INFORMATION ON JAPANESE REGULATORY AFFAIRS

Regulatory Information Task Force
Japan Pharmaceutical Manufacturers Association

Pharmaceutical Administration and Regulations in Japan

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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 external organizations. 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 the National Institute of Health Sciences and the National Institute of Infectious Diseases. 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 Council (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 and to introduce a specific system for reviewing tasks for drugs, etc. 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 polices to assure the efficacy and safety of drugs, quasi-drugs, cosmetics and medical devices, and policies for safety in medical institutions, the PFSB tackles problems directly related to the lives and 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 functions described below.

1.1 General Affairs Division

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) The relief systems operated by the PMDA for damage caused by adverse drug reactions including biological products-induced infection
  2) Measures for handling health injury caused by drugs, quasi-drugs, cosmetics, and medical devices (drugs, etc.)

1.2 Evaluation and Licensing Division

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
4) Issues related to the Japanese Pharmacopoeia (JP)
5) Standards and specific precautions concerning drugs, etc.
6) Designation of orphan drugs
7) Work related to the PMDA (KIKO) (limited to approval to manufacture and market drugs, medical devices, etc.)

- Office of Medical Devices and Regenerative
Medicine Products Evaluation

1) Technical guidance and supervision concerning the production of medical devices, extracorporeal diagnostic medicines and regenerative medicine products
2) Manufacturing business licenses for regenerative medicine products and manufacturing business registrations for medical devices and extracorporeal diagnostic medicines, as well as approvals to manufacture and market medical devices, extracorporeal diagnostic medicines and regenerative medicine products
3) Reexamination and reevaluation of regenerative medicine products
4) Evaluation of treatment outcomes of medical devices and extracorporeal diagnostic medicines
5) Business license and approvals to market, loan, or repair medical devices (excluding areas under the control of Health Policy Bureau [HPB])
6) Standards and specific precautions concerning medical devices, extracorporeal diagnostic medicines and regenerative medicine products
7) Designation of orphan medical devices and orphan regenerative medicine products
8) Work related to the Pharmaceutical and Medical Devices Agency, Independent Administrative Agency (limited to work listed in Article 15, Paragraph 1, Item (5) (a) to (d) of the Law on Pharmaceuticals and Medical Devices Agency, Independent Administrative Agency (Law No. 192 of 2002) (with respect to work listed in (a), (b) and (d) of said item, limited to work relating to medical devices, extracorporeal diagnostic medicines and regenerative medicine products and, with respect to work listed in (c) of said item, only manufacturing business licenses for regenerative medicine products and manufacturing business registrations for medical devices and extracorporeal diagnostic medicines, as well as approvals to manufacture and market medical devices, extracorporeal diagnostic medicines and regenerative medicine products, reexamination and reevaluation of regenerative medicine products, evaluation of treatment outcomes of medical devices and extracorporeal diagnostic medicines, standards and specific precautions concerning medical devices, extracorporeal diagnostic medicines and regenerative medicine products, and control and dissemination of Industrial standards for medical devices, other hygiene products and regenerative medical products, and other industrial standards)
9) Control and dissemination of industrial standards for medical devices, other hygiene products, and regenerative medicine 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 from the standpoint of environment and public health, as well as regulations related to manufacturing, importing, using, 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

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 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) (limited to matters related to improve safety of drugs, etc. and excluding items handed by the Evaluation and Licensing Division)

1.4 Compliance and Narcotics Division

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, etc.
5) Control of substances designated by the Law on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (PMD Law
6) Matters related to inspectors of poisonous and deleterious substances
7) Control of narcotics, psychotropics, cannabis, opium, and stimulants
8) Duties of narcotics control officers and staff as judicial police officials
9) Cooperation with international criminal investigations concerning narcotics, psychotropics, cannabis, opium, and stimulants
10) Work related to the PMDA (KIKO) (limited to matters related to on-site inspection, etc. by the PMDA)

1.5 Blood and Blood Products Division

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 functions described below.

2.1 Economic Affairs Division

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 Medical Device Policy
1) Promotion, improvement and coordination of manufacturing, marketing and consuming medical devices and other sanitary products (other than those handled by PFSB and the Research and Development Division)
2) Promotion, improvement and coordination of business of manufacturing, manufacturing/marketing, selling, leasing and repairing medical devices and other sanitary products (other than those handled by the Research and Development Division)
3) Foreign trades (import and export) of medical devices and other sanitary products
4) Installation and use of medical devices (other than medical, dental, and sanitary supplies) (other than those handled by the Guidance of Medical Service Division)

2.2 Research and Development Division

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. (limited to 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)

• Office of Clinical Trial Promotion

Promotion of clinical trials specified in Article 2, Paragraph 16 of the Pharmaceutical Affairs Law (Law No. 145 issued in 1960) (other than those handled by PFSB)

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), 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 Pharmaceuticals 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 25 offices, 3 groups, and the Kansai branch as shown in Fig. 2, and, the duties are indicated below.
The PMDA is currently working to achieve goals under the Third Medium Range Plan (2014-2018), including strengthening and enhancing post-marketing safety measures to ensure the quality of products and prevent the occurrence or escalation of health hazards and striving to speed up and improve the quality of reviews, in order to be the first in the world to facilitate practical use of innovative drugs, pharmaceutical medical devices and regenerative medicine products, as well conducting publicity activities so that relief systems are definitely used when necessary.

1) Drug ADR Relief Work
- Provision of medical benefits to cover healthcare expenses, disability pensions, and survivors 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 Drugs and Medical Devices Law
- Guidance and advice related to clinical trials
- Reviews of GLP and GCP compliance of attached data of approval applications and reexamination and reevaluation applications
- Reviews of manufacturing facilities, processes, and quality control based on GMP, QMS, etc.
- Confirmation of reexaminations and reevaluations based on the Drugs and Medical Devices 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, and receipt and processing of reports including 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 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, 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 Cellular and Tissue-based Products
This office confirms clinical trial notifications and adverse drug reactions and conducts reviews required for approval, reexaminations, and reevaluations of regenerative medical products (cellular and tissue-based products and gene therapy products), preliminary reviews for approval or verification based on the Cartagena Protocol, and quality review of antibody preparations.

4.11 Office of Vaccines and Blood Products
This office confirms clinical trial notifications and adverse drug reactions of globulins, blood coagulation-factor products, vaccines, and antidotes and performs the reviews required for approval, reexamination, or reevaluation.

4.12 Office of OTC and Generics
This office conducts reviews required for the approval, export certification, and quality reevaluations of guidance-mandatory drugs non-prescription drugs, quasi-drugs, and cosmetics.

4.13 Office of Generics
This office conducts reviews required for the approval, export certification, and quality reevaluations of generic drugs, etc. (ethical drugs excluding new drugs and extracorporeal diagnostic medicines).

4.14 Office of Medical Devices I
This office 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.

4.15 Office of Medical Devices II
This 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, otolaryngology, dentistry, gastroenterology, urology, obstetrics/gynecology, orthopedic surgery, plastic and reconstructive surgery, dermatology, and laboratory testing (in vitro diagnostics).

4.16 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).

4.17 Office of Compliance and Standards
This office reviews the documentation included with applications for approval, reexamination, or reevaluation of drugs, medical devices, and regenerative medicine products 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) (hereinafter “Reliability Criteria”) and examined on site and on paper. Compliance of facilities performing GLP-based studies is also examined and certified.

4.18 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.

4.19 Office of Safety II
This office undertakes analysis and evaluation of adverse reactions of drugs and medical devices.

4.20 Kansai Branch
This branch undertakes pharmaceutical strategy consultations and GMP and QMS inspections in the Kansai area.

4.21 Electronic Data Promotion Group
This group makes plans and proposals concerning the use of electronic application data and undertakes surveys and adjustments associated with this. It also proposes education and training relating to the viewing and analysis of electronic application data, and gathers and organizes information concerning the use of electronic application data.

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

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

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

6. PHARMACEUTICAL AFFAIRS AND FOOD SANITATION COUNCIL (PAFSC)

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

The Council has as members experts in various fields\(^1\) including the medical and pharmaceutical sciences.

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

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 for the Committee on Non-prescription 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) The Pharmaceutical Affairs Committee meets in March, June, September, and December in principle.

Note 6) For recent new drugs, refer to the homepage on drug information.

(http://www.info.pmda.go.jp)

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
Fig. 1  Organization of Ministry of Health, Labour, and Welfare
(Health-related organizations only)
Fig. 2 Organization of Pharmaceutical and Food Safety Bureau (PFSB) and Pharmaceuticals and Medical Devices Agency (PMDA [KIKO])
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**Fig. 3  Organization of the Pharmaceutical Affairs and Food Sanitation Council (PAFSC)**

(17 Committees and 19 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 Drugs and Medical Devices Law, (2) Law Concerning the Establishment for Pharmaceuticals and Medical Devices Organization, (3) Law Concerning Securing Stable Supply of Blood Products, (4) Poisonous and Deleterious Substances Control Law, (5) Narcotics and Psychotropics Control Law, (6) Cannabis Control Law, (7) Opium Law, and (8) 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 Drugs and Medical Devices 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. DRUGS AND MEDICAL DEVICES LAW

The objectives of the Drugs and Medical Devices Law are to improve public health through regulations required to assure quality, efficacy, and safety of drugs, quasi-drugs, cosmetics, medical devices, and regenerative medicine products and to prevent hazard and expansion of hazard in public health caused by use of those products, as well as through measures required to promote R&D of drugs, medical devices and regenerative medicine products 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 reevaluation of new drugs after reexamination, 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 dated 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. According to the revised Law, the Provisions on the enhancement of safety measures for biological products came into effect on July 30, 2003 and the provisions related to the manufacturing/marketing approval system, manufacturing/marketing businesses, and manufacturing businesses, as well as the 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 dated June 14, 2006) to revise the OTC drug selling system and strengthen the control of illegal drugs was issued in June 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 2013, the Law for Partial Amendment of the Pharmaceutical Affairs Law (Law No. 84 dated November 27, 2013) was issued for strengthening safety measures and for establishing regulations and control on medical devices and regenerative medicine products in view of their properties and characteristics. The Law was enacted on November 25, 2014. In conjunction with this law, the Law for Partial Amendment of the Pharmaceutical Affairs Law and the Pharmacists Law (Law No. 103 dated December 13, 2013) was issued in the same year for clarifying the Internet retailing rules of non-prescription drugs and for tightening regulations on designated drugs/substances. The Law was enacted on June 12, 2014 (provisions strengthening regulation of designated substances were enacted on April 1, 2014).

In the revised Pharmaceutical Affairs Law enacted on November 25, 2014, regulations on drugs, medical devices and regenerative medicine products were divided into individual chapters to restructure the entire framework, as well as the Pharmaceutical Affairs Law was renamed to be the Law for Ensuring Quality, Efficacy, and Safety of Drugs and Medical Devices (commonly-called the Drugs and Medical Devices Law).

The revised Law, Drugs and Medical Devices Law, consists of 17 chapters and 91 articles as outlined below.

Chapter 1: General Provisions (Articles 1 to 2)
Chapter 2: Prefectural Pharmaceutical Affairs Councils (Article 3)
Chapter 3: Pharmacies (Articles 4 to 11)
Chapter 4: Manufacturig/Marketing Businesses of Drugs, Quasi-drugs and Cosmetics (Articles 12 to 23)
Chapter 5: Manufacturig/Marketing Businesses, etc. of Medical Devices and in vitro Diagnostics
  Section 1 Manufacturig/Marketing Businesses of Medical Devices and in vitro Diagnostics (Article 23-2 to 23-2-22).
  Section 2 Third-party Certification Bodies (Article 23-2-23 to 23-19)
Chapter 6: Manufacturig/Marketing Businesses of Cellular and Tissue-based Products (Article 23-20 to 23-42)
Chapter 7: Retail Sellers, etc. of Drugs,
Various regulations apply to the development, manufacture, import, marketing, and proper use of drugs and medical devices in the form of the Drugs and Medical Devices Law, cabinet orders, MHLW ordinances, etc. An outline of the main regulations affecting pharmaceuticals is presented here.

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 Drugs and Medical Devices 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 Drugs and Medical Devices Law are defined as follows in Article 2, Paragraph 1 of the Law.
The term "drugs" refers to the following substances:
1) Substances listed in the Japanese Pharmacopoeia.
2) Substances (other than quasi-drugs and regenerative medicine products), which are intended for use in the diagnosis, treatment, or prevention of disease in humans or animals, and which are not equipment or instruments, including dental materials, medical supplies, sanitary materials, and programs.
3) Substances (other than quasi-drugs, cosmetics or regenerative medicine products) which are intended to affect the structure or functions of the body of humans or animals, and which are not equipment or instruments.

3.2 Definition of Drugs

Drugs (medicinal products) ("iyakuhin" in Japanese) can be classified as follows based on the regulatory provisions in the Drugs and Medical Devices Law, etc. among others.

1) Classification according to use and supply

(1) Pharmacy drugs (Article 4 in the Law)
Drugs other than guidance-mandatory drugs and non-prescription drugs
Includes prescription drugs
(drugs intended for use by a physician or dentist or under the prescription or instructions of a physician or a dentist)

(2) Guidance-mandatory drugs (Article 4 in the Law)
Guidance-mandatory drugs are designated by the MLHW as drugs which clinical effects are not as significant as prescription drugs and intended to be selected and used by the consumer based on information provided by the pharmacist, etc. and must be sold via face-to-face consultation with a pharmacist. Deleterious substances and early switch OTC products are applicable. This is a new classification created in amendment of the Pharmaceutical Affairs Law enacted on June 12, 2014 (Law No. 103 dated December 13, 2013).

(3) Non-prescription drugs (Article 4 in the Law)
Non-prescription drugs are defined as those in which clinical effects are not as significant as in prescription drugs and which a consumer may select and use based on information provided by a pharmacist, etc. Those are neither pharmacy drugs nor guidance-mandatory drugs. Those are classified into three types based on the degree of risks to humans: Type 1 (highly risky), Type 2 (moderately risky) and Type 3 (relatively low risky). In the revised Pharmaceutical Affairs Law enacted on June 12, 2014, non-prescription drugs may be retailed via the Internet in accordance with the proper rule.

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 Drugs and Medical Devices 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) Narcotics (Narcotics and Psychotropics Control Law).

(7) Psychotropics drugs (Narcotics and Psychotropics Control Law).

(8) Opium and powdered opium (Opium Law).

(9) Cannabis (Cannabis Control Law).

(10) Stimulants (Stimulant Control Law).

3) Biological products and specified biological products

Biological products were classified as follows based on the definition by the regulations and risk of infection as specified in Notification No. 0731011 of the PMSB, 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 PMSB dated May 20, 2003 that came into effect on July 30, 2003.

Based on the provisions in the Drugs and Medical Devices 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 PMSB dated May 20, 2003),” “Periodic Infection Reporting System (Notification No. 0515008 of the PMSB 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 PMSB dated May 15, 2003 and Notification No. 0520004 of the PMSB dated May 20, 2003, etc.

4) Regenerative medicine products

The Drugs and Medical Devices Law specifies a new definition for cellular and tissue-based products to be distinguished from “drugs” and “medical devices”. These are specifically defined as products derived from human cells via cultures, etc., to be used for (1) reconstruction, repair or formulation of structure or function of the body and (2) treatment or prevention of disease, or to be induced into human cells for gene therapy.

