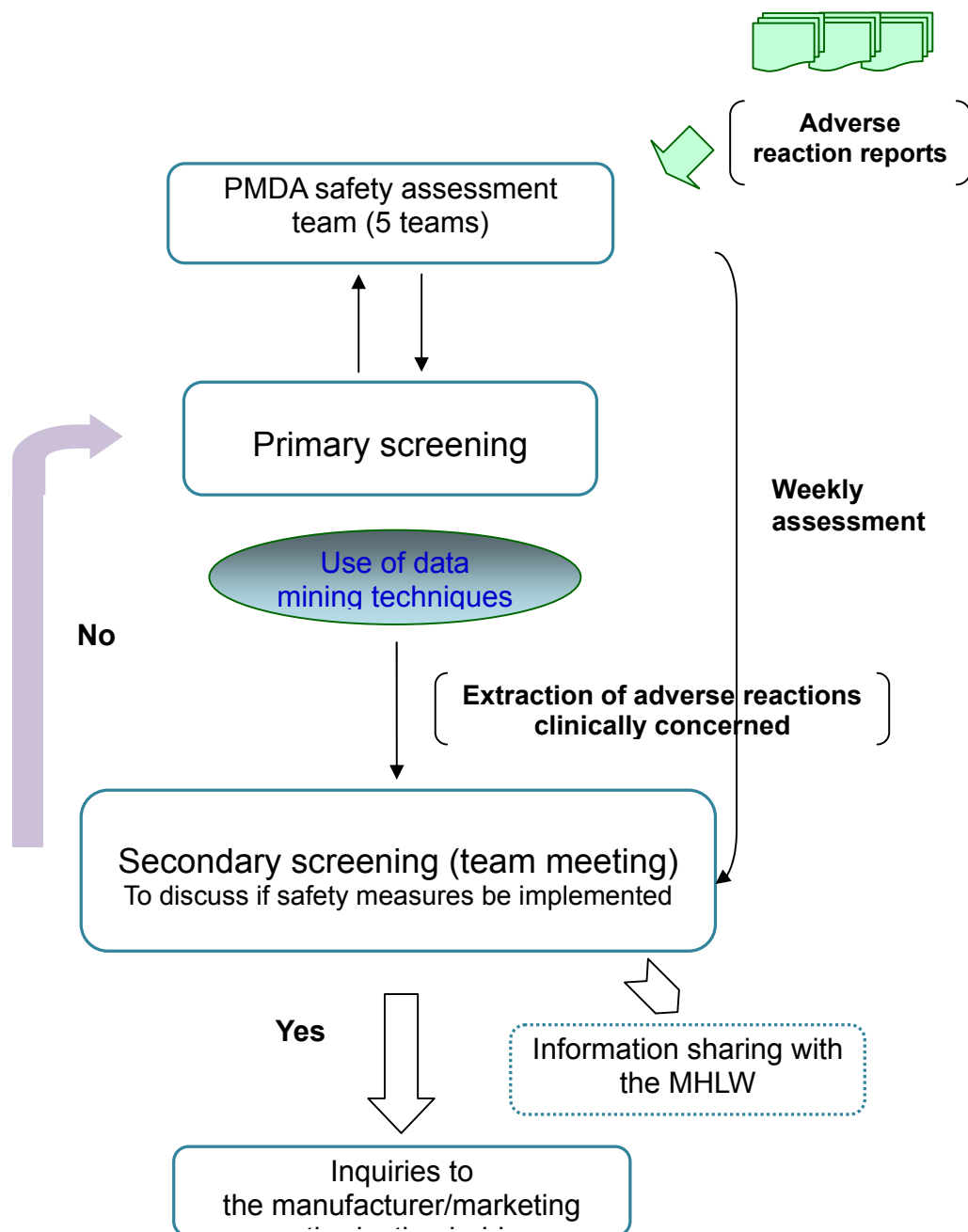
DATE OF PREPARATION AND/OR REVISION(S) OF THE PACKAGE INSERT	THERAPEUTIC CATEGORY	STANDARD COMMODITY CLASSIFICATION No. OF JAPAN
STORAGE, HANDLING, ETC.	BRAND NAME	APPROVAL NUMBER
REGULATORY CLASSIFICATION	NAME IN THE JAPANESE PHARMACOPOEIA, ETC.	DATE OF LISTING IN THE NHI REIMBURSEMENT
	NON-PROPRIETARY NAME	DATE OF INITIAL MARKETING IN JAPAN
	NAME IN ROMAN LETTERS	DATE OF LATEST REEXAMINATION OR REEVALUATION
		DATE OF LATEST APPROVAL OF INDICATION(S), ETC.