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. In addition, separate notifications were issued specifying the basic technical requirements to assure the quality and safety of human-derived (autologous) somatic stem cells, human-derived (homologous) somatic stem cells, human-derived (autologous) iPS (-like) cells, human-derived (homologous) iPS (-like) cells, and human-derived ES cells, (Notification Nos. 0907-(2) to (6) of the PFSB dated September 7, 2012).

3.3 License for Manufacturing/Marketing Businesses

A person wishing to start manufacturing/marketing business for drugs, medical devices and cellular and tissue-based products, etc. must obtain a manufacturing/marketing business license of the prefectural governor depending on the type of business.

These licenses are of the following nine types. Manufacturing/Marketing businesses of in vitro diagnostics and cellular and tissue-based products were newly established in accordance with amendment of the Pharmaceutical Affairs Law enacted on November 25, 2014.

(1) Type 1 drug manufacturing/marketing business license: Marketing of prescription drugs

(2) Type 2 drug manufacturing/marketing business license: Marketing of drugs other than prescription drugs

(3) Quasi-drug manufacturing/marketing business license: Marketing of quasi-drugs

(4) Cosmetic drug manufacturing/marketing business license: Marketing of cosmetics

(5) Type 1 medical device manufacturing/marketing business license: Marketing of specially controlled medical devices

(6) Type 2 medical device manufacturing/marketing business license: Marketing of controlled medical devices

(7) Type 3 medical device manufacturing/marketing business license: Marketing of general medical devices

(8) Manufacturing/marketing business license of in vitro diagnostics: Marketing of in vitro diagnostics

(9) Manufacturing/marketing business license of cellular and tissue-based products: Marketing of cellular and tissue-based products

The licensing requirements for drug manufacturing/marketing businesses include the appointment of a general marketing compliance officer of drugs, etc., who is a pharmacist, and compliance with Good
Quality Practice (GQP) for quality control and Good Vigilance Practice (GVP) for postmarketing safety surveillance. Manufacturing/marketing business license is valid for a period of 5 years after every renewal.

The general drug 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.

3.4 License for Manufacturing Business and Accreditation of Overseas Manufacturers

1) Licenses for manufacturing businesses

A person wishing to start manufacturing business for drugs, quasi-drugs or cosmetics is required to comply with the Regulations for Buildings and Equipment of Pharmacies, etc., that specify standards for structures and equipment in manufacturing plants for each manufacturing category specified by the applicable Ministerial ordinance and must obtain a manufacturing business license for individual manufacturing categories from the prefectural governor. These licenses are of the following five categories:

- (1) Category of biological products
- (2) Category of radioactive products
- (3) Category of sterile products
- (4) General category of products
- (5) Category of packaging forms, etc.

Manufacturing business license is valid for a period of 5 years after every renewal.

A person wishing to start manufacturing business for cellular and tissue-based products is required to comply with the Regulations for Buildings and Equipment of Pharmacies, etc., and must obtain a manufacturing business license for cellular and tissue-based products in each manufacturing plant from the prefectural governor.

Of note, a requirement for starting manufacturing business for medical devices or in vitro diagnostics has been changed, therefore a person wishing to start manufacturing business for such products is required to obtain registration instead of license in each manufacturing plant.

2) Accreditation of manufacturing business of overseas manufacturers

A person wishing to manufacture drugs, quasi-drugs or cosmetics exported to Japan from overseas (overseas manufacturers) must receive accreditation from the Minister. The specifications for accreditation are the same as those for manufacturing licenses for domestic manufacturers. A person intending to start manufacturing regenerative medicine products to be exported to Japan in a foreign country must also obtain accreditation of an overseas manufacturer of regenerative medicine products.

Of note, requirements for overseas manufacturing business of medical devices or in vitro diagnostics have been changed from an accreditation basis to a registration basis, therefore a person intending to start manufacturing business of such products is required to register manufacturing business in each manufacturing plant.

The procedures for obtaining the accreditation are available in 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.


English website: http://www.pmda.go.jp/english/review-services/reviews/foreign-mfr/0001.html

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

- When the applicant is a corporation, the representative (director with representative authority) makes the application.
- The agent applying on behalf of a person intending to obtain a manufacturing/marketing business license should apply with the confirmed type of corporation, name, address and representative of the overseas manufacturer. The name and contact information for the agent is entered in the Remarks section of the application form. The note “Application by an associated manufacturing/marketing business license holder” should also be entered in the form, if the application is filed by an agent manufacturing/marketing authorization holder (of drugs, etc. manufactured by the person applying for accreditation of an overseas manufacturer).

An application by an agent should be made by an authorized agent of the manufacturing/marketing business license holder, as a rule; however, there are other permissible cases of application not involving authorized agent (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 cannot 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 cannot 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
When a GMP compliance survey is performed 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.

3.5 Manufacturing/Marketing Approvals

Formal approvals are required for individual formulations of drugs in order to market the drugs in Japan. Formal approval 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 product quality, efficacy, and safety.

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 the marketing authorization holder and confirmation that the product has been manufactured in a plant compliant with GMP. Whenever any approved items are to be revised, the license holder must submit a notification of minor variations or partial changes of approved items and obtain approval of the revision.

3.6 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 dated July 2, 2009).

MHLW, PMDA, and prefectures had submitted bid for membership to the office of Pharmaceutical Inspection Cooperation Scheme (PIC/S) in March 2012, which guarantees a high level of the implementation of the internationally recognized GMP rules, to further promote international standardization and conformity in GMP inspection, and then became members since July 1, 2014. The enforcement notification of the GMP was amended accordingly in August 2013 to meet criteria in the PIC/S. (Notification No. 0830-(1) of the Compliance and Narcotics Division dated August 30, 2013.)

3.7 Drug Master File (MF)

With the amendment of the Pharmaceutical Affairs Law enforced in April 2005, approvals for drug substances that had been necessary in the past were no longer required and instead the information of quality and manufacturing method of drug substance are required to be included in the application document of finished product. The master file (MF) system aims at protecting intellectual property of relevant information at the time of license application and facilitating review work by allowing a registrant (master file registrant) of drug substances to separately submit information on quality and the manufacturing method of drug substances to be used in drug products (Notifications No. 1117-(3) of the Evaluation and Licensing Division of PFSB and No. 1117-(1) of the Director of Medical Devices Evaluation, Evaluation and Licensing Division of PFSB dated November 17, 2014). MF registration is optional.

Itemsthat may be registered through the MF system are drug substances, intermediates, and additives, nevertheless raw materials of regenerative medicine products (e.g., cells, media, medium additives or processing materials of cells) may also be registered through the system.

When an overseas drug substance manufacturer submits an MF registration application, it is necessary to appoint an in-country caretaker 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 minor MF modification notification must be submitted.

When an application to change of the MF is submitted, the manufacturing/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 in the MF are slight, the manufacturing/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 manufacturing/marketing authorization holder of the change(s) in advance of the implementation of such changes.

Information of chemicals, drug substances, drug products, etc. registered under the MF system is publicly available at the following PMDA websites.

Japanese website:
http://www.pmda.go.jp/review-services/drug-reviews/master-files/0008.html

English website:
http://www.pmda.go.jp/english/review-services/ mf/0001.html

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 1, 2009 (Law No. 69 dated from June 14, 2006):

1. **Store-based drug sellers**
2. **Drug sellers by household distribution**
3. **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 type 2 and type 3 non-prescription drugs.

Non-prescription drugs may be marketed on the Internet since June 2014, only if these are also marketed in an actual store with an applicable marketing business license.

### 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. In addition, all ingredients used as excipients must be included. Entries in the package inserts of biological products are specified in Notification No. 0515005 of the PMSB dated May 15, 2003 and labeling on the immediate container or packaging of biological products is specified in Notification No. 0515017 of the PMSB 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.

The Law for Partial Amendment of the Pharmaceutical Affairs Law enacted on June 1, 2009 (Law No. 69, June 14, 2006) 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, ensure traceability, and improve the efficiency in prescription drug distribution, the implementation of barcode labeling for prescription drugs (excluding in vitro diagnostics) (Notification No. 1 of the Economic Affairs Division, HPB and No. 1 of the Safety Division, PFSB both dated June 29, 2012) 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 both dated February 28, 2006).

In the revised Pharmaceutical Affairs Law enacted on November 25, 2014 (Law No. 84, November 27, 2013), the new package insert notification system was introduced to enhance safety assurance measures. Manufacturing/marketing authorization holders must prepare package inserts based on scientific knowledge and information obtained from latest literatures, etc. to provide related information. Furthermore, the PMDA must be notified of the name and necessary information in precautions for usage and handling in the package insert prior to initiation of manufacturing/marketing or amendment. The package insert must be published on the PMDA website immediately after submission of the notification.

### 3.11 Proper Advertisement

The "Standards for Proper Advertisement of Drugs, etc.” have been established for the purpose that advertisement of drugs, etc. should made properly and should not include false information or exaggerated statement, so that harm caused by drugs, etc. should be prevented in public health. A person intending to advertise drugs, etc. should make efforts to disseminate accurate information so that users may use the drug, etc. properly. The standards include interpretation of the Law about description of names, indications or dosage/administrations, etc. of the drug, etc. as well as matters to be adhered to otherwise misuse or abuse may be encouraged or confidence may be lost among general users (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 PMSB 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 on March 26, 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. Notification No. 0620059 of the PMDA entitled “Establishment of Guidelines for Drug GLP and Medical Device GLP On-site Inspections” was issued on June 20, 2008 and partially amended on November 21, 2014 (Notification No. 1121005 of the PMDA).

### 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
and currently the director of medical institution is permitted
the information (Request)” (Notification No. 1001013 of the
rationalize the type and scope of documents necessary for
the Common Application Form for Clinical Trial
relaxed as measures for securing the reliability of the IRB
On receiving results of discussion from the MHLW
In accordance with a report compiled by the Council of
2006
On receiving results of discussion from the MHLW
2007
In accordance with a report compiled by the Council of
2008
The GCP ordinance (MHLW Ordinance No. 24, 2008)
and including the activation of clinical trials, including the
certain ministerial ordinances and notifications for implementation have been issued.

Other: History of major changes in GCP Ordinance, etc.:

● 2005
The procedures for proper conduct of investigator-initiated clinical trials and for improvement of quality and performance of institutional review board (IRB) were reviewed based on outcomes of discussion at The Council on Efficient Conduct of Clinical Trials.

● 2006
On receiving results of discussion from the MHLW Council of Ideal Registration-Directed Clinical Trials, the requirements for designating IRB members have been relaxed as measures for securing the reliability of the IRB and improving the functions of the IRB (MHLW Ordinance No. 72 issued in 2006).

● 2007
In accordance with a report compiled by the Council of Ideal Registration-Directed Clinical Trials, the Notification entitled “the Common Application Form for Clinical Trial Notification” was jointly issued by the Research and Development Division of HPB (No. 0307-(1) dated March 7, 2012) and the Evaluation and Licensing Division of PFSB (No. 0307-(2) dated the same date) to reevaluate and rationalize the type and scope of documents necessary for the conduct of clinical trials.

● 2008
The 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. 1001013 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 to inform the public of such information.

Further, limitations for selecting the IRB were reviewed and currently the director of medical institution is permitted to select the IRB from among IRBs available inside and outside the institution (MHLW Ordinance No. 24 issued in 2008).

ADR reporting requirements have been revised to request the sponsor to disseminate cases of serious ADRs unexpected from the investigator’s brochure to medical institutions at 6-month intervals in addition to conventional reporting on occurrence and serious but expected ADRs are required to periodically report at 6-month intervals.

● 2011
Notifications for GCP operating procedures were revised to include changes in procedures made with the intent of enhancing efficiency in the conduct of clinical trials and the requirement of precision controls in laboratory tests in global clinical trials, etc.

● 2012
The latest amendment to the GCP was a partial revision entitled “Ordinance for Partially Modifying the Pharmaceutical Affairs Law Enforcement Regulations, Etc.” (the Ministerial Ordinance No. 161) issued on December 28, 2012. The main objectives of the amendment were to improve the efficiency of trial procedures, accelerate trial processes, reduce burden on study personnel in investigator-initiated trials, and promote industrial-academic cooperation in order to fulfill unmet medical needs while promoting global harmonization on the conduct of clinical trials.

Specific points of revision included removal of trial parameters of low significance (e.g., target number of subjects) from clinical trial contract and change from “the coordinating investigator” who submitted trial notification to the regulatory body to “a person” who submitted trial notification to the regulatory body in multicenter investigator-initiated trial.

The requirement for medical institutions in reporting ADRs was changed from a 6-month to a 12-month period, and the periodic safety reporting requirement on ADRs, etc. was replaced with the Development Safety Update Report (DSUR) on July 1, 2013.

● 2013
Subsequent to the issue of a report entitled “the Study on the Conduct of Investigator-Initiated Clinical Trials, etc.” the following clinical trial-related reports were issued in July 2013: “the Basic Concept of the Use of Electronic Medical Records in Preparing Clinical Trial-Related Documents,” “the Basic Concept of Precision Control in Laboratory Tests, etc. in Clinical Trials,” and “the Basic Concept of Monitoring System Based on Risks Associated with Clinical Trials.”

3.14 Good Post-marketing Study Practice (GPSP)
The GPSP 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 MHW dated March 10, 1997) Thereafter, the GPSP 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
Manufacturing/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 is eight years as a rule (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. Branded products are protected from generics during this period.

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

When manufacturing/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 of the PFSB dated March 17, 2005). Handling of safety reporting is described in CHAPTER 4.

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, PFSB dated March 25, 2004).

Since October 27, 2003, electronic adverse drug reaction reports have been accepted (Notification No. 0828010 of the PFSB dated August 28, 2003. Refer to the following site). The reports are required to be sent to the PMDA from April 1, 2004. (Notification No. 0325013 of PFSB dated March 25, 2004)

The final report of the “Special Committee 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 Risk Management Plan

The basic requirement to ensure the safety of drugs in clinical practice is to develop and implement appropriate measures to manage potential risks of drug-related events based on information collected during the development to post-marketing phases of a new drug’s life cycle. The Ministry issued the Risk Management (RMP) Guidance (Notification No. 0411-(1) of the Safety Division of PFSB and No. 0411-(2) of the Evaluation and Licensing Division of PFSB both dated April 11, 2012) to support the manufacturing/marketing authorization holder in developing risk minimization plans for the reduction of treatment-related risks in addition to conventional pharmacovigilance plans following drug approval.

The RMP Guidance has applied to new drugs and biosimilar products for which manufacturing/marketing approval application is made on or after April 1, 2013 and to generic drugs for which manufacturing/marketing approval application is made on or after August 26, 2014. Subsequently, details of the guidance have been presented by the notification entitled, “Formulation of the RMP” (Notification Nos. 0426-(2) of the Evaluation and Licensing Division and 0426-(1) of the Safety Division, PFSB both dated April 26, 2012), “Formulation of the RMP Questions and Answers” (Office communication dated September 7, 2012), “Publication of the RMP” (Notification No. 0304-(1) of the Evaluation and Licensing Division and 0304-(1) of the Safety Division, PFSB dated March 4, 2013), and “Formulation of the RMP Questions and Answers (2)” (Office communication dated March 6, 2013).

The RMPs of certain drugs have been published on the PMDA website.

http://www.pmda.go.jp/safety/info-services/drugs/items-information/rmp/0001.html

### 3.18 Dissemination of Information

Marketing authorization holders of drugs or medical devices, wholesalers, marketing authorization holders or leasers 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.

### 3.19 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, 2001, 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, on 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.), as a rule, 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 six 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. Out of attached application data, 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 and subsequently issued Notification No. 0325-(1) of the Evaluation and Licensing Division, PFSB dated March 25, 2013 partially modified the procedures for public disclosure.

3.20 Patent System

The patent term is 20 years from the time of application as a rule. However, if the patent cannot be implemented because of laws and regulations to ensure safety of drugs and regenerative medicine products, 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. (For regenerative medicine products, the term may be extended until acquisition of conditional approval and the extension does not cover the subsequent period to acquisition of approval.) 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 to the Commissioner of Patents. 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. Flow chart of Patent-Life Extension).

Generic drugs will not be approved until the substance (application) patent has expired. Branded products are protected from generics during this period. However, in the past if some of the indications or dosage and administration of branded products were patented, partial approvals were not granted because of patent protection, but with Notification No. 065001 of the Economic Affairs Division, HPB and 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 website of the Patent Office:
http://www.jpo.go.jp/indexj.htm

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

3.21 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 was to strengthen control of “dangerous 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 Drugs and Medical Devices Law as countermeasures against “dangerous illegal drugs”. In particular, importing, manufacturing, marketing, giving and storing for selling, etc. of such designated drugs with intended use other than healthcare have been prohibited. On February 28, 2007, the Guidelines on Monitoring of Import of Designated Drugs were issued (Notification No. 0228009 of the PFSB). On February 20, 2013, MHLW Ordinance No. 19 was revised and issued to implement comprehensive control of
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 Drugs and Medical Devices Law.

4.2 Marketing Approval Reviews

The entire process of approval review from review-related inspections and clinical trial consultation to review works is undertaken by the PMDA (KIKO).

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). The applicant can confirm the status of review progress for each product applied for with the manager of the PMDA review team (Notification No. 1227001 of the PMDA dated December 27, 2010).

http://www.pmda.go.jp/review-services/drug-reviews/0001.html

(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) (very uncommon)
(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 on site by the National Institute of Infectious Diseases prior to approval, as necessary.

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. Later, following repeated revisions and with the enactment of the Drugs and Medical Devices Law, “On Drug Approval Applications” (PFSB Notification No. 1121-(2) dated November 21, 2014) was issued. The current categories are as follows:

(1) Drugs containing new active ingredients
(2) New prescription combination drugs
(3) Drugs with new routes of administration
(4) Drugs with new indications
(5) Prescription drugs with new dosage forms
(6) Drugs with new dosages
(7) Biosimilar Products
(8) Prescription drugs with additional dosage forms
Regarding the total review time for new drugs, it was time in stages starting from FY2014, aiming to reach a (format) of the CTD guidelines.

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 (organization and format) of the CTD guidelines.

Regarding the total review time for new drugs, it was decided to raise the percentile of the standard total review time in stages starting from FY2014, aiming to reach a review time of 9 months for priority review products and 12 months for ordinary review products at 80th percentile by 2018. In view of this, “On the Handling of Approval Applications for Improvement of the Predictability, etc. of New Drug Approvals and Approach to Total Review Time” Notification No. 1006-(1) of PFSB and Notification No. 1006-(1) of Compliance and Narcotics Division dated October 6, 2014” was issued, setting out the policy of conducting preliminary interviews for planned reviews and indicating procedures, etc. for contacting applicants in case of difficult approval reviews, with a view to improving the predictability of reviews and the transparency of the review process. A timeline for the standard process of new drug approval reviews was also indicated (Administrative Notice of the Evaluation and Licensing Division, PFSB dated January 30, 2015). 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/review-services/outline/0002.html

English website :
http://www.pmda.go.jp/english/review-services/review/s/0001.html

4.3 Manufacturing/Marketing Approval Application with Electronic Data

The specifications of the electronic CTD (eCTD) have been published for electronic application documents submitted since April 1, 2005. (Notification Nos. 0527004, 0825001, and 0707-3) [partial amendment] of the Evaluation and Licensing Division, PFSB dated May 27, 2004, August 25, 2008, and July 7, 2009, respectively).

For products for which marketing application will be made since fiscal 2016, clinical trial data should be submitted in accordance with the specifications in the

Clinical Data Interchange Standards Consortium (the CDISC standards), so that PDMA itself may proceed with analyses or investigation with clinical data, etc. and establishment of more reasonable and efficient evaluation and assessment process in review and consultation. In line with submission according to the CDISC specifications, application documents are required to be submitted in the form of eCTD. (Notification No. 0620-(6) of the Evaluation and Licensing Division, PFSB dated June 20, 2014)

4.4 Regulatory Strategy Consultations for Regenerative Medicine Products

It is specified in the notifications that safety- and quality-related issues on drugs, etc. processed from cells and tissues as well as drugs for gene therapy 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 Consultations” dated June 30, 2011 and Notification of No. 0701-(13) of PFSB entitled “Abolition of the Verification Application System for Products for Gene Therapy” dated July 1, 2013). Procedures for requesting and holding a regulatory strategy consultation are available in Notification No. 1121001 of PMDA entitled “Guidelines for Regulatory Strategy Consultations” dated November 21, 2014. For regenerative medicine products, clinical trials should be initiated after a regulatory strategy consultation for quality and safety with PMDA.

4.5 Approval System Implemented to Promote the Application of Regenerative Medicine Including Cellular and Tissue-Based Products for Commercialization (Approval with Conditions and Time Limit)

Following enforcement of the Law for Partial Amendment of the Pharmaceutical Affairs Law (Law No. 84, November 27, 2013), a new approval system was introduced for regenerative medicine: non-homogenous quality tissue-engineered medical products can be approved earlier than with the routine approval system with conditions and time limit if they are assumed to be effective and proven to be safe in humans. The applicant is required to verify the efficacy and safety and resubmit the application within seven years after the conditioned approval.

4.6 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
(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) Other

(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 interview advice

When products have been designated for priority interview advice at the development stage, it is possible to obtain priority interview 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 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 interview advice and an application is not required.

4.7 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.

4.8 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 8 years to a maximum of 10 years for drugs and from 4 years to a maximum of 7 years for medical devices.

4.9 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).

The ICH E11 guidelines: Clinical Investigation of Medicinal Products in the Pediatric Population have reached Step 5, and in Japan, Guidance on Clinical studies on Drugs in Pediatric Populations was issued (Notification No. 1334 of the Evaluation and Licensing Division, PMSB dated December 15, 2000). PMDA consultations include those on clinical development of drug in pediatric populations and development of pediatric formulations.

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 whole 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 Special Committee on Unapproved Drugs was founded in December 2004 to study drugs not approved in Japan for which efficacy was established and approvals granted in the West and perform periodic surveys and scientific evaluations of requests of academic societies and patients. Separately, in March 2006, the Special Committee on Pediatric Drug Treatment was established to collect and evaluate evidence on the efficacy and safety of unapproved pediatric drugs. Thereafter, both special committees were developmentally reorganized into a new “Special Committee 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.

4.10 Unapproved Drugs and Drugs of Off-label Use

In May 2010, “a List of Drugs for Which Developing Companies are Being Recruited or Requests for Development Made” was issued based on the results of discussions by the Special Committee on Unapproved Drugs and Drugs of Off-label Use Urgently Required for Healthcare. As a result of the first recruitment, the development request was issued for 165 items, and the clinical development of 20 unapproved items or those of off-label use requested for development was started. In the second recruitment, the development request was issued for 83 items, and the clinical development of 17 unapproved items or those off-label use was started in sequence one after the other (the latest version of the drug list is available at the following site). The third recruitment started in August 2013 was closed in December 2013 for overview of applications received. Nonetheless, recruitment is still ongoing.

http://www.mhlw.go.jp/shingi/2010/05/s0521-5.html (the development requests, etc., at the first recruitment)
http://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_iryou/iyaku/kaishoujuusei/list120423.html (the development requests, etc., at the second recruitment)

In August 2010, a new approach was introduced to make unapproved drugs and drugs of off-label use available for use in clinical practice: the cost of drugs with unapproved indications, etc. can be reimbursed by the national health insurance system even prior to the official approval of such unapproved indications, etc., provided that the Review Conference on Unapproved or Off-label Use Drugs of High Therapeutic Needs has approved the rationale for the public knowledge-based application of the drug use and the Pharmaceutical Affairs and Food Sanitation Council has accepted the public knowledge-based application.

4.11 Packaging Strategy for World-first Products

In June 2014, the “Strategy of Sakigake” for leading the world in the practical application of innovative medical products was drawn up. The strategy covers everything from basic research to clinical research/trials, approval reviews, insurance coverage, and global expansion. Specific measures are expected to take shape from April 2014, and include, as measures relating to the approval review process, the “Review system for designated world-first products” and the “Scheme for prompt practical use of unapproved drugs”.

1) Review system for designated world-first products

A drug, etc. to treat a disease, etc. for which the practical application of a groundbreaking treatment is required as soon as possible shall be designated as a world-first product, if it is expected to have marked efficacy and has been developed and applied for in Japan earlier than anywhere else in the world. Subsequently, priority treatment in consultations and reviews shall be given to accelerate realization of practical use.

2) Scheme for prompt practical use of unapproved drugs

The extent of products considered for review from the Special Committee on Unapproved Drugs and Drugs Off-label Use Urgently Required for Healthcare has been expanded to include drugs with high medical needs that are unapproved in the West provided they are drugs for serious or life-threatening diseases that satisfy any of the requirements set out in 1. to 3. below; 1. a Phase III clinical trial in Japan initiated by a medical investigator is ongoing or has been completed, 2. excellent study outcome has been published in literatures, etc. and 3. it is applicable to the advanced medical technology B with certain experience, so that practical use of world-first therapeutic drugs may be realized.

4.12 Biosimilar Products

For biological products, it is difficult to prove the equivalence of 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 PFSB dated March 4, 2009) were formulated in Japan. "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 Nos. 0304011 and 0214-(1) of the Evaluation and Licensing Division, PFSB dated March 4, 2009 and February 14, 2013, respectively) 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,
4.13 Combination Products

A “combination product” is defined as a drug that was approved to be manufactured/marketed with other components including devices or equipment in an integrated fashion. It would be categorized as a medical device, if distributed alone. Handling of combination products are specified in “Handling of Approval Application for Combination Products” (Notification No. 1024-(2) of the Evaluation and Licensing Division, PFSB, Notification No. 1024-(1) of the Director of Medical Devices Evaluation, Evaluation and Licensing Division, PFSB, Notification No. 1024-(9) of the Safety Division, PFSB, and Notification No. 1024-(15) of the Compliance and Narcotics Division, PFSB, dated October 24, 2014).

Though a combination product is deemed a drug, when the device or equipment constituting the product caused a defect, the manufacturing/marketing authorization holder of the combination product should report the defect in accordance with the defect reporting of medical devices. Handling of defect reporting is specified in “Reporting of Adverse Drug Reactions to Drugs, etc.” (Notification No. 1002-(20) of the PFSB, October 2, 2014).

4.14 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.

4.15 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.

4.16 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 approval 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.

4.17 Issuing of Certificates for Exported Drugs by MHLW

Upon request, the MHLW issues a certificate indicating to the effect that a drug, quasi drug, or medical device to be exported has been manufactured in compliance with provisions of the Drugs and Medical Devices Law in the format designated by the destination country requesting the certificate.

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 based on the WHO certification system, statements of approval and licensing status of pharmaceutical products, and GMP compliance for drugs, and GMP compliance for investigational drugs. (Table 2. Divisions of the Pharmaceutical and Food Safety Bureau in Charge of Certification Work). Export certificates on drugs, quasi-drugs, etc., are issued using the specified format via the PMDA. The notification of export certifications requires the applicant of certification to inquire the Ministry of Health, Labour, and Welfare of the requesting country is different from that specified in the notification (Notification No. 0128-(1) of the PFSB dated January 28, 2011).

The certificates are also issued, when final products manufactured in an overseas plant are exported to a third country (Notification No. 06048-(3) of the Evaluation and Licensing Division, PFSB dated June 4, 2014).

In October 2013, the issue of GMP certificate based on the mutual recognition system for drug GMP (MRA) with the EU countries was terminated and replaced with product registration in the EudraGMDP database that was provided by the European Medicines Agency (EMA). The countries to which the certification system is applied are required to be those with which the mutual agreements for GMP were exchanged with Japan. The product items that are subject to this certification system do not include biological products, bulk drugs, or sterile products. The contents to be certified are prepared and registered by the PMDA in the EudraGMDP database based on information submitted by the manufacturer. Registered information is publicly accessible in the database, as a rule (Notification No. 0628-(4) of the Compliance and Narcotics Division, PFSB dated June 28, 2013).
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 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 Drugs and Medical Devices Law specifies that the JP must be subjected to a complete revision at least once every 10 years, and such revisions have actually appeared every 5 years since the 9th revision in April 1976. In addition, the JP has been partially revised before the complete revision even 5 years since the 11th Edition.

Japanese website:
http://www.pmda.go.jp/rs-std-jp/standards-development/jp/0001.html

English website:

The PAFSC held a meeting of its Subcommittee on the Japanese Pharmacopoeia to cope with recent progress in the medical and pharmaceutical sciences and the requests from ICH 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” in December 2002. The 16th edition of the JP was finalized in March 2011, and then the basic compilation policies of the 17th edition were announced in September 2011.

The 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) Role and characteristics of the JP

The JP is an official compendium of standards, specifications, and test methods in Japan necessary for assuring the quality of drugs in accordance with the scientific and technological progress and medical demand at the time.

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.

Further, the JP is a public book that requires the assurance of transparency in the revision process, disseminates information on drug product quality to the public, and fulfills accountability on the reliability of drug products.

In addition, the JP is requested to undertake the role of and achieve an expected level of contribution to the maintenance and assurance of global harmonization on drug product quality among advanced countries as a code book of medicinal product quality in the international community.

(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. The edition was updated by Notice No. 519 (Supplement 1) dated September 27, 2012 and was enforced from October 1, 2012. Supplement II was issued on February 28, 2014 and enacted on the same date.

(4) Selection of products for entry in the JP

New drugs that are prioritized to be entered in the JP are those expected to be in wide medical use, those expected to have high medical needs, “first-in-class” drugs approved by priority review, those with no alternative drugs available, and those already entered in the USP and EP and are globally in wide use. New drugs which are important in healthcare must also be entered as soon as possible after marketing.

(5) The compilation review organization for the JP

Revisions of the JP had been initiated by the Councils of the MHLW, but at present, the draft is prepared by the PMDA’s JP Expert Committees and is approved by the MHLW’s Committee on JP. The JP Expert Committees are headed by the Expert Committee and include Committee on Chemicals, Committee on Biologicals, etc. for a review of draft text. The committees may organize working groups to discuss and make recommendations on specific issues, as needed.