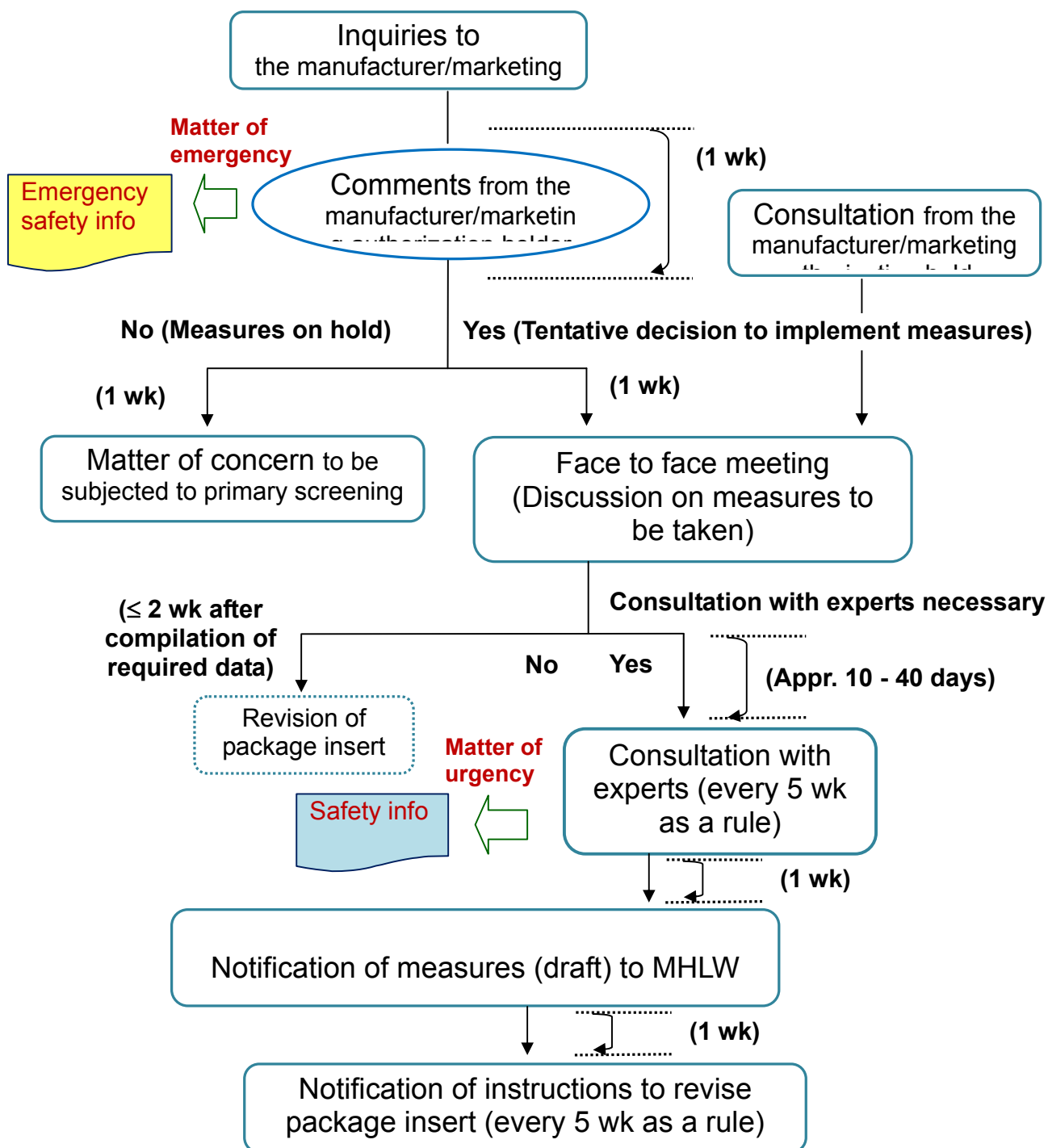
INFORMATION ON SPECIFIED BIOLOGICAL PRODUCTS WARNING(S) CONTRAINDICATIONS (RELATIVE CONTRAINDICATIONS) COMPOSITION AND DESCRIPTION INDICATION(S) PRECAUTIONS (RELATED TO INDICATIONS) DOSAGE AND ADMINISTRATION PRECAUTIONS (RELATED TO DOSAGE AND ADMINISTRATION) PRECAUTIONS CAREFUL ADMINISTRATION IMPORTANT PRECAUTION(S) DRUG INTERACTIONS CONTRAINDICATIONS FOR COADMINISTRATION PRECAUTIONS FOR COADMINISTRATION ADVERSE REACTIONS CLINICALLY SIGNIFICANT ADVERSE REACTIONS OTHER ADVERSE REACTIONS	USE IN THE ELDERLY USE DURING PREGNANCY, DELIVERY, OR LACTATION PEDIATRIC USE EFFECTS ON LABORATORY TESTS OVER DOSAGE PRECAUTIONS CONCERNING USE OTHER PRECAUTIONS PHARMACOKINETICS CLINICAL STUDIES CLINICAL PHARMACOLOGY PHYSICOCHEMISTRY OF ACTIVE INGREDIENT PRECAUTIONS CONCERNING USE CONDITIONS FOR APPROVAL PACKAGING REFERENCES AND REFERENCE REQUEST INFORMATION ON LONG-TERM ADMINISTRATION NAME AND ADDRESS OF MARKETING AUTHORIZATION
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(PMS Subcommittee, Drug Evaluation Committee, JPMA)

Note: Sections in      refer to Precautions



**Fig. 18-(1) Structure and layout of package inserts for prescription drugs and standard procedures for revision of package inserts**



**Fig. 18-(2) Structure and layout of package inserts for prescription drugs and standard procedures for revision of package inserts**

## CHAPTER 6

# Health Insurance Programs and Drug Pricing in Japan

### 1. HISTORY OF HEALTH INSURANCE PROGRAMS

Health insurance programs in Japan began in 1922 with enactment of the Health Insurance Law which was aimed only at workers for the purpose of ensuring sound development of national industries through increases in labor efficiency and close cooperation between workers and employers by eliminating workers' anxiety about their daily life. This law was implemented in 1927. The National Health Insurance Law, enacted in 1938, and the Employees' Health Insurance Law and the Seamen's Health Insurance Law, both enacted in 1939, were subsequently enforced. In 1961, it was ruled that every citizen was required to join either one of the various industry-managed employees' health insurance programs or the NHI, which is a regional insurance program. At this point, "health insurance covering the entire population" was established.