The technical research committees of the Osaka Pharmaceutical Manufacturers Association and Pharmaceutical Manufacturers Association of Tokyo, and many other organizations every time cooperate in preparation of new versions of the JP.

The draft JP monograph of a candidate item to be listed in the JP is first developed by the applicant. The draft is reviewed by the JP Draft Committee and then, after collecting public comments, by the Committee on JP. After the review and approval by the Committee on JP, public comments are collected again and then listed in the JP (refer to Fig. 7).

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 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

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, Paragraph 1 (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 MHLW Notice No. 211 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.

In line with the revised Pharmaceutical Affairs Law enacted on November 25, 2014 (Law No. 84 of 2013), the Standards for Biological Materials were partially revised as for the standards for human- or animal-derived materials to be used in drugs, medical devices or regenerative medicine products, etc. based on reviews of such materials with latest scientific knowledge and information (Notice No. 375 issued by MHLW of 2014).

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
- Japan Standards of Quasi-drug Ingredients

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 Drugs and Medical Devices 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,
Recall orders

- Improvement orders in cases where the buildings and equipment, etc. do not comply with regulatory requirements

### 6.2 Product Recalls

A manufacturing/marketing authorization holder of drugs or medical devices, etc., or a manufacturing authorization holder of drugs or medical devices to be exported, intending to recall its manufactured/marketed, manufactured or approved products should report to the effect that it initiated recall, recall status, and to the effect that it has completed recall to the prefectural governor. (Article 68-11 of the Law and Article 228-22 of the Regulation.) Such products should be recalled as having a concern in safety or efficacy due to a failure or as violating the Drugs and Medical Devices Law or approved condition, and all recall information is published on the PMDA website.

- Depending on the class of the drug and whether or not it is exported overseas, a Rapid Alert Notification of Quality Defect/Recall should be issued to PIC/S member countries and the EU. Class I: Serious health damage or death may be caused by use of the product.
- Class II: Transient or medically-curable health damage may be caused by use of the product, or serious health damage may not be caused by use of the product.
- Class III: Health damage may not be caused by use of the product.

(Notification No. 1121-(10) of the PFSB dated November 21, 2014)

### 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 22, 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 List 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.

### 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. 0414004 of the PMSB 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 PMSB 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 of the Notification No. 1069 of the PMSB of 2001.

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 jointly issued by the Evaluation and Licensing Division and 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 Safety Assurance 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. Incidents of BSE were reported in Brazil in December 2012 and in Norway in January 2015 and, in both cases, the Ministry issued a notification to local departments and the industry to implement voluntary inspection and preventive measures (Notification No. 1211-(8) of the PFSB dated December 11, 2012 and Notification No. 0130-(12) of the PFSB dated January 30, 2015 ).
Procedures based on the PAL*

Start of clinical study

Approval

Date approval received for a drug pursuant to the provisions of Article 14, Paragraph 1 of the Pharmaceutical Affairs Law

Calculated from the latest date

Patent right 1

Patent application

Registration of establishment of patent right

Expiration (20 years)

Period in which patent invention cannot be exploited = Patent right extension period

Patent right 2

Patent application

Registration of establishment of patent right

Expiration (20 years)

Fig. 4  Flowchart of Patent-Life Extension

* PAL: Pharmaceutical Affairs Law
Fig. 5  Flowchart of Approval Review
Fig. 6 Procedure for manufacturing and marketing approval of drugs for overseas manufacturers in Japan
Fig. 7  Flowchart of Drug Listing in Japanese Pharmacopoeia
Table 1  List of Main Controlled Substances

<table>
<thead>
<tr>
<th>Category</th>
<th>Topics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poisonous and deleterious</td>
<td>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.</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>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.</td>
</tr>
<tr>
<td>Habit-forming drugs</td>
<td>Habit-forming drugs are drugs designated by the MHLW as habit-forming.</td>
</tr>
<tr>
<td>Drugs for designated diseases</td>
<td>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.</td>
</tr>
<tr>
<td>Narcotics</td>
<td>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.</td>
</tr>
<tr>
<td>Psychotropics</td>
<td>Psychotropics are drugs designated by the MHLW, as drugs which affect psychological function by their effects on the central nervous system, are habit forming and cause less severe damage than narcotics or stimulants when abused. The psychotropics specified in the Narcotics and Psychotropics Control Law include hypnotics such as barbital, anxiolytics such as diazepam, and analgesics such as pentazocine.</td>
</tr>
<tr>
<td>Opium and powdered opium</td>
<td>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.</td>
</tr>
<tr>
<td>Stimulants</td>
<td>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), phenylmethylanopropenes (methamphetamine), their salts and products containing any of them.</td>
</tr>
<tr>
<td>Raw materials for stimulants</td>
<td>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.”</td>
</tr>
<tr>
<td>Division</td>
<td>Certification Item</td>
</tr>
<tr>
<td>----------</td>
<td>--------------------</td>
</tr>
</tbody>
</table>
| **Evaluation and Licensing Division** | 1. Items related to business licenses for manufacturing of drugs, quasi-drugs, etc.  
2. Items related to manufacturing/marketing approvals (notification) for drugs, quasi-drugs, etc.  
3. Items related to attached documentation for new drug manufacturing/marketing approval applications  
4. Items related to compliance of drugs with GLP Ordinance (Standards for Conduct of Nonclinical Studies on the Safety of Drugs)  
5. Items related to certification of pharmaceutical products (drugs)  
6. Items related to statements of approval and licensing status of pharmaceutical products  
7. Items related to clinical trial protocol notifications for drugs |
| **Medical Device and Regenerative Medicine Product Evaluation Division** | 1. Items related to business registrations for manufacturing of medical devices  
2. Items related to manufacturing/marketing approvals (notification) for medical devices  
3. Items related to business registrations and licenses for manufacturing of extracorporeal diagnostic medicines and regenerative medicine products  
4. Items related to manufacturing/marketing approvals (certification/notification) for extracorporeal diagnostic medicines and regenerative medicine products  
5. Items related to attached documentation for manufacturing/marketing approval applications for regenerative medicine products  
6. Items related to compliance of regenerative medicine products with GLP Ordinance (Standards for Conduct of Nonclinical Studies on the Safety of Regenerative Medicine Products)  
7. Items related to certification of pharmaceutical products (extracorporeal diagnostic medicines and regenerative medicine products)  
8. Items related to statements of approval and licensing status of pharmaceutical products (extracorporeal diagnostic medicines and regenerative medicine products) |
| **Safety Division** | 1. Items related to business licenses for manufacturing/marketing of drugs, quasi-drugs, medical devices, extracorporeal diagnostic medicines and regenerative medicine products (Note: The certificate is issued by other division in case the certification is originally requested as an attachment to the application to such division.) |
| **Compliance and Narcotics Division** | 1. Items related to compliance of drugs and quasi-drugs with GMP requirements (except for items related to certification of pharmaceutical products)  
2. Items related to compliance with requirements of Ministerial Ordinance on QMS for Medical Devices and In Vitro Diagnostics  
3. Items related to compliance with requirements of Ministerial Ordinance on GCTP for Regenerative Medicine Products  
4. Items related to compliance of drug manufacturing plants with GMP requirements for investigational products |
CHAPTER 3
Drug Development

1. PROCESS FROM DEVELOPMENT TO APPROVAL

New drugs are defined as drugs with active 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 Law).

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 of previous clinical studies.

The Drugs and Medical Devices 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 (GCP) (MHW Ordinance No. 28 dated March 27, 1997, partially revised by MHW Ordinance No. 127 dated October 20, 2000, MHLW Ordinance No. 106 dated June 12, 2003, MHLW Ordinance No. 172 dated December 21, 2004, MHLW Ordinance No. 72 dated March 31, 2006, MHLW Ordinance No. 24 dated February 29, 2008, MHLW Ordinance No. 163 dated November 28, 2008, MHLW Ordinance No. 68 dated March 31, 2009, and MHLW Ordinance No. 161 dated December 28, 2012; the Ordinance on Standards for Conduct of Nonclinical Studies on the Safety of Drugs (GLP) (MHW Ordinance No. 21, March 26, 1997, partially revised by MHW Ordinance No. 127 dated October 20, 2000 and MHLW Ordinance No. 114 dated June 13, 2008) and Standards for the Reliability of Application Data (Article 43 in the Enforcement Regulations) 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. 8 (Flowchart of New Drug Development and Approval).

1.2 Procedures for Clinical Trials

For clinical studies (trials) to be conducted for collection of data to be submitted in marketing approval application of a new drug, etc., the Law and the GCP specified sponsor’s responsibility for submitting a notification of the clinical trial plan in advance and matters that a sponsor must comply with in requesting a medical institution to conduct a clinical trial.

Scope of GCP includes not only clinical trials in patients but also Phase I studies in healthy volunteers, bioequivalence studies in human, studies for additional indication of an approved drug and post-marketing clinical trials after marketing. Furthermore, its partial amendment 2003 specifies investigator-initiated clinical trials as well.

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, as a rule). 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 15, 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 1.4: Interview Advice Meetings).

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 drugs with new active ingredients, 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 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.

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)

b. Clinical study protocol

c. Explanatory materials and consent form used for obtaining informed consent

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.)

e. Latest investigator's brochure

(2) Notification of changes in clinical study protocols (submitted as a rule for each clinical trial protocol notification before changes in notification items)

Data related to the changes as required:

(3) Clinical study discontinuation notification (This notification must be submitted for each clinical trial protocol notification without delay when a clinical study is discontinued.)

Data related to the reason for discontinuation as required (including information on study subjects collected until discontinuation):

(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.)

(5) Development discontinuation notification (to be submitted, when development for the drug is discontinued as a whole in Japan.)

From April 1, 2011, attachments to the clinical trial notification (including protocol revision notification, clinical trial completion notification, clinical trial discontinuation notification and development 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).

In view of a recent increase of international multi-center clinical trials, the sponsor of a clinical trial is required to include information concerning international clinical trials in the clinical trial notification submitted on or after April 1, 2008 (Notification No. 0321001 of the Evaluation and Licensing Division, PFSB dated March 21, 2008). Additionally, in view of a trend of development of drugs with associated companion diagnostics relating to the individualized medicine, a sponsor is required to include whether a companion diagnostics is being developed for the drug with its development status, if any, in the remarks in a clinical trial notification of a drug to be submitted since February 1, 2014 (Notification No. 0701-(10) of the Evaluation and Licensing Division, PFSB dated July 1, 2013).

### 1.3 Safety information on Adverse Reactions and Infections during the Study

Safety information obtained during the study must be reported promptly, as is specified in the ICH guidelines (ICH E2A) on Clinical Safety Data Management (Notification No. 227 of the Evaluation and Licensing Division, PAB dated March 20, 1995).

In the revision of the Enforcement Regulations of the 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.

- Any case that requires hospitalization for treatment or prolongs the duration 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 of 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.

The Enforcement Regulation of the Law, which was 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. Later, this reporting period was changed to 1-year intervals by further revising the Enforcement Regulations (Ministerial Ordinance No. 161 entitled “Ordinance for Partially Modifying the Pharmaceutical Affairs Law Enforcement Regulations, etc.” dated December 28, 2012) to harmonize the period with relevant ICH guidelines.
Basic standards for periodically reporting safety information during the development phase, common to all drugs, etc., are available in “Development Safety Update Report (DSUR)” (Notification No. 1228-(1) of the Evaluation and Licensing Division, PFSB dated December 28, 2012: ICH E2F)

1.4 Interview advice meetings

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, preparation of records, etc. as measures to meet the demands for those requesting consultations (Notification No. 0302070 of the PMDA dated March 2, 2012, partially revised on June 30, 2014 and November 21, 2014). Main items of the interview advice meeting (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 interview advice meeting are available at the following websites of the PMDA. Preparatory consultation is also available to assure smooth interview advice.

-Consultation items and fees:
-Application procedures:

(1) Clinical trial consultation
- Consultations on procedures
- Consultations on bioequivalence studies
- Consultations on safety
- Consultations on quality
- Consultations before start of Phase I studies
- Consultations before start of early Phase II studies
- Consultations before start of late Phase II studies
- Consultations after completion of Phase II studies
- Consultations before license application
- Consultations on post-marketing clinical studies plans of drugs
- Consultation at completion of post-marketing clinical studies of drugs
- Additional consultations on drugs

(2) Consultations on preliminary assessment of new drugs
Assessment of data in preparation for license application (preliminary assessment of data concerning the following areas planned to be submitted for application in order to identify potential issues to be addressed during review):
- Quality
- Nonclinical: Toxicology
- Nonclinical: Pharmacology
- Nonclinical: Pharmacokinetics
- Phase I studies
- Phase II studies
- Phase II/III studies

(3) Consultations on eligibility of drugs for priority review
Evaluation of new drugs to determine the eligibility 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. The consultation fee is different between the case of only priority assessment consultation and that in conjunction with the consultation before license application.
- Consultations on the applicability of priority review status
- Consultations on the applicability of priority review status (consultation in conjunction with that before license application)

(4) Consultations on the applicability as pharmacogenomics markers or biomarkers
- Assessment of applicability
- Assessment of major aspects of clinical trial design
- Additional consultation (on the applicability)
- Additional consultation (on major aspects of clinical trial design)

(5) Consultations on generic drugs
- Consultations on bioequivalence of generic drugs
- Consultations on quality of generic drugs

(6) Consultations on generic drugs before start of clinical studies or license application
- Switch OTC drugs
- Major aspects of clinical trial design
- Rationale for clinical development as a new generic drug

(7) Consultations on GCP/GLP/GPSP of a drug

(8) Simple consultations
Brief consultations with reviewers in charge of the approval review of generic prescription drugs, non-prescription drugs, etc. as well as the registration of drug master files
- Generic drugs
- Non-prescription drugs
- Insecticides and rodenticides
- Quasi drugs
- Revision of text in labeling of new drugs
- GCP/GLP/GPSP inspection of a drug
- GMP/QMS inspection
- GCTP inspection

(9) Post-interview consultations
These are additional consultations for matters for which both of PMDA and the consulter agreed to be addressed later in an interview advice meeting.
Matters such as data evaluation should not be addressed in a post-interview consultation, because those should have been addressed already in the previous interview advice meeting. A post-interview consultation may be recorded at an extra charge, if required by the consulter.

(10) Preparatory consultation or meeting

Preparatory consultations or meetings prior to formal consultation to sort out consultation items and assure smooth interview advice. In the preparatory consultation, data are not evaluated and official meeting records are not issued.

(11) Evaluation of drugs for the designation of priority interview advice

Drugs are evaluated to determine if they should be reviewed and discussed at prioritized interview advice meetings.

(12) Consultations on compliance with reliability standards

Based on data planned to be submitted together with the application form, guidance and advice are provided to the applicant concerning GCP and GLP compliance of drugs that have undergone “the evaluation of drug products for the designation of priority interview advice” and of new drugs that have undergone “a preparatory consultation or meeting”.

(13) Consultations on regulatory strategies

Consultations to discuss plans for necessary clinical trial or development mainly with universities, research institutes, and venture companies who have found seeds throughout the field of lead compound or candidate medical device selection mainly until the early phase of clinical development [Phase IIa]). In addition, guidance and advice for quality and safety may be provided from an early development phase in a regulatory strategy consultation for regenerative medicine products or preventive products to be used for expressing transgenes in the human body (other than regenerative medicine products; e.g., recombinant live vaccine). The verification application system for products for gene therapy has been abolished.