Increasing efforts were made thereafter to improve the structure of medical benefits

given under various health insurance programs. In addition, under the Law for the Welfare of the Aged, all medical costs for the elderly have been provided free of charge since 1973. These measures all helped to alleviate the burden placed on patients by high medical costs.

Because of the long-term deficit in the health insurance system, radical measures as well as temporary financial measures were conceived.

Free medical care for the elderly resulted in sharp increases in the cost of their medical treatment, which seriously affected the financial status of the health insurance program. In addition, it created an imbalance in the contributions for medical costs of the elderly between the different health insurance programs due to differences in the proportion of elderly persons covered under each program. This made it necessary to radically review the health insurance system in Japan, and as a result, the Health and Medical Services Law for the Aged was enacted and was enforced in 1983.

This law encourages general health related projects for the elderly, including the prevention and treatment of diseases and rehabilitation efforts. A new system was introduced in which medical costs for the elderly are shared by public expenditure and by contributions from individual health

insurance programs in order to distribute the costs more fairly.

Thereafter, anxiety increased concerning home care because of the aging of society and changes in family function, and the excessive burden of home care on families has become a social problem. Another problem is stringency on health insurance finances by social hospitalization, i.e., long-term hospitalization of the elderly for nursing care. There are limits on solving the home care problem under the current system, and a reform of the health insurance system together with the introduction of a new social security system was debated. The Home Care Insurance Law was passed together with the third revision of the Medical Service Law on December 19, 1997 and it was enforced from April 1998. It is amended every 5 years.

Concurrently health insurance reforms were as studied in 1997 and were made to change the coverage on benefits by employee's health insurance to 80% and to introduce a partial cost-sharing for medication. Thereafter, in 2002 the revision of the Health Insurance Law containing the 30% copayment for the insured was passed by the Diet. The 30% burden for the insured was enforced from April 2003 and the partial burden for dispensing fees was abolished.

The law to reform the health insurance system was discussed from 2005 and was

enacted in June 2006. From October 2006, persons 70 or older with the same incomes as during their working years were subject to a copayment of 30% and limits on copayments and food costs for inpatients of nursing home increased. The overall reform, including establishment of a new healthcare system for the elderly, will continue until 2012. From April 2008, a healthcare system for very old people was initiated (refer to [Table 6. Drug Pricing-Related Laws](#)).

## 2. MEDICAL BENEFITS OFFERED UNDER HEALTH INSURANCE PROGRAMS

As mentioned above, there are several types of health insurance programs in Japan and the medical benefits available vary from one program to another. The percentage of the cost that the insured person and their family members are required to pay can also differ from one program to another. Under industry-managed health insurance programs, 90% of medical costs of insured persons is covered by health insurance programs according to the revision of the Health Insurance Law in 1984 (80% coverage but this became 90% from April 1986 based on a notification of the Minister of Health and Welfare after approval by the Japanese Diet). From September 1997,

coverage was changed to 80% of medical costs to medical institutions where patients are treated under health insurance programs. A copayment by patients for outpatient medication fees was also introduced with children less than 6 years of age and low-income elderly patients excluded.

Thereafter, problems related to the burden on the elderly were pointed out and the government adopted a policy of exemption of the elderly from outpatient partial cost sharing for medication as an extraordinary measure in July 1999. In December 2000, the Health Insurance Law was promulgated and from January 1, 2001, it became possible to select a copayment system with 10% of the medical expenses as the upper limit or a fixed copayment for the elderly. For family members of insured persons, regardless of type of health insurance program, at least 70% of actual costs are covered by the programs. From October 2002, the burden on elderly patients 70 and older was set at 10% and at 20% for those with a certain level of income. This was revised to 30% from October 2006.

Medical costs for the insured are covered by at least 70% under any health insurance programs. 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 special healthcare expenditure system that permits selection of treatment by patients. These all contribute to overall improvement in medical care.

Under these health insurance programs, medical benefits are almost always provided to insured persons in the form of actual treatment rather than as a cash reimbursement. In exceptional cases where this rule is difficult to apply, money is provided to cover treatment costs.

### 3. REIMBURSEMENT OF MEDICAL FEES

Medical institutions where patients are treated under health insurance programs apply to respective health insurance associations, after treatment has been rendered, for reimbursement of actual treatment costs after subtracting the amount paid directly by patients. Medical fees are set by the MHLW, which consults with the Central Social Insurance Medical Council ("Chuikyo"). The fees are calculated based on the Rules to Calculate Treatment Fees According to the Health Insurance Law (MHW Notification No. 177 issued in June 1958). Under these rules, a point value is assigned for each of the thousands of medical procedures listed. Fees are then calculated by multiplying the number of points by 10. This system, in which medical

fees are paid to medical institutions for the procedures performed, is called the “payment for services system” as the basis of the medical cost reimbursement system in Japan. There are many types of points set for lump sum payment for hospitalized treatment, etc. of patients with chronic disease. From April 2003, the Diagnosis Procedure Combination (DPC) system was introduced by university and other large hospitals (university hospitals, National Cancer center, and National Cardiovascular Center: 82 hospitals in total) for diagnosis-based assessment of lump sum payments for emergency admissions and treatments. With this system, medical bills per day per patient are determined using 1,860 diagnosis procedure combinations. The medical bills include basic admission fees, laboratory test fees, imaging diagnosis fees, drug dispensing fees, injection fees and treatment fees of less than 1,000 points. The medical bill is calculated by the following formula.

Number of points per day for each DPC x coefficient by medical institution x number of admissions x ¥10

The coefficient by medical institution is set by the function and past performance records of the hospital. No. of points per day is set higher for cases of earlier discharge than the mean number of hospitalization days of the DPC.

The number of DPC classifications was 2,241 as of March 2012 and the application of this billing system has been extended to 1,505 hospitals (about 480,000 beds) as of April 2012.

Medical procedures, such as medication and injection, require the use of drugs, and the list of reimbursement prices of drugs permitted under health insurance programs is called the National Health Insurance (NHI) Drug Price List.

#### **4. NATIONAL HEALTH INSURANCE DRUG PRICE LIST**

The National Health Insurance (NHI) Drug Price List is a list of drugs for which medical providers can be reimbursed under the health insurance programs as specified in the regulations for hospitals and nursing homes covered by health insurance. The rules used to calculate healthcare 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. Thereby, the prices to be invoiced for drugs used in hospitals are set by the Minister and shown in the NHI Drug Price List.

#### **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 been a problem since the latter half of the 1980s, 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 sales conditions, should be 10%. Since stable supply of all necessary drug products could not be ensured if the price range was set at 10% from the beginning, Chuikyo recommended that it be set at 15% initially so as not to have too strong an effect on business conditions at the time, and that it be reduced to 13%, 11%, and finally 10% on a step-by-step basis each time the reimbursement prices were revised in the future.

Thereafter, price increases of some products presented a problem, and a Chuikyo recommendation was issued on November 22, 1995. In addition to the usual price revision in April 1996, repricing was undertaken for products that showed a much greater market scale (at least double) that originally expected at the time of listing and for which annual sales (converted to reimbursement prices) exceeded 15 billion yen. Repricing was also undertaken for drugs for which indications were added after the original listing.

The price range decreased gradually from

15% in 1992 to 13% in 1994, 11% in 1996, 10% (8% for products listed for a long time) in 1997, and 5% (2% for high price products with relatively large margin) in 1998. In 2000, the range was set at 2% to secure stable drug supply involved over the need of reimbursement system reform. The pricing formula was changed to the weighted average market price and range adjustment method.

The pricing formulas for drugs included in the list were specified in March 2000 to assure transparency of drug pricing. The most recent revision is given in Notification No. 0210-(4) of the Health Insurance Bureau dated February 10, 2012, "Drug Pricing Standards."

## 6. RECENT REVISIONS OF THE NHI DRUG PRICE LIST

Based on the 1991 Chuikyo recommendation, the MHW undertook a complete revision of the reimbursement prices of all products already in the NHI Drug Price List using the weighted average pricing formula from 1992.

The actual reimbursement price revisions covers the drugs sold in the month of September of a previous year. A survey of all products in the NHI Drug Price List is conducted on about 4,000 sellers, all first-class wholesalers, and about 3,400

purchasers consisting of hospitals, clinics and pharmacies selected at random using specified sampling fractions in each case. Supplemental price surveys including those on changes with time are performed six times. The new reimbursement price is calculated by adding a reasonable adjustment zone (R) to the weighted average marketing price obtained from these surveys in consideration of the consumption tax (refer to the calculation formula).

### Calculation formula:

New drug price = weighted average value of market price in survey x (1 + consumption tax rate) + current reimbursement price x R/100 (however, the new price shall not exceed the current reimbursement price).

This pricing formula is applied to products that are sold in large quantities, and the prices for drugs sold in lower quantities are adjusted using the revision rate for drugs of the same type and same indications.

From 1992, prices were revised at about 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 2% further by the range-adjustment method in 2000. In 2002, the adjustment range was kept at 2%, and an additional reduction of an average of 5% was

made for original drugs of generic drugs (excluding those in the JP) in the case of drugs entered in the NHI price list for a long time. In 2004, a price range of 2% and exceptions for long-listed products were applied. Among JP products entered by brand name, original products for which generic products are available on the market were subjected to an additional price reduction of one half of the rate for non-JP products. In 2006, a further reduction of 2% was applied as an exception for long-listed products.

In order to deal with of the pending “drug lag” issue (unavailability for use or longer approval time of foreign new drugs), the Central Social Insurance Medical Council (“Chuikyo”) discussed the issue and proposed a new “premium for promoting new drug research and resolving problems of treatment not covered by insurance. In 2010, the premium was applied for prescription drugs that have been in the reimbursement list within 15 years and not followed by generic drugs (for negative price divergence from average price of all drugs in class confirmed by price surveys). This premium pricing system on trial still continues to be implemented in 2012.