1.5 Approval review

A detailed team review is performed by the review staff in the PMDA in parallel with 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, and partially revised by Notification No. 0304015 of the Evaluation and Licensing Division, PFSB dated March 4, 2009). 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).

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


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 (“CTD Format for Reducing Total Review Time for New Drugs,”
1.6 Compliance review

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 review had been conducted as directed in the “Application Procedures for Paper Review of the Conformity of New Drug Application with Relevant Regulations” (Notification No. 0528027 of the PMDA dated May 28, 2010) and on-site inspection as directed in the “Application Procedures for On-site GCP Inspection for Drug Application” (Notification No. 0528028 of the PMDA dated May 28, 2010). These notifications were integrated into the “Application Procedures for Paper Review-Conformity Inspection and On-site GCP Inspection for Drug Application” (Notification No. 1012063 of the PMDA dated October 12, 2012) and paper review and on-site inspection have been regulated to be conducted simultaneously, as a rule.

- **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) when the applicant provides the PMDA with data as evidence for approval reviews. The review is basically performed by reviewing approval application data brought into the PMDA (“document-based inspection”); however, the Agency’s personnel may visit sites (including those outside Japan) where application data as well as source data are archived, as needed, to inspect such data (“on-site inspection”). The PMDA issued “Checklists for On-site and Document-Based GCP Compliance Review of New Drug Application (for Sponsor’s Use)” in November 2012 and Checklists for Compliance Review of New Drug Application (Quality/Non-clinical) in March 2014. The checklists are publicly available for self-compliance review by the applicant.

  When case report forms are prepared by using Electronic Data Capture (EDC) system, EDC management sheets are required to be prepared and submitted in advance of application as directed in “Compliance Inspection Procedures for Clinical Trials, Post Marketing Clinical Trials, and Use Results Survey by Using EDC System” (Office Director’s Notification No. 0327001 of PMDA dated March 31, 2006; Partially revised by Notification No. 0328001 of the Evaluation and Licensing Division, PFSB dated March 31, 2009). 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. The PMDA also provides a checklists, “Checklists for GCP Compliance On-site Review of New Drug Application (for Medical Institution’s Use)” and “EDC Checklists” (for Medical Institution’s Use), as references for self-inspections before on-site inspections of medical institutions.

- **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 are available as the “Inspection Procedures for the On-site Verification of GCP Compliance for Drug Application” (Notification No. 0131006 of the Evaluation and Licensing Division, PFSB dated January 31, 2006; Partially revised by Notification No. 0325001 of the Evaluation and Licensing Division, PFSB dated March 25, 2009) and “Partial Modification of ‘the Guidelines for Paper Compliance Review for New Drug Approval Application Data’, etc.” (Notification No. 0331009 of the Evaluation and Licensing Division, PFSB dated March 31, 2009).

  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. The PMDA also provides a checklists, “Checklists for GCP Compliance On-site Review of New Drug Application (for Medical Institution’s Use)” and “EDC Checklists” (for Medical Institution’s Use), as references for self-inspections before on-site inspections of medical institutions.

  Checklists and management sheets for paper reviews and on-site reviews are available at the following PMDA website.


1.7 GMP compliance inspection

Formal approvals are required for individual formulations of drugs in order to market the drugs in Japan. Formal approval 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 product quality, efficacy, and safety.

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. Thus, GMP compliance is a requirement for manufacturing and marketing approval of drugs, etc. (Article 14-2, Paragraph 4 of the Pharmaceutical Affairs Law).

When a manufacturing plant does not conform to GMP standards, the MHLW minister or prefectural governor may not grant a license.

1.7.1 GMP Compliance Reviews

When an application is submitted for a new drug manufacturing and marketing approval, the plant must be inspected by 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 cannot be ruled out and improvement necessary for compliance with control regulations.
D (Seriously defective): Clear violation of control 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.
- 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.

1.7.2 Global Harmonization 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 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, partially revised by Notification No. 0825-(12) of the Compliance and Narcotics Division, PFSB, Notification No. 0528004 of PFSB, and Notification No. 0428001 of PFSB dated April 28, 2004).

Positive utilization of the internationally recognized GMP rules contained in Pharmaceutical Inspection Cooperation Scheme (PIC/S) is recommended by the Office Communication dated February 1, 2012 (partially revised by the Office Communication dated March 28, 2013) to secure closer international standardization and conformity in GMP inspections. MHLW, PMDA, and prefectural governments bid membership to the office of PIC/S in March 2012 and became a member on July 1, 2014.

The enforcement notification of the GMP (Notification No. 0330001 of the Compliance and Narcotics Division, PFSB dated March 30, 2005) was amended in August 2013 in order to align with the GMP guideline in PIC/S (Notification No. 0830-(1) of the Compliance and Narcotics Division, PFSB dated August 30, 2013).

1.7.3 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 (MHW Ordinance No.62, June 2, 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 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: 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; and that the records of tests performed by the manufacturer of the drug are provided to the importer in Japan.
2. DATA REQUIRED FOR APPROVAL APPLICATIONS

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, PFSB dated July 1, 2003, No. 0525003 of the Evaluation and Licensing Division, PFSB 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 dated April 8, 1999). In addition, in association with enforcement of the revised Pharmaceutical Affairs Law in April 2005, revised handling procedures of documents to be attached to manufacturing/marketing approval application for drugs were specified in “Approval Applications for Drugs” (Notification No. 0331015 of PFSB dated March 31, 2005; Notification No. 1020001 of PFSB dated October 20, 2008 for partial amendment on non-prescription drugs; Notification No. 0304004 of PFSB for partial amendment on biosimilar products; Notification No. 0701-(10) of the Evaluation and Licensing Division, PFSB dated July 1, 2013 for partial amendment on companion diagnostics and associated drugs; and Notification No. 0612-(1) of the Evaluation and Licensing Division, PFSB dated June 12, 2014 for partial amendment on guidance-mandatory drugs) with abolishment of Notification No. 481 of PFSB, as well as the handling procedures were detailed in “Points to Consider in Approval Application of Drugs” (Notification No. 0331009 of the Evaluation and Licensing Division, PFSB dated March 31, 2005; Office Communication dated April 22, 2005 for its partial amendment; Notification No. 1020002 of the Evaluation and Licensing Division, PFSB dated October 20, 2008 for partial amendment on non-prescription drugs; Office Communication dated October 30, 2008; Notification No. 0304015 of the Evaluation and Licensing Division, PFSB dated March 4, 2009 for partial amendment on biosimilar products; Notification No.0701-(10) of the Evaluation and Licensing Division, PFSB dated July 1, 2013 for partial amendment for companion diagnostics and associated drugs; and Notification No. 0612-(1) of the Evaluation and Licensing Division, PFSB dated June 12, 2014 for partial amendment on guidance-mandatory drugs).

Later, with the enactment of the Pharmaceutical and Medical Device Law, “Approval Application for Drugs” (Notification No. 1121-(2) of the PFSB) and “Points to Consider in Approval Application of Drugs” (Notification No. 1121-(12) of the Evaluation and Licensing Division, PFSB) were issued. The new notifications were based on the information contained in the old notifications, with some changes such as the addition of information in attached data, etc. as data to be attached to approval applications.

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 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.


It was also decided that, with the start of submission of electronic clinical study data from FY2016, as explained later, data attached to approval applications will, as a general rule, be in eCTD format.

As the PMDA was required to progress further in the “Japan Revitalization Strategy” (Cabinet Decision dated June 14, 2013) and to utilize clinical data for review by itself in the “Health and Medicine Strategy” (Related Ministers’ Consensus dated June 14, 2013), the notification entitled “Basic concept of electronic data submission in approval application” (Notification No. 0620-(6) of the Evaluation and Licensing Division, PFSB dated June 20, 2014) was issued with its Q&A (Office Communication dated June 20, 2014). The notification specifies that an applicant should submit the following documents in a form of electronic data in each individual subject among those to be submitted for evaluation in approval application as for prescription drugs in the application categories of (1) through (7), (9) and (9-2). Receipt of electronic data is scheduled to be started since fiscal 2016. Applicable clinical trial data should be submitted in the formats according to the specifications in Clinical Data Interchange Standards Consortium.
A. Outcome data from all Phase II and Phase III studies (including long-term treatment studies) that may commonly be handled as pivotal evidences for efficacy, safety and dosage/administration.

B. Outcome data from the following studies among other Phase I studies and clinical pharmacology studies;
   - Phase I studies for an anticancer drug
   - Phase I studies in both Japanese and non-Japanese (such as multinational clinical studies and bridging studies)
   - QT/QTC studies according to the ICH E14 guideline

1) Module 1: Administrative information such as application forms and prescribing information
   (1) Application documentation table of contents (including 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 risk management plan (RMP) (draft):
        As directed by the Guidelines on Risk Management Plan issued by the PFSB (Notification Nos. 0426-(2) of the Evaluation and Licensing Division and 0426-(1) of the Safety Division of the PFSB both dated April 26, 2012), the applicant is required to attach the RMP (draft), in place of the plan of post-marketing surveillance (draft), to the new drug application submitted on or after April 1, 2013.
   (12) List of attached documentation
   (13) Other
        <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)]

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> Human 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. 10. Organization of ICH Common Technical Documents)

2.1 Data to be Attached to Approval Application of Drugs

2.1.1 Prescription drugs

   in Attached Tables 1 and 2-(1) of the basic notification of application, “Approval Applications for Drugs”(Notification No. 1121-(2) of the PFSB dated November 21, 2014).

   (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), (10-2), 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 Law for Partial Amendment of the Pharmaceutical Affairs Law and the Pharmacists Law (Law No. 103, 2013) was enacted on June 12, 2014, and a category of guidance-mandatory drugs was newly established in addition to the conventional categories of prescription drugs and non-prescription drugs. The range of data to be submitted with applications for non-prescription drugs is specified as shown in Table 4 (Data to be Submitted with an Application for a Non-prescription Drug) (Notification No. 1121-(2) of the PFSB dated November 21, 2014). 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 and 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). In addition, the notice “Basic Principles on Global Clinical Trials (Reference Cases)” (Office Communication dated September 5, 2012) was issued based on achievements of mutual cooperation and latest knowledge obtained relating to multinational clinical trials among Japanese, Chinese, and South Korean regulatory authorities with an objective of a smooth and appropriate conduct of global clinical trials, especially in East Asia.

In addition, “Basic Approach to Conduct of Phase I Clinical Trial in Japanese Before Start of Global Clinical Trial” (Office Communication of the Evaluation and Licensing Division of the PFSB, MHWL dated October 27, 2014) indicates points to consider when examining whether or not a phase I clinical trial is necessary in the case where Japan takes part in a global clinical trial.

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 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 whole 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) Text (Items) on Analytical Validation (ICH Q2A, currently Q2(R1)) (Notification No. 755 of the Evaluation and Licensing Division, PAB dated July 20, 1995)
(2) 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, PFSB dated December 16, 2002, partially revised by Notification No. 1204001 of the Evaluation and Licensing Division, PFSB dated December 4, 2006)
(4) Text (analytical procedures) 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 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. 0211-(1) of the Evaluation and Licensing Division, PFSB dated February 21, 2011)
(6) 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)
(7) 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)
(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, PFSB dated June 28, 2010).
(10) Handling of Application of Drugs Containing a Substance with Different Crystalline (Notification No. 0616-(1) of PFSB dated June 16, 2011).

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

For sustained-release drugs, refer to the Guidelines for Design and Evaluation of Sustained-Release (Oral) Preparations (Notification No. 5 of the First Evaluation and Registration Division, PAB dated March 11, 1998) in addition to the above guidelines.

2) Guidelines for stability tests

Stability tests for approval application of drugs are
conducted to evaluate change in quality over time with various environment factors including temperature, humidity or light, through which necessary information may be obtained for establishing a period of retest of an active pharmaceutical ingredient, an available period of a formulation and storing conditions of a drug.

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, PMSB 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, PMSB dated June 26, 2003) but they were abolished (Notification No. 0703001 of the Evaluation and Licensing Division, PMSB dated July 3, 2006) with the expansion of application of the ICH Q1A 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 Bracketting and Matrixing Methods in Stability Tests on Drug Substances and Drug Products (ICH Q1D) (Notification No. 0731004 of the Evaluation and Licensing Division, PMSB dated July 31, 2002, partially revised by Office Communication dated June 3, 2003).

For generic drugs, etc., standard methods for long-term stability studies, stress stability studies and accelerated stability studies 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).

3) Guidelines for toxicity tests

The notification entitled “Guidelines for Toxicity Studies for Manufacturing (Importing) Approval Application of Drugs” (Notification No. 24 of the First Evaluation and Registration Division, PAB dated September 11, 1989) was issued to establish the “Guidelines for Toxicity Studies of Drugs” with the purpose of specifying standards how to conduct safety studies for approval application of drugs and contributing proper safety evaluation 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) 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)
(3) 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(R1)) (Notification No. 551 of the Evaluation and Licensing Division, PMSB dated July 9, 1998)
(4) Guidance on Requirements for Carcinogenicity Tests of Drugs (ICH S1A) (Notification No.315 of the Evaluation and Licensing Division, PAB dated April 14, 1997)
(5) Guidelines for Reproductive and Developmental Toxicity Studies (Notification No. 316 of the Evaluation and Licensing Division, PAB dated April 14, 1997 (ICH S5A/S5B) and Notification No. 1834 of the Evaluation and Licensing Division, PMSB dated December 27, 2000 (ICH S5B(M), currently S5(R2))
(6) Guidance on the Need for Carcinogenicity Studies of Pharmaceuticals (ICH S1B) (Notification No. 548 of the Evaluation and Licensing Division, PMSB dated July 9, 1998)
(7) Timing of Preclinical Studies in Relation to Clinical Trials (ICH M3(M), currently M3(R2)) (Notification Nos. 1019 and 1831 of the Evaluation and Licensing Division, 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, and Q&A: Office Communication dated August 16, 2012)
(8) Guidance on Genotoxicity Tests of Pharmaceuticals (ICH S2) (Notification No. 1604 of the Evaluation and Licensing Division, PMSB dated November 1, 1999)
(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, PFSB dated November 27, 2008)
(10) Guidance on Immunotoxicity Studies for Human Pharmaceuticals (ICH S8) (Notification No. 0418001 of the Evaluation and Licensing Division, PFSB dated April 18, 2006)
(11) 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, PFSB dated October 23, 2009)

(12) Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use (ICH S2(R1)) (Notification No. 0920-(2) dated September 20, 2012)

(13) Guidance on non-clinical evaluation of medicinal products in pediatric population using juvenile animals (Notification No. 1002-(5) of the Evaluation and Licensing Division, PFSB dated October 2, 2012)

(14) Guideline on Photosafety Evaluation (ICH-S10) (Notification No. 0521-(1) of the Evaluation and Licensing Division, PFSB dated May 21, 2014)

Data on the following studies that should be conducted in accordance with the above guidelines are required for the review and evaluation of a new drug application by the Ministry (Table 3 Data to be Submitted with an Application for Approval to Manufacture/Market: A New Prescription Drug):

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

Drug dependence studies were specified separately from the toxicity guidelines in the Scope of Application and the Guidelines for Animal Studies and 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 biotechnological products, the guideline “Nonclinical Safety Evaluation of Biotechnological Drugs” (Notification No. 0323-(1) of the Evaluation and Licensing Division, PFSB dated March 23, 2012) 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, PFSB 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, PFSB 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, PMSB 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.)