The results of reimbursement price revisions from 1992 through 2010 are shown in [Table 7. Methods of Previous Reimbursement Price Revisions](#) and [Table](#)

## [8. Revision Rates of Reimbursement Prices.](#)

### **7. DETERMINATION OF REIMBURSEMENT PRICES FOR NEW DRUGS**

In view of trends in the new drug development environment in recent years, Chuikyo stated in their May 1991 recommendation concerning the reimbursement price of new drugs that a more appropriate premium system should be introduced with a new premium for innovation that would be applicable to only truly innovative new drugs. Specifically, it was recommended that the reimbursement price of new drugs should be determined on the basis of comparison with existing drugs from the same category as before but marked up using premiums for innovation, usefulness, and market size; and that requirements for each premium be clearly defined. The price of a daily dose of a new but non-innovative drug approved on or after April 1, 1966, for which several drugs with similar pharmacological action and indications are already listed and for which the efficacy and safety are objectively evaluated to be about the same as these drugs (excluding drugs within 3 years from the appearance of the first drug or within three drugs with the same pharmacological action) was set at a lower price for a daily dose. Coordination with

foreign reimbursement prices was also clarified (maximally twice the foreign price).

The six premium rates as of February 2010 were set at 70–120%, 35–60%, 5–30%, 5–20%, 10–20%, and 5% for innovation, usefulness I and II, pediatric use and market size I and II, respectively. Requirements for applying premiums are listed in **Table 9. Requirements for Applying Premiums.**

A special calculation formula was introduced for new combination drugs (oral preparations): as a rule, the price is set at 80% of the total of prices of individual drugs.

To assure transparency of the pricing system, drug pricing formulas were made public in March 2000 (the most recent revision is given in Notification No. 0210-(4) of the Health Insurance Bureau dated February 10, 2012, “Drug Pricing Standards”). Procedures for calculation of drug prices were issued in detail in September 2000 (the most recent revision is given in Notification No. 0210-(4) of the Health Policy Bureau dated February 10, 2012, “Handling of Entries of Prescription Drugs in the NHI Drug Price List”).

Methods for submission of requests for inclusion of new drugs in the price list were most recently revised in Notification No. 0210-(3) of the Health Policy Bureau dated February 10, 2012.

A drug pricing organization was established to undertake scientific surveys

concerning selection of products for comparison and the applicability of premiums by experts in the medical and pharmaceutical fields. This organization deals especially with pricing and repricing of new drugs in the NHI Drug Price List.

With the establishment of the pricing organization, flowcharts of the process from new drug approval until entry in the NHI price list are shown in **Fig. 19 (Reimbursement Pricing Flow-sheet for New Drugs).**

Entries of new drugs in the NHI Drug Price List are made as a rule four times a year.

## **8. ENTRY OF GENERIC DRUGS IN THE NHI DRUG PRICE LIST**

In the past, generic drugs have been entered in the NHI Drug Price List once every 2 years, but the entry has been made once a year from 1994 and twice a year since 2008 (entries in May and November from 2009). The reimbursement prices for the drugs listed since 1996 are calculated as follows in principle.

As in the case of new drugs, the drug pricing formulas were issued in March 2000 with the aim of assuring transparency of the generic drug pricing system. (The most recent revision is given in Notification No. 0210-(4) of the Health Insurance Bureau dated February 10, 2012, “Drug Pricing

Standards.” Procedures for calculation of reimbursement prices were specified in detail in September 2000 (most recent revisions: Notification No. 0210-(4) of the Health Policy Bureau dated February 10, 2012, “Handling of Entries of Prescription Drugs in the NHI Drug Price List” and Notification No. 0210-(3) of the Health Policy Bureau dated February 10, 2012 “Method for Submission of Requests for Entry in the NHI Drug Price List for Prescription Drugs”).

- 1) When the brand drug is already entered in the list and a generic drug identical to the brand drug is entered for the first time, the price of the generic drug is obtained by multiplying the brand drug price by a factor of 0.7. The factor is 0.6 for oral preparations, in the case that more than 10 brands are already on the market. When both the brand and 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. A special formula was introduced for biosimilar products. A premium

(maximally 10/100 of the standard) is added to the standard price depending on qualitative and quantitative data obtained from clinical trials.

## 9. ISSUES RELATED TO THE USE OF DETERMINATION OF UNAPPROVED DRUGS AND OFF-LABEL USE

There have been major issues related to the use of unapproved drugs and the “time-lag” in new drug approval in this country. The Ministry formed the Review Conference on Unapproved Drugs in 2005 to address these issues. In view of an increasing need for regulatory and industry measures to lend greater support to the use of unapproved drugs and indications, the Ministry and member companies of the JPMA worked together and established the Pharmaceutical Development Support Center in May 2009 to improve regulatory systems and structures to support the development of such drugs and indications by pharmaceutical companies. The Chuikyo also joined the support: they discussed potential approaches and introduced the New Premium System for the Promotion of Innovative Drug Discovery and Resolution of Off-Label Use in April 2010 on a trial basis.