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 one 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 On-site Reviews Based on the Pharmaceutical GLP and Medical Device GLP” (Notification No. 23 of the PMDA dated 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, No. 0815008 dated August 15, 2008, and No. 1121005 dated November 21, 2014) GLP compliance conditions are evaluated in two categories: compliant or non-compliant, based on the results of the GLP compliance review.

Compliant: The inspected testing facility has no items that deviate from GLP for drugs, etc. or, if it does, appropriate improvement measures have been taken with respect to such aspects or the effects of such aspects on the operation and management of testing facility in general are considered tolerable. Non-compliant: The effects of items that deviate from GLP for drugs, etc. at
the inspected testing facility are not tolerable and inspected testing facility cannot be considered compliant with GLP.

When evaluated as compliant 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 from the date of the GLP Compliance Confirmation Letter. These GLP requirements also apply to data generated in other countries when they are used to support applications in Japan. In principal, a judgment on the GLP compliance of a trial conducted at a testing facility in a foreign country is made based on data submitted by a government agency, etc. of the foreign country evidencing that the trial is conducted in accordance with GLP (Notification No. 1121-(9) of the Evaluation and Licensing Division, PFSB and Notification No. 1121-(13) of the Evaluation and Licensing Division, PFSB dated November 21, 2014).

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) 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 studies 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, PFSB dated July 11, 2013) and Q&A on this guidance (Office Communication dated July 11, 2013).

A guidance for the reliability assurance of drug concentration analysis in pharmacokinetic study is available as “the Guidelines on Bioanalytical Methods Validation for Human Studies in New Drug Development” (Notification No. 0711-(1) of the Evaluation and Licensing Division, PFSB dated November 21, 2013) and Q&A on this guidance (Office Communication dated July 11, 2013).

The notification entitled “Methods of Investigating Drug Interactions” (Notification No. 813 of the Evaluation and Licensing Division, PMSB dated June 4, 2001) was enacted to be referred in investigation of pharmacokinetic interaction. Additionally, the “Guidelines for Pharmacokinetic Drug Interaction for Drug Development and Proper Information Provision (Final Draft)” was published on July 8, 2014.

7) Guidelines for bioequivalence studies

The following guidelines have also been issued concerning bioequivalence:


(7) Guidelines for Bioequivalence Testing of Topical Dermatological Dosage Forms with Formulation Modifications (Notification No. 1101-(1) of the Evaluation and Licensing Division, PFSB dated November 1, 2010).

A guidance for partial changes in the manufacturing method of solid oral immediate-release, enteric-coated, and controlled-release preparations is available as “the Guidelines for Bioequivalence Studies of Solid Oral Preparations for Handling Changes in Manufacturing Method” and Q&A on this guidance (Office Communication dated April 19, 2013).

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, MHLW Ordinance No. 24 dated February 29, 2008, and MHLW Ordinance No. 161 dated December 28, 2012) was issued with the aim 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 importance of precision control of laboratory data in clinical trial to ensure the reliability of laboratory data and the trial is shown in “the Basic Concept of Precision Control of Laboratory Data in Clinical Trial” (Office Communication of the Evaluation and Licensing Division, PFSB dated July 1, 2013).

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 Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (Notification No. 1019 of PMSB dated November 13, 1998, partially revised on February 19, 2010: ICH M3R(R2), and Office Communication (Q&A on the guidelines) dated August 16, 2012).

1) 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) and Q&A on this notification (Office Communication dated July 2, 2009) 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) and the dose but variable correlations between the development phase and study type are shown in Fig. 11 (Correlation between Development Phase and Type of Study).

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. The four clinical development phases are described below.

(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 I 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 Clinical Pharmacokinetic Studies on Drugs (Notification No. 796 of the Evaluation and Licensing Division, PMSB dated June 1, 2001) and Guidance on Ensuring Safety of Human Subjects in the Initial Clinical Trial of New Investigational Medicinal Product (Notification No. 0402-(1) of the Evaluation and Licensing Division, PFSB dated April 2, 2012).

(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 are 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 manufacturing/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. Even though test doses are extremely low, microdose studies must also be conducted in accordance with the cGCP. Basic concepts for the microdose studies, including points to consider, are given in the Guidance for Conducting Microdose Clinical Studies (Notification No. 0603001 of the Evaluation and Licensing Division, PFSB dated June 3, 2008).

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
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 new 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.

Currently, the following 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


(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).


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


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

(10) Guidelines for Clinical Evaluation of
Antimalignant Tumor Drugs (Notification No. 1101001 of the Evaluation and Licensing Division, PFSB dated November 1, 2005, partially revised by Office Communication dated November 2, 2005).


(12) 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).

(13) Guidelines for Clinical Evaluation of Prophylactic Vaccines against Infections (Notification No. 0527-(5) of the Evaluation and Licensing Division, PFSB dated May 27, 2010).

(14) Guidelines for Clinical Evaluation of Oral Hypoglycemic Drug (Notification No. 0709-(1) of the Evaluation and Licensing Division, PFSB dated July 9, 2010).

The draft amendment was presented on May 19, 2014.

(15) Guidelines for Clinical Evaluation of Antidepressant Drugs (Notification No. 1116-(1) of the Evaluation and Licensing Division, PFSB dated November 16, 2010).

(16) 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).

(17) Guidelines for Clinical Evaluation of Therapeutic Drugs for Renal Anemia (Notification No. 0930-(1) of the Evaluation and Licensing Division, PFSB dated September 30, 2011).


(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&A dated September 17, 2010).

(20) Dose-Response Information to Support Drug Registration* (ICH E4) (Notification No. 494 of the Evaluation and Licensing Division, PAB dated July 25, 1994).


(22) Structure and Content of Clinical Study Reports* (ICH E3) (Notification No. 335 of the Evaluation and Licensing Division, PAB dated May 1, 1996)

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

(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, Q&A by Office Communication dated February 25, 2004, and Q&A-(2) by Office Communication dated October 5, 2006).


(30) Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (ICH M3(R2)) (Notification No. 0219-(4) of the Evaluating and Licensing Division, PFSB dated February 19, 2010 and Q&A by Office Communication dated August 16, 2012).

[3] Other guidelines


(36) Guidance for Developing Prototype Vaccines in Preparation for Influenza Pandemic (Notification No. 1031-(1) of the Evaluation and Licensing Division, PFSB dated October 31, 2011)
(37) Guidance for Clinical Evaluation of Diagnostic Radiopharmaceuticals (Notification No. 0611-(1) of the Evaluation and Licensing Division, PFSB dated June 11, 2012)
(38) Points to Consider in Application of Companion Diagnostics and Related Drug Products (Notification No. 0701-(10) of the Evaluation and Licensing Division, PFSB dated July 1, 2013)
Technical Guidance for Companion Diagnostics and Related Drug Products (Office Communication dated December 26, 2013)
*: ICH guidelines

6) 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 Ministerial Ordinance on the GCP was amended thereafter (partially revised by MHW Ordinance No. 127 dated October 20, 2000, MHLW Ordinance No. 106 dated June 12, 2003, MHLW Ordinance No. 172 dated December 21, 2004, MHLW Ordinance No. 72 dated March 31, 2006, MHLW Ordinance No. 24 dated February 29, 2008, MHLW Ordinance No. 163 dated November 28, 2008, MHLW Ordinance No. 68 dated March 31, 2009 and MHLW Ordinance No. 161 dated December 28, 2012), and the current GCP Ordinance is comprised of 6 chapters and 59 articles. The contents are briefly divided into the 3 parts consisting of "Standards for sponsoring clinical trials" and "Standards concerning management of clinical trials" for persons intending to request or conduct a clinical trial, and "Standards for conduct of clinical trials" for medical institutions.

The major points of revision in Ordinance No. 161 dated December 28, 2012 are as follows:
(1) Paragraphs 22 and 23 in Article 2, etc.

To enhance the efficiency of clinical trial to be conducted by "a person who intends to conduct a trial" or "a person who conducts a trial," "a person who intends to conduct a trial" or "a person who conducts a trial" may be not only an investigator of the trial but also, in the case of multicenter trial with a common protocol, a coordinating investigator who is going to submit or has submitted a trial application to the Ministry as the representative of the investigators.
(2) Paragraph 1-(2) in Article 7, etc.
Operating procedures related to a request (preparation for trial conduct) and/or control of a clinical trial may be contracted out in part or in whole to a third party(ies) in order to enhance the efficiency of clinical trial.
(3) Paragraph 1 in Article 13
It is not necessary to state the title of investigators, name and title of subinvestigators, and target number of study subjects in a trial contract in order to enhance the efficiency of negotiating and exchanging a contract between parties.
(4) Paragraph 2 in Article 13
"A person who intends to conduct a trial" may exchange a trial contract with a medical institution(s), etc. by electronic means instead of in paper format if the institution(s), etc. accepts electronic means.
(5) Paragraph 6 in Article 16 and Paragraph 6 in Article 26-(2), etc.
SOPs for the control or accountability of investigational products may be provided to the medical institution instead of to the director of medical institution.
(6) Paragraph 2 in Article 20
The sponsor shall notify investigators and the director of medical institution of any diseases or other ADRs suspected to be related to investigational product within 3 months after the end of each 1-year period.
(7) Article 20 referred to in Article 56
The scope of information (limited to ADRs, etc. occurring in Phase IV studies) that the sponsor of post-marketing study is required to report to investigators and the director of medical institution in accordance with Article 77-(4)-2 of the PAL (Law No. 145 issued in 1960) is limited to that stipulated in Paragraph 1-(1) and (2) in Article 253.

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. (Article 1)

1) Standards to be followed by prospective sponsors in the collection and preparation of data related to results of clinical trials on drugs to be attached to approval applications.
2) Standards to be followed by prospective sponsors of clinical trials, institutions or persons performing clinical trials and sponsors of clinical trials to conduct or manage clinical trials which are both ethically and scientifically sound.
3) Standards to be followed by sponsors in the collection and preparations of data from
 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 whole or part of the clinical trial management is contracted out.
- When persons or participating medical institutions who perform clinical trials on their own outsource whole or 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.
- 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.
- 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 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 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 3 months after completion of the period every 12 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 prepare an audit report and an audit certificate proving that the audit has been performed, and these documents must be submitted to the sponsor, the person who performs the trial, or the director of the medical institutions involved.
- When the trial is completed or discontinued, the results obtained must be compiled in a clinical study report. When the person conducting the clinical trial learns that the study results collected from the trial
concerned were not attached to the application form as application data, this fact and the reason for it must be notified in writing to the directors of the medical institutions performing the trial.

- Records related to the clinical trial must be retained for the specified period.

Chapter 4: Standards for conduct of clinical trials (Articles 27 to 55)
Provisions to be followed by the medical institutions performing clinical trials scientifically and ethically

1) Provisions concerning the Institutional Review Boards (IRB) (Articles 27 to 34)
- An Institutional Review Board (IRB), which should meet the requirements specified in Article 28, must be established by the director of the medical institution performing the trial to review and discuss the proper conduct of clinical trials and other matters related to the trials. (However, it is not always necessary to establish an IRB in each medical institution performing the study.)
  - The IRB must review the ethical and scientific appropriateness of the clinical trial subject to review on the basis of the documents specified in Article 32, and state its opinion.
  - The 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.
  - 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.
  - The medical institution is not allowed to conduct a clinical trial when the opinion of the IRB is that it is not appropriate to conduct the trial.
  - When 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.
  - IRB may disclose information related to IRB review to enhance the level of transparency and secure quality of its review activities.

2) Provisions related to medical institutions performing clinical trials (Articles 35 to 41)
- Medical institutions performing clinical trials must have the facilities and personnel to undertake adequate clinical observations and laboratory testing, and they must be able to take the measures required when emergencies arise among the trial subjects.
- The director of the medical institution performing the trial must prepare SOP for work related to the trial, and take the necessary measures so that the clinical trial is conducted properly and smoothly in compliance with the trial protocol and the SOP.
- The director of the medical institution performing the trial must cooperate with monitoring or audits by the sponsor or the person conducting the clinical trial and review by the IRB.
- The director of a medical institution must appoint a person or persons to carry out trial-related clerical work.

3) Provisions related to investigators (Articles 42 to 49)
- The investigator must have sufficient clinical experience to be able to conduct the trial properly.
- The investigator must select the trial subjects in accordance with the objectives of the trial from the ethical and scientific standpoints. The necessary measures so that appropriate treatment can be given to subjects when adverse events occur must be taken beforehand.
- The investigator must prepare the proper case report forms as specified in the protocol, etc. and sign or seal them.
- When deaths suspected of being caused by adverse reactions of the investigational product or other serious adverse events occur, the investigator must immediately report this to the director of the medical institution performing the trial and inform the sponsor or the person supplied with the investigational product when the trial is investigator-initiated.

4) Provisions concerning informed consent of subjects (Articles 50 to 55)
- When a prospective subject is asked to participate in a clinical trial, the investigator must appropriately explain the contents of the clinical trial and other matters beforehand to the subject using "written information" containing required items, and obtain the written consent of the subject.
- The investigator making the explanation and the prospective subject must date and sign or seal the consent form to make the consent effective.

Chapter 5: Standards concerning reexamination data (Article 56)
GCP standards also apply to the collection and preparation of data concerning the results of post-marketing clinical trials to be submitted for reexaminations or reevaluations, but taking account of the nature of post-marketing clinical trials, certain provisions for clinical trials for new drug application are applied to those for reexamination and the required changes in reading shall be made accordingly in this article.

Chapter 6: Standards concerning sponsoring of clinical trials (Article 57 to 59)
These GCP standards also contain provisions concerning the acts of prospective sponsors of clinical trials or persons conducting the clinical trials (Article 57), institutions requested to perform clinical trials (Article 58) and clinical trial sponsors
(Article 59). However, since the scope of application differs from that of the standards related to approval review data, certain provisions for clinical trials for new drug application are applied for those for reexamination and the required changes in reading shall be made accordingly in this article.

Clinical trials performed to obtain data for approval applications must be conducted, results collected and data prepared in accordance with the GCP. In addition to clinical trials sponsored by companies, it is also possible for investigator-initiated clinical trials to be performed for the preparation of approval application data in compliance with the GCP.

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.

7) **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
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.

Further, the adoption of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) Guidelines in Japan has been proposed by the Ministry in light of the need for international harmonization and other reasons (Office Communication dated February 1, 2012).

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. Other

4.1 Biotechnological Products

The Guidelines for Manufacturing Drugs by using Recombinant DNA Technology were published to ensure manufacturing safety of products during the manufacture of pharmaceuticals with recombinant DNA technology (Notification No. 1051 of the PAB dated December 11, 1986, partially revised by Notification Nos. 434 and 769 of the PAB dated May 21, 1987 and August 18, 1995, respectively). The guidelines specify methods of safety evaluation of recombinants (live cells), classify the level of each working process into four levels, 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, identify the type of facilities and equipment necessary for the manufacture, and also specify the requirements for 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 MHLW 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 (the preceding guidelines were replaced by the Ordinance).

Separately, a notification entitled “Preparation of Data Required for Approval Applications for Drugs Manufactured by Using Recombinant DNA Technology” was issued as Notification No. 243 of the Evaluation and Regulation Division, PAB dated March 30, 1984 for the evaluation of the quality, efficacy, and safety of drugs produced by recombinant DNA technology, and then “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 notifications were issued based on discussion at ICH:


2. Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of R-DNA Derived Protein Products (ICH-Q5B): Notification No. 3 of the Evaluation and Licensing Division, PMSB dated January 6, 1998


5. Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process (ICH-Q5E): Notification No. 0426001 of the Evaluation and Licensing Division, PFSB dated April 26, 2005


7. Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH-S6(R)): Notification No. 0323-(1) of the Evaluation and Licensing Division, PFSB dated March 23, 2012

There are other notifications issued in relation to medicinal products to be developed and manufactured by using cells and tissues and those products for gene therapy.

- Guidelines of Quality and Safety Assurance of Drugs for Gene Therapy: Notification No. 0701-(4) of the Evaluation and Licensing Division, PFSB dated July 1, 2013

- Reporting of Information and Findings that May Affect the Evaluation of Drugs for Gene Therapy: Notification No. 0701-(7) of the Evaluation and Licensing Division, PFSB dated July 1, 2013

4.2 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
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, additional notifications have been issued to undertake self-inspection and coordinate various notifications. Manufacturers have been requested to undertake self-inspection and coordinate various notifications. The Standards for Biological Materials were specified in May 2003 and specifications for raw materials and packaging materials were used in the manufacture of biological products. The Standards for Biological Materials were partially amended (Notification No. 375, issued by MHLW in 2014).

In 2013, regenerative medicine products were characterized in the law separately from drugs or medical devices, and biological materials used in regenerative medicine products have been discussed to be standardized. In conjunction with global trends for the BSE risk in bovine-derived raw materials or the like, the Standards for Biological Materials were partially amended (Notification No. 210 issued by the MHLW in 2003).

4.3 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 the Guidelines on the Assurance of Quality, Efficacy, and Safety of Biosimilar Products were formulated (Notification No. 0304007 of the Evaluation and Licensing Division, PFSB 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 the Guidelines on the Assurance of Quality, Efficacy, and Safety of Biosimilar Products 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.

The application for a biosimilar product is required to contain detailed procedures and programs of postmarketing surveillance and risk management as directed in Appendix 9 of the Guidelines on the Assurance of Quality, Efficacy, and Safety of Biosimilar Products (Notification No. 0304007 of the Evaluation and Licensing Division, PFSB dated March 4, 2009). However, the Guidelines on the Risk Management Plan (RMP) issued later (Notification No. 0426-(2) of the Evaluation and Licensing Division, PFSB dated April 26, 2012) requires to attach an RMP, in place of post-marketing surveillance plan, to be included in the biosimilar product application submitted on or after April 1, 2013.

4.4 Public Disclosure of Information on New Drug Development

A notification concerning publication of information on new drug approvals was issued (Notification No. 1651 of the Evaluation and Licensing Division, PFSB 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, PFSB 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. 0422004 of the PMDA dated April 22, 2005, Notification No. 1126005 of the Licensing and Evaluation Division of PFSB dated November 26, 2007, and Notification No. 0325-(1) of the Evaluation and Licensing Division, PFSB dated March 25, 2013).

Information on approval reviews for new drugs is provided on the following websites: Japanese: 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 on 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, PFSB dated October 1, 2008 and Office Communication dated April 2, 2009).

4.5 ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use)

ICH is operated via the steering committee. The committee is the governing body of the ICH that determines policies and procedures and is consisted of six parties of regulators and research-based pharmaceutical industry representatives of the EU, Japan, and the United States: the Ministry of Health, Labour and Welfare (MHLW), Japan Pharmaceutical Manufacturers Association (JPMA), Food and Drug Administration (FDA), Pharmaceutical Research and Manufacturers of America (PhRMA), European Medicines Agency (EC/EMEA or EMEA as from December 2009), and European Federation of Pharmaceutical Industries’ Associations (EFPIA). World Health Organization (WHO), Canadian and the European Free Trade Association (EFTA) attend ICH meetings as observers. At present, ICH has expert working groups (EWG) 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 and analysis of topics to be addressed, analysis of issues, establishment of EWGs, and preparation of draft ICH guidelines
- **Step 2**: Consensus on technical issues for the drafted ICH guidelines and approval for public consultation in each ICH region
- **Step 3**: Regulatory consultation in the three regions, call for public comments, and revision of the draft guidelines based on comments received
- **Step 4**: Sign-off and adoption of the guidelines
- **Step 5**: Regulatory implementation of the guidelines according to regional requirements

Currently, over 70 topics (guidelines), including revised versions, have been agreed and approved (Step 4 or 5) based on ICH activities. As shown in Fig. 12 (ICH Topics and Guidelines—Progress of Harmonization).

In June 2012, ICH parties agreed on new principles of governance as summarized below:

1. To better define the roles of the parties in the process of guideline development, Step 2 was divided into 2a and 2b to request regulators and industry parties to cooperate in developing ICH guidelines as consensus technical documents at Step 2a and request regulators to release draft guidelines in each region for public consultation at Step 2b. Thereafter, the regulators have the ultimate responsibility in implementing the guidelines.

2. Each EWG is led by chairperson other than rapporteur during the guideline development process, and the chairperson is a representative of the regulators.

3. In circumstances when regulators and industry in 3 regions may not agree on a proposed topic for harmonization, the three ICH regulatory parties, when agree, may proceed with the topic, as an exceptional measure, irrespective of whether or not the topic is supported by the industry parties.

Visit the following websites for details of ICH guidelines.


Basic investigation
Screening tests
Study of manufacturing techniques/formulation and pharmaceutical research

Nonclinical studies
1. Physicochemistry
2. Toxicity on GLP
3. Pharmacology & pharmacokinetics

Evaluation of nonclinical studies
Clinical trial notification to PMDA
(Studies based on GCP)
1. Phase 1
2. Phase 2
3. Phase 3

Evaluation of clinical and nonclinical studies
New drug approval application

Clinical studies

Approval review
Pharmaceutical Affairs and Food Sanitation Council (PAFSC)
Nomination
Consultation
Experts
Notice of review results
Inquiry
Response
MHLW (Evaluation & Licensing Div, PFSB)
Minister of MHLW (final evaluation)

PMDA (KIKO)
Approval review
Compliance review
GMP review

Pharmaceutical Affairs Sections
Evaluation committees

Post-marketing surveillance (PMS)
1. Collection, documentation, and storing of PMS survey results
2. Postmarketing clinical studies
3. Reexamination
4. Reevaluation

(PGP · GPSP ordinances)

Approval and entry in NHI Price List

Fig. 8  Flowchart of New Drug Development and Approval
Timeline of the standard process of new drug approval

review time of 12 months from application to approval for new drugs for which applications are made from FY2014, assuming that no specific time-consuming situation may occur during the review.

Note 1) Past records of approval reviews for new drugs in FY2013 were used to determine a rough indication of review time. The number of individual processes from application to approval used in the calculation were as follows: Initial interview meeting: 35, Questions on key issues: 31, Expert review: 85, Evaluation by PAFSC: 83, Manufacturing/marketing authorization: 96.

Note 2) Questions on key issues: First questions issued following the initial interview

Fig. 9  Timeline of the standard process of new drug approval
<table>
<thead>
<tr>
<th>Left Column</th>
<th>Right Column</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A 1 2 3</td>
</tr>
<tr>
<td>(1) Drugs containing new active ingredients</td>
<td>○ ○ ○</td>
</tr>
<tr>
<td>(2) New prescription combination drugs</td>
<td>○ ○ ○</td>
</tr>
<tr>
<td>(3) Drugs with new routes of administration</td>
<td>○ ○ ○</td>
</tr>
<tr>
<td>(4) Drugs with new indications</td>
<td>○ ○ ○</td>
</tr>
<tr>
<td>(5) Prescription drugs with new dosage forms</td>
<td>○ ○ ○</td>
</tr>
<tr>
<td>(6) Drugs with new dosages</td>
<td>○ ○ ○</td>
</tr>
<tr>
<td>(7) Biosimilar Products</td>
<td>○ ○ ○</td>
</tr>
<tr>
<td>(8) Prescription drugs with additional dosage forms (during reexamination period)</td>
<td>○ ○ ○</td>
</tr>
<tr>
<td>(9) Prescription combination drugs with similar formulations (during reexamination period)</td>
<td>○ ○ ○</td>
</tr>
<tr>
<td>(10) Other prescription drugs (during reexamination period)</td>
<td>× × ×</td>
</tr>
</tbody>
</table>

Note 1) The marks and numbers in the columns on the right indicate the marks and numbers of the data specified in Attached Table 1, and the marks have the following meanings, in principle: ○: Data required ×: Data not required Δ : Data required depending on individual cases

Note 2) Note 1) in column on the right signifies as follows.

1) Only for applications that do not involve any change to information contained in the attached data, including change to the manufacturing method or change to the testing method, the attachment of data under H is not required, in principle.
(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.

<table>
<thead>
<tr>
<th>A</th>
<th>Origin or background of discovery, conditions of use in foreign countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Origin or background of discovery</td>
</tr>
<tr>
<td>2.</td>
<td>Conditions of use in foreign countries</td>
</tr>
<tr>
<td>3.</td>
<td>Special characteristics, comparisons with other drugs, etc.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B</th>
<th>Manufacturing methods, standards and test methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Chemical structure and physicochemical properties, etc.</td>
</tr>
<tr>
<td>2.</td>
<td>Manufacturing methods</td>
</tr>
<tr>
<td>3.</td>
<td>Standards and test methods</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C</th>
<th>Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Long-term storage tests</td>
</tr>
<tr>
<td>2.</td>
<td>Tests under severe conditions (stress tests)</td>
</tr>
<tr>
<td>3.</td>
<td>Accelerated tests</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D</th>
<th>Pharmacological action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Tests to support efficacy</td>
</tr>
<tr>
<td>2.</td>
<td>Secondary pharmacology, Safety pharmacology</td>
</tr>
<tr>
<td>3.</td>
<td>Other pharmacology</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>E</th>
<th>Absorption, distribution, metabolism, and excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Absorption</td>
</tr>
<tr>
<td>2.</td>
<td>Distribution</td>
</tr>
<tr>
<td>3.</td>
<td>Metabolism</td>
</tr>
<tr>
<td>4.</td>
<td>Excretion</td>
</tr>
<tr>
<td>5.</td>
<td>Bioequivalence</td>
</tr>
<tr>
<td>6.</td>
<td>Other pharmacokinetics</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>F</th>
<th>Acute, subacute, and chronic toxicity, teratogenicity, and other types of toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Single dose toxicity</td>
</tr>
<tr>
<td>2.</td>
<td>Repeated dose toxicity</td>
</tr>
<tr>
<td>3.</td>
<td>Genotoxicity</td>
</tr>
<tr>
<td>4.</td>
<td>Carcinogenicity</td>
</tr>
<tr>
<td>5.</td>
<td>Reproductive toxicity</td>
</tr>
<tr>
<td>6.</td>
<td>Local irritation</td>
</tr>
<tr>
<td>7.</td>
<td>Other toxicity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>G</th>
<th>Clinical studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trial results</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>H</th>
<th>Information in the attached data, etc. provided for in Article 52, Paragraph 1 of the Law</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information in the attached data, etc.</td>
<td></td>
</tr>
</tbody>
</table>
Table 4  Data to be Submitted with an Application for a Non-prescription Drug
(Attached Table 2-2 in PFSB Notification No. 1121-(2) dated November 21, 2014)

<table>
<thead>
<tr>
<th>Left Column</th>
<th>Right Column</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 1 2 3</td>
<td>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 H</td>
</tr>
<tr>
<td>(1) Drugs containing new active ingredients</td>
<td>○ ○ ○</td>
</tr>
<tr>
<td>(2) Drugs with new routes of administration</td>
<td>○ ○ ○</td>
</tr>
<tr>
<td>(3-1) Drugs with new indications</td>
<td>○ ○ ○</td>
</tr>
<tr>
<td>(3-2) Prescription drugs with new dosage forms</td>
<td>○ ○ ○</td>
</tr>
<tr>
<td>(3-3) Drugs with new dosages</td>
<td>○ ○ ○</td>
</tr>
<tr>
<td>(4) Non-prescription drugs with new active ingredients for non-prescription drugs</td>
<td>○ ○ ○</td>
</tr>
<tr>
<td>(5-1) Non-prescription drugs with new administration routes for non-prescription drugs</td>
<td>○ ○ ○</td>
</tr>
<tr>
<td>(5-2) Non-prescription drugs with new indications for non-prescription drugs</td>
<td>○ ○ ○</td>
</tr>
<tr>
<td>(5-3) Non-prescription drug with new formulation for non-prescription drug</td>
<td>○ ○ ○</td>
</tr>
<tr>
<td>(5-4) Non-prescription drugs with new doses for non-prescription drugs</td>
<td>○ ○ ○</td>
</tr>
<tr>
<td>(6) New non-prescription combination drugs</td>
<td>○ ○ ○</td>
</tr>
<tr>
<td>(7-1) Non-prescription combination drugs with similar formulations</td>
<td>× × ○</td>
</tr>
<tr>
<td>(7-2) Non-prescription combination drugs with similar dosage forms</td>
<td>× × ○</td>
</tr>
<tr>
<td>(8) Other non-prescription drugs (drugs with approval standards, etc)</td>
<td>× × ○</td>
</tr>
</tbody>
</table>

Note 1) The marks and numbers in the columns on the right indicate the marks and numbers of the data specified in Attached Table 1, and the marks have the following meanings, in principle: ○: Data required ×: Data not required △: Data required depending on individual cases

Note 2) Notes 1) and 2) in column on the right signify as follows.

1) 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.

2) 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.

5) (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.

(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.

“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 a new dosage form leading to changes in dosage/administration because of pharmaceutical changes such as sustained release, which are classified into either of non-prescription drugs or guidance-mandatory drugs.

“Non-prescription drugs with new dosage/administrations for non-prescription drugs” refer to non-prescription drugs other than drugs with new dosage/administrations and have the same active ingredients and routes of administration as approved non-prescription drugs but have different dosage/administrations, which are classified into either of non-prescription drugs or guidance-mandatory drugs.

6) “New non-prescription combination drugs” refer to non-prescription drugs with the same ingredients as active ingredients of approved non-prescription drugs but with a different active ingredient composition, which are classified into either of non-prescription drugs or guidance-mandatory drugs. Those determined to have a similar active ingredient composition to approved non-prescription drugs are excluded. Basically, the drugs in No. 1. (1)-(1) a) to f) in Notification No. 0331053 of the PFSB dated March 31 2008 are equivalent to new non-prescription combination drugs.

7) (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.

(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.