In addition, the Ministry established the Review Conference on Unapproved Drugs

and Off-label Use of Drugs of High Therapeutic Need in February 2010 and, since that time, it has been working to realize the early approval of unapproved drugs and indications of high medical need that are available in foreign countries, by requesting pharmaceutical companies to develop such drugs and indications. Since August 2010, the Conference has been evaluating individual drugs and indications to determine if they are worthy to be reimbursed by the National Health Insurance System without license approval, provided that the Social Insurance Council, Pharmaceutical Affairs and Food Sanitation Council (PAFSC) accept the use of unapproved indications (off-label use) without domestic clinical trial data.

**Table 6. Drug Pricing-related Laws**

Issue date	Main points of amendment	Law
4/2006 (enforced)	<ul style="list-style-type: none"> <li>Continuation of the national policy to strengthen the financial base of healthcare</li> </ul>	National Health Insurance Law
10/2006	<ul style="list-style-type: none"> <li>Revision of burden on elderly patients who are currently employed or have an income (20%→30%)</li> <li>Revision of food and accommodation expenses for the elderly in convalescent hospitals</li> <li>Reorganization of combined insured and non-insured healthcare</li> </ul>	Health insurance-related laws including Health Insurance Law
	<ul style="list-style-type: none"> <li>Initiation of a project for collaborative stabilization of health insurance finances</li> </ul>	Health Insurance Law
	<ul style="list-style-type: none"> <li>Establishment of regional health insurance societies (unions)</li> </ul>	Health Insurance Law
3/2007	<ul style="list-style-type: none"> <li>Review of the membership of the Central Social Insurance Medical Council and abolition of regulations on endorsement from organizations</li> </ul>	Social Insurance Council Law
4/2007	<ul style="list-style-type: none"> <li>Revision of payment rates for illness and delivery benefits</li> </ul>	Health Insurance Law
4/2008	<ul style="list-style-type: none"> <li>Revision of burden on elderly patients aged 70 to 74 years (10%→20%)</li> <li>Expansion of liability relief measures (20%) for young children (children not older than 3 years→children before school age)</li> </ul>	Health insurance-related laws including Health Insurance Law
	<ul style="list-style-type: none"> <li>Revision of the name of the law to “Law for Assuring Healthcare for the Elderly”</li> <li>Program for the optimal utilization of health expenditures</li> <li>Obligation to provide preventive medical examinations for citizens covered by health insurance</li> </ul>	Health and Medical Service Law for the Elderly

	<ul style="list-style-type: none"> <li>• Establishment of a health care system for the very elderly (older than 75 years of age)</li> <li>• Establishment of a fiscal control system for healthcare spending for the pre-elderly (65 to 74 years old)</li> </ul>	
10/2008	<ul style="list-style-type: none"> <li>• Public incorporation of government-controlled health insurance programs</li> </ul>	Health Insurance Law
4/2012	<ul style="list-style-type: none"> <li>• Abolition of nursing homes for the elderly</li> </ul>	Home-care Insurance Law

**Table 7. Methods of Previous Reimbursement Price Revisions**

Year	Survey	R zone	Special items
1992	June 1991	15%	
1994	June 1993	13%	Repricing
1996	June 1995	11%	Repricing
1997	Sept. 1996	10% 8% (Long listed products)	Repricing Long listed products
1998	Sept. 1997	5% 2% (Long listed products)	Repricing Long listed products
2000	Sept. 1999	Range adjusted, 2%	Repricing Range adjusted, 2%
2002	Sept. 2001	Range adjusted, 2%	Repricing Long listed products (Special adjustment, 4, 5, 6%)
2004	Sept. 2003	Range adjusted, 2%	Repricing Long listed products (Special adjustment, 4, 5, 6%) 1/2 : JP products entered by brand name
2006	Sept. 2005	Range adjusted, 2%	Repricing Long listed products (Special adjustment, additional 2%, new 8%) 5%: JP products entered by brand name
2008	Sept. 2007	Range adjusted, 2%	Repricing Long listed products (Special adjustment, 4%, 5%, 6%) 1/2: JP products entered by brand name
2010	Sept. 2009	Range adjusted, 2%	Repricing Long listed products (Special adjustment, additional 2.2%, new 6%) 1/2: JP products entered by brand name

**Table 8. Revision Rates of Reimbursement Prices**

Year	Number of products with price decrease	Number of products with price increase	Number of products with price unchanged	Total	Revision rate
1992	7,681 (–8.5%)	2,121 (0.4%)	3,771	13,573	– 8.1%
1994	8,613 (–6.8%)	2,083 (0.2%)	2,679	13,375	– 6.6%
1996	9,568 (–7.0%)	1,697 (0.2%)	1,604	12,869	– 6.8%
1997	7,718	3,394	862	11,974	– 3.0% *
1998	9,921 (–9.7%)	6 (0.0%)	1,762	11,692	– 9.7%
2000	8,935 (–7.5%)	61 (0.5%)	2,291	11,287	– 7.0%
2002	9,096	98	1,997	11,191	– 6.3%
2004	9,645	39	2,309	11,933	– 4.2%
2006	10,113	75	3,123	13,311	– 6.7%
2008	12,740	77	1,542	14,359	– 5.2%

\* In 1997, the overall drug price revision was -3.0% when a 1.4% rise based on the increased consumption tax rate is included.

Since a new premium formula was introduced for the promotion of new drug research and resolution of problems of treatment not covered by insurance on a trial basis in 2010, above data for 2010 are not available. The numbers of drugs by formulation type are shown below for reference purpose.

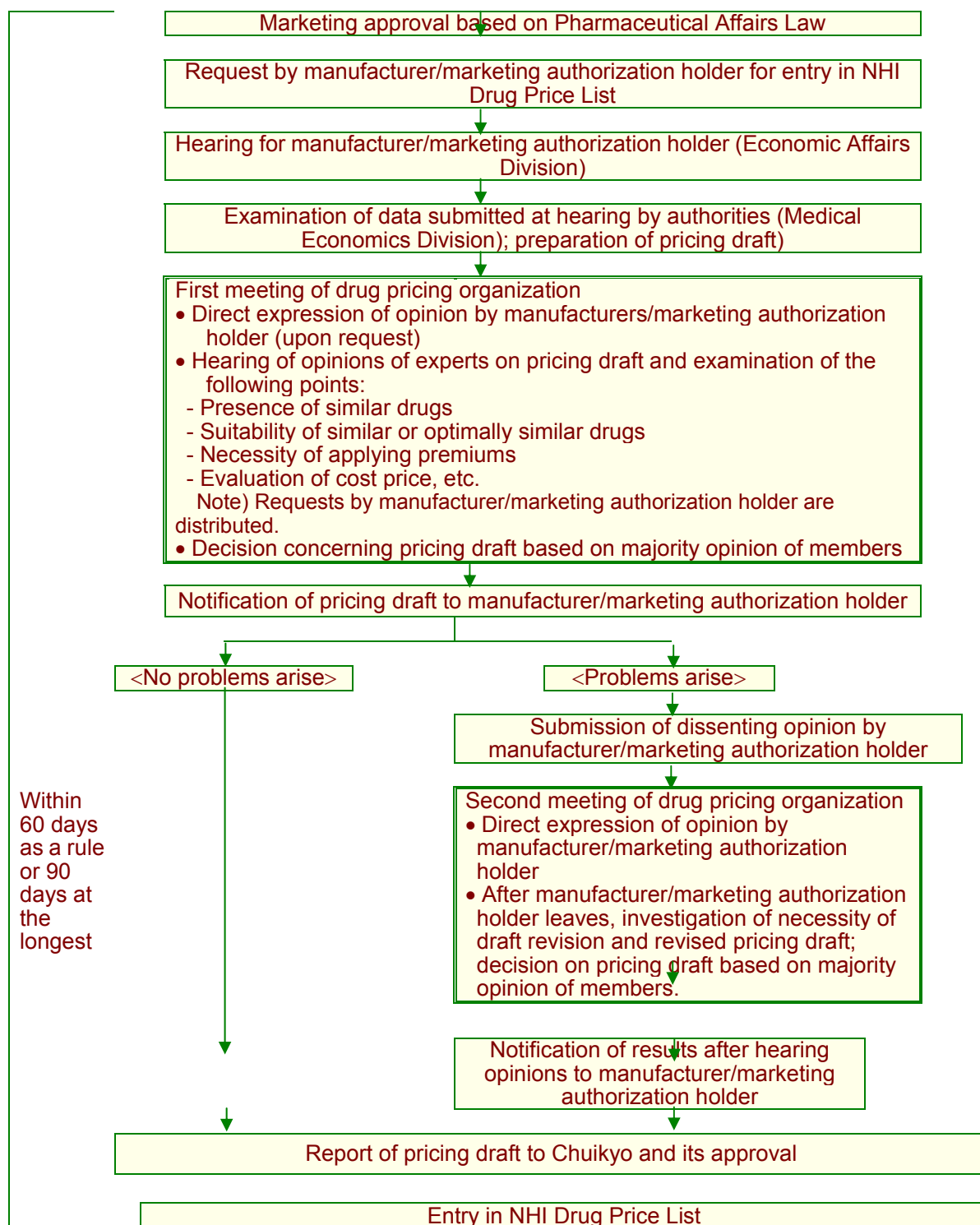
	Oral	Injection	Topical	Dental	Total
Number announced	8,676	4,010	2,733	36	15,455

**Table 9. Requirements for Applying Premiums**

<Premium types, requirements and rates>

(1)	<b>Premium for innovativeness (rate: 70-120%)</b> Applied to new drug products in the NHI price lists meeting all of the following requirements:
	1) The newly entered drug has a clinically useful new mechanism of action.
	2) The newly entered drug has been shown objectively to have greater efficacy and safety than existing (comparator) drugs in the same class.
	3) The newly entered drug has been shown objectively to improve treatment of the indicated disease or trauma.
(2)	<b>Premium for usefulness I (35-60%)</b> Applied to new drug products in the NHI price lists that meet two of the three requirements listed above
(3)	<b>Premium for usefulness II (5-30%)</b> 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 newly entered drug has a clinically useful new mechanism of action.
	2) The newly entered drug has been shown objectively to be more effective and safe than existing (comparator) drugs in the same class.
	3) The newly entered drug has been shown objectively to offer, as a result of formulation improvement, greater therapeutic usefulness than other drugs in the same class.
	4) The newly entered drug has been shown objectively to improve treatment of the indicated disease or trauma.
(4)	<b>Premium for pediatric use (5-20%)</b> Applied to new drug products in the NHI price lists meeting all of the following requirements:
	1) The newly entered drug is explicitly shown in the Indications section or Dosage and Administration section to be indicated for children (including infants, suckling infants, newborns, and low-birthweight infants).
	2) The premiums for pediatric use must not have been given to comparator drugs available in the NHI price lists.