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 |
| H | Information in the attached data, etc. provided for in Article 52, Paragraph 1 of the Law | Information in the attached data, etc. |
Table 5  Classification of Clinical Studies According to Objectives

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Objective of study</th>
<th>Study examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human pharmacology studies</td>
<td>• Assess tolerance</td>
<td>• Dose-tolerance studies</td>
</tr>
<tr>
<td></td>
<td>• Define/describe PK and PD</td>
<td>• Single and multiple dose PK and/or PD studies</td>
</tr>
<tr>
<td></td>
<td>• Explore drug metabolism and drug interactions</td>
<td>• Drug interaction studies</td>
</tr>
<tr>
<td></td>
<td>• Estimate activity</td>
<td>• ADME studies</td>
</tr>
<tr>
<td>Therapeutic exploratory studies</td>
<td>• Explore use for the targeted indication</td>
<td>• Earliest studies of relatively short duration in well-defined narrow patient populations, using surrogate or pharmacological endpoints or clinical measures</td>
</tr>
<tr>
<td></td>
<td>• Dose-response exploration studies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Provide basis for confirmatory study design, endpoints, methodologies</td>
<td></td>
</tr>
<tr>
<td>Therapeutic confirmatory studies</td>
<td>• Demonstrate/confirm efficacy</td>
<td>• Adequate, and well controlled studies to establish efficacy</td>
</tr>
<tr>
<td></td>
<td>• Establish safety profile</td>
<td>• Safety studies</td>
</tr>
<tr>
<td></td>
<td>• Provide an adequate basis for assessing the benefit/risk relationship to support licensing</td>
<td>• Large simple studies</td>
</tr>
<tr>
<td>Therapeutic use studies</td>
<td>• Refine understanding of benefit/risk relationship in general or special populations and/or environments</td>
<td>• Comparative effectiveness studies</td>
</tr>
<tr>
<td></td>
<td>• Identify less common adverse reactions</td>
<td>• Studies of mortality/morbidity outcomes</td>
</tr>
<tr>
<td></td>
<td>• Refine dosing recommendation</td>
<td>• Large simple studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pharmacoeconomic studies</td>
</tr>
</tbody>
</table>
Fig. 10  Organization of ICH Common Technical Documents
This matrix graph illustrates the relationship between the phases of development and types of study by objective that may be conducted during each clinical development of a new medicinal product. The shaded circles show the types of study most usually conducted in a certain phase of development, the open circles show certain types of study that may be conducted in that phase of development but are less usual. Each circle represents an individual study. To illustrate the development of a single study, one circle is joined by a dotted line to an inset column that depicts the elements and sequence of an individual study.
### Table 6  ICH topics and guidelines - Progress of harmonization


<table>
<thead>
<tr>
<th>Code</th>
<th>Previous code</th>
<th>Topics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 5</td>
<td></td>
<td>Stability testing: New drug substances and products</td>
</tr>
<tr>
<td>Q1A(R2)</td>
<td></td>
<td>Stability testing: Photostability</td>
</tr>
<tr>
<td>Q1B</td>
<td></td>
<td>Validation of analytical procedures: Text and methodology</td>
</tr>
<tr>
<td>Q1C</td>
<td></td>
<td>Impurities in new drug substances</td>
</tr>
<tr>
<td>Q1D</td>
<td></td>
<td>Impurities in new drug products</td>
</tr>
<tr>
<td>Q1E</td>
<td></td>
<td>Impurities: Residual solvents</td>
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<tr>
<td>Q2(R1)</td>
<td>Q2A, Q2B</td>
<td>Pharmacopoeias: Harmonized texts for use in ICH regions</td>
</tr>
<tr>
<td>Q3A(R2)</td>
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<td>Test for residue on ignition</td>
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<tr>
<td>Q3B(R2)</td>
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CHAPTER 4
Post-marketing Surveillance of Drugs

Post-marketing surveillance (PMS) to assure the quality, 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 ADRs and infections collection and reporting system, the reexamination system, and the reevaluation system (Fig. 13. Pharmaceutical Post-marketing Surveillance System).

The re-examination system for new drugs was introduced in the October 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 in “MHW Ordinance for Good Post-Marketing Surveillance Practice of Drugs (Drug GPMSP)” and came into effect in April 1997 (MHW Ordinance No. 10 dated March 10, 1997). The Drug GPMSP was partially revised by MHW Ordinance No. 151 dated December 27, 2000, and “Early Post-marketing Phase Vigilance” for new drugs was newly established to reinforce safety measures in an early phase of marketing (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, PMSB dated March 27, 1997 to replace the previous annual reporting system with the PSUR (MHW Ordinance No. 29 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, PMSB dated March 27, 1997) were specified for drug use-result surveys to be intensively implemented after marketing. 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, PMSB and entries in case report forms for ADRs and infections (Office Communication) were specified in March 11, 1998. Furthermore, additional guidelines, “Periodic Infection Reporting System for Biological Products” (Notification No. 0515008 of the PMSB dated May 15, 2003) and “Implementation of Early Post-marketing Phase Vigilance for Prescription Drugs” (Notification No. 0324001, the Safety Division, PFSB dated March 24, 2006) were issued to further strengthen the safety monitoring of medical products (Fig. 14. Post-marketing Collection and Reporting of Pharmaceutical Safety Information).

In the revised Pharmaceutical Affairs Law enforced on April 1, 2005, the historical manufacturing approval system was changed to the marketing (as well as manufacturing) authorization system to internationally harmonize the concept of approval system, and 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 was separated from 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, quasi-drugs, Cosmetics and Medical Devices, MHLW Ordinance No. 135 dated September 22, 2004), and the latter in the MHLW Ordinance on GSP (MHLW Ordinance Related to Standards for Conducting Post-Marketing Surveys and Studies on Drugs; MHLW Ordinance No. 171 issued by MHLW on December 20, 2004). The MHLW Ordinance on GPMSP was abolished.

The Guidelines on Pharmacovigilance Planning (ICH E2E guidelines) (Notification No. 0916001 of the Evaluation and Licensing Division, PFSB and Notification No. 0916001 of the Safety Division, PFSB both dated September 16, 2005) were issued with an objective of guiding and assisting the applicant in planning pharmacovigilance activities for new drug in the early post-marketing phase. In 2012, the Risk Management (RMP) Guidance (Notification No. 0411-(1) of the Safety Division, PFSB and No. 0411-(2) of the Evaluation and Licensing Division, PFSB both dated April 11, 2012) was issued to support the manufacturing/marketing authorization holder in developing the RMP including risk minimization plans for the reduction of treatment-related risks in addition to conventional pharmacovigilance plans following drug approval. These Notifications are applicable to manufacturing/marketing approval application for new drugs and biosimilar products submitted on or after April 1, 2013 and August 26, 2014, respectively. Further, the MHLW Ordinances on GVP and GSP were revised on March 11, 2013 to ensure the development and subsequent implementation of risk management plan (RMP).

The Law for Partial Amendment of the Pharmaceutical Affairs Law (Law No. 84, 2013) was issued on November 27, 2013, in which regenerative medicine products were newly defined. In line with the provisions in Article 23-21, Item 2 in the revised Law, the “Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices”, the MHLW Ordinance on GVP (MHLW Ordinance for the standards for post-marketing safety management of drugs, quasi-drugs, cosmetics, medical devices and regenerative medicine products) was partially revised to be the standards for licensing manufacturing/marketing authorization holder in developing the RMP including risk minimization plans for the reduction of treatment-related risks in addition to conventional pharmacovigilance plans following drug approval. These Notifications are applicable to manufacturing/marketing approval application for new drugs and biosimilar products submitted on or after April 1, 2013 and August 26, 2014, respectively. Further, the MHLW Ordinances on GVP and GSP were revised on March 11, 2013 to ensure the development and subsequent implementation of risk management plan (RMP).

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Based on the Guidelines, Periodic Safety Update Reports (PSUR) for Marketed Drugs which objective was the standardization of the format and time of safety reporting, the new Guidelines, the Periodic Benefit-Risk Evaluation Report (PBRER: ICH E2C (R2)) with the objective of assessing not only risks but also integrated risk-benefit balance and a guidance for assisting safety report writing was issued (Notification No. 0517-(1) of the Evaluation and Licensing Division, PFSB both dated May 17, 2013). In August 2014, Q&A on PBRER was also issued (Office Communication, August 25, 2014).

The use of the Medical Dictionary for Regulatory Activities (MedDRA) as agreed by ICH is recommended to standardize international regulatory-related medical terminology (M1) use at all regulatory levels before and after marketing for regulatory communication in August 25, 2014).

Licensing Division, PFSB both dated May 17, 2013). In August 2014, Q&A on PBRER was also issued (Office Communication, August 25, 2014).

The use of the Medical Dictionary for Regulatory Activities (MedDRA) as agreed by ICH is recommended to standardize international regulatory-related medical terminology (M1) 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 ADRs 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 manufacturing/marketing authorization holder, development and implementation of relevant SOPs, marketed drugs, etc., and to the implementation of measures for safety assurance. On March 11, 2013, the GVP was revised to incorporate the RMP in the GVP guidelines.

The extent of duties of the manufacturing/ market authorization holder in post-marketing safety management to be entrusted to third parties is defined in the Ordinance for Enforcement of the Drugs and Medical Devices Law.

This GVP consists of 17 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 Drugs and Medical Devices 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] The RMP refers to safety assurance activities including clinical information collection, post-marketing surveys, clinical studies, and other activities for minimizing potential risks inherent in the use of new drugs, etc. with an objective of adequate risk control of new drugs, etc. by analyzing safety and efficacy information to be thus obtained and implementing necessary safety assurance measures. These activities are undertaken by the manufacturing/marketing authorization holder following commencement of marketing of new drugs, etc. that poses specific safety and/or efficacy concerns. The RMP 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 manufacturing/marketing authorization holder (manufacturing/marketing authorization holders of prescription drugs, highly controlled medical devices or regenerative medicine product).

(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 involved in safety management.

[4] To closely collaborate with the supervisor of post-marketing surveys, etc. in implementing the RMP.

(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 whole 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 reporting from safety management implementation supervisor to safety management supervisors
- Procedures for implementing the RMP (including procedures for early post-marketing phase vigilance) when the RMP is required in practice
- 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
- Procedures for collaborating with the supervisors on post-marketing surveillance and other post-marketing obligations when the RMP is required in practice
- 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 proper and smooth implementation of safety assurance activities must be specified in writing.


[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)

[1] The safety management supervisor shall perform the following duties:
- Overall supervision of safety assurance work
- Confirmation that safety assurance work is being performed properly 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
- To closely collaborate with the supervisor of post-marketing surveys, etc. in implementing the RMP.

(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 thereof shall be prepared.
- 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 manufacturing/marketing authorization holders
- Other safety management information


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

[1] The safety management supervisor shall perform the following duties:
- Examine the collected safety management information without delay and record the results thereof.
- Supply all safety information that the quality assurance supervisor must be familiar with in
writing without delay to the quality assurance supervisor.

• When it is confirmed necessary from an examination of safety management information, measures shall be drafted to discard, recall or suspend 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.

• Drafts of safety assurance measures shall be reported in writing to the general marketing compliance officer and copies shall be retained.

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

(9) Implementation of safety assurance measures

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

• Appropriately evaluate drafts of safety assurance measures, decide the safety assurance measures to be taken and prepare and retain records thereof.

• When safety management supervisors undertake safety assurance measures, instructions shall be issued in writing and retained.

• When safety management implementation supervisors undertake safety assurance measures, instructions shall be issued in writing and the safety management supervisor shall retain copies. The safety management implementation supervisor shall prepare records and make reports in writing. The copies shall be given to the safety management supervisor.

[2] The safety management supervisor shall perform the following duties:

• Safety assurance measures shall be undertaken based on instructions from the general marketing compliance officer and records thereof shall be prepared and retained.

• When safety assurance measures are undertaken by safety management implementation supervisors, instructions shall be issued in writing and copies shall be retained. Records shall be prepared, reported in writing and retained.

• The results of implementation of safety assurance measures shall be reported in writing to the general marketing compliance officer, and copies 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) Risk management plan (RMP) (Article 9-(2))

[1] The general marketing compliance officer or the safety management supervisor must undertake the following duties in implementing the RMP:

• Preparation of protocol for individual RMPs ("RMP protocol") that contain the following information:
  
  • Specific safety and efficacy issues to be addressed
  
  • Outline of plans and procedures for information collection, survey, and study of safety and efficacy issues to be resolved
  
  • Outline of risk minimization activities
  
  • Time schedules of the RMP implementation status and evaluation
  
  • Other necessary items

• Revision of the RMP protocol as situations may require

• When the RMP protocol is prepared or revised, the protocol shall be dated and retained.

[2] The general marketing compliance officer must make available the RMP protocol in his/her office and also must make available copies of the RMP protocol specifying assigned activities and procedures in other offices performing the compliance activities.

[3] The safety management supervisor must confirm that the RMP is being adequately and smoothly implemented, and shall retain records of such confirmation.

[4] Whenever performing RMP-related activities, the safety management implementation supervisor must records the activities performed and report the activities in writing to the safety management supervisor, and the safety management supervisor must retain the reports.

(11) Early post-marketing phase vigilance (Article 10)

[1] The general marketing compliance officer and the safety management supervisor must undertake the following duties in implementing early post-marketing phase vigilance (a survey performed for risk management of new drugs, etc. over a 6-month period following launch to promote optimal use in practice and closely monitor serious ADRs of new drugs, etc.).

• Preparation of a protocol based on the RMP for individual post-marketing phase vigilances (early post-marketing phase vigilance protocol) containing the following
The safety management supervisor shall make available early post-marketing phase vigilance protocol in the office performing the work and also must make available copies in other offices performing surveillance work.

The safety management supervisor shall confirm that early post-marketing phase vigilance is being performed appropriately and smoothly and records of such confirmation shall be prepared and retained.

When early post-marketing phase vigilance 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.

(12) In-House inspections (Article 11)

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

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

(3) When the person appointed beforehand in [1] is a person other than the safety management supervisor, that person shall prepare records of in-house inspections and report in writing to the safety management supervisor. The safety management supervisor shall retain these reports.

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

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

(13) Education and training (Article 12)

(1) The general marketing compliance officer shall prepare and retain education and training protocols for employees engaged in duties related to post-marketing safety 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. GPSP

The 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 manufacturing/marketing authorization holders, and to assure the reliability of data submitted when applying for reexamination or re-evaluation. On March 11, 2013, the GPSP was revised to harmonize its provisions with those of GVP in view of the incorporation of the RMP in the GVP.

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 manufacturing/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 re-evaluation 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 manufacturing/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 manufacturing/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 manufacturing/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 manufacturing/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.

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

1) A supervisor of the manufacturing/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 surveys, etc.:

- To prepare and preserve a basic protocol for post-marketing surveys, etc. for each drug individually.
- To set forth in writing protocols for the implementation of drug-use result surveys, protocol for post-marketing clinical studies, and any other matters necessary for conducting post-marketing surveys, etc. in accordance with the standard operating procedures for post-marketing surveys, etc. and the basic protocol on post-marketing surveys, etc. (instead, the RMP, if available)
- To revise the basic protocol for post-marketing surveys, etc. as required.
- In cases in which a basic protocol for post-marketing surveys, etc. is prepared or revised, to date and preserve it.
- When it is considered necessary for the conduct of post-marketing surveys, etc., to provide written opinions to the manufacturing/marketing authorization holder, and to preserve these documents or
Duties to be performed by the supervisor of post-marketing surveys, etc