(5)	<p><b>Premium for marketability I (10-20%)</b></p> <p>Applied to new drug products in the NHI price lists meeting all of the following requirements:</p>
	<p>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.</p>
	<p>2) The premium for marketability (I) must not have been given to comparator drugs available in the NHI price lists.</p>
(6)	<p><b>Premium for marketability (II) (5%)</b></p> <p>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):</p>
	<p>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.</p>
	<p>2) The premium for marketability (I) or (II) must not have been given to comparator drugs available in the NHI price lists.</p>



**Fig. 19. Reimbursement Pricing Flow-sheet for New Drugs**

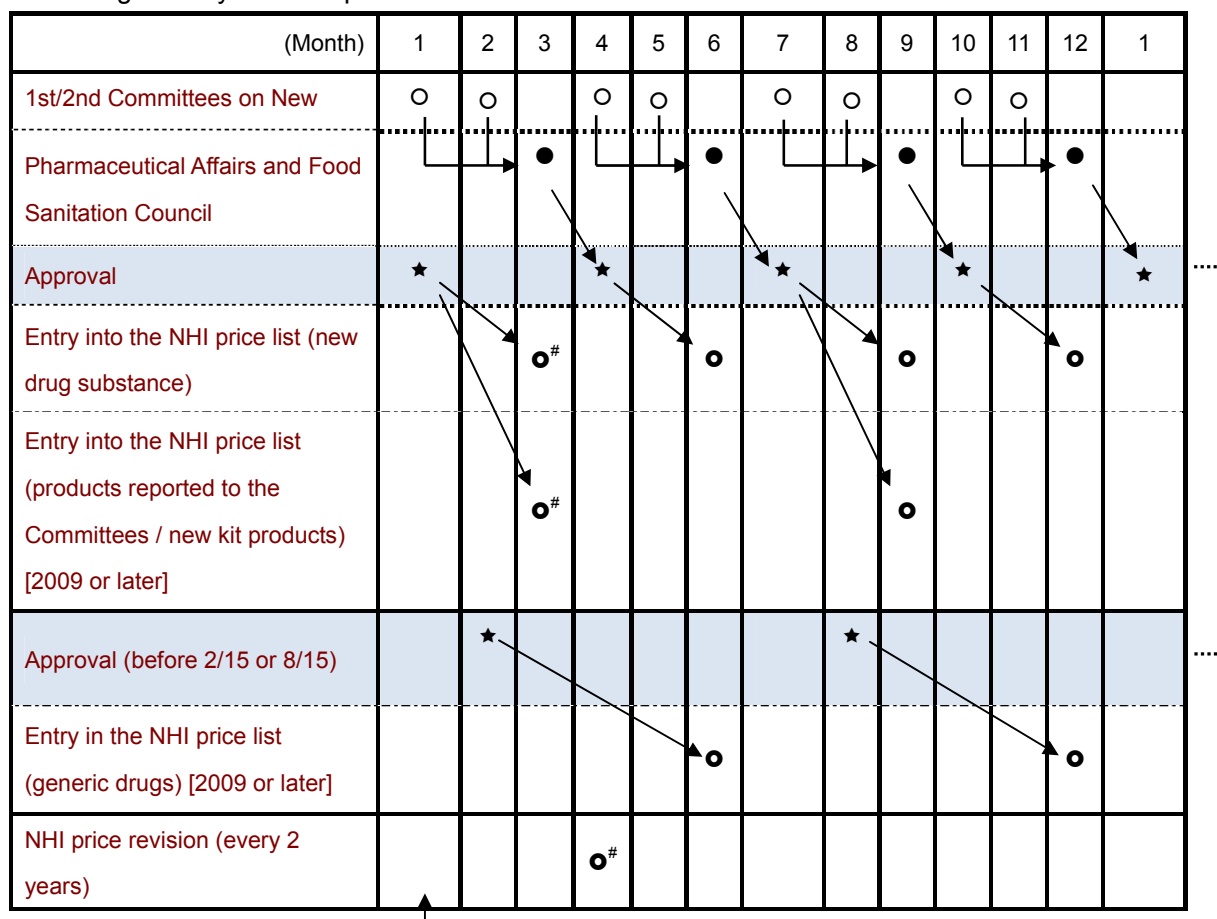
(Note 1) The parts in the double box  show parts involving the drug pricing organization

(Note 2) Time clock (agreed on at MOSS conferences)

2012-3

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.

### Handling of entry into NHI price list from 2012



- Rule on the entry into the NHI price list: Generally, within 60 days (or within 90 days at the latest) after approval
  - New formulations of drugs approved after the reexamination period: Classified as generic drugs (time of entry: twice a year)
  - Drugs reported to but not reviewed by the Committee (PAFSC) are handled by the principle of “change on late notice.” Approvals indicated with ★ means those that do not require price listing (there are 4 times/year of approval that requires price listing procedures).
- # Special entry in the year of NHI price revision (at every 2 years)
- # Entry in February is changed to April (based on the 90-day rule) in the year of NHI price revision.

**Fig. 20. Correlation between the Time of Marketing Approval Based on Pharmaceutical Affairs Law and the Time of Entry in the NHI Drug Price List**

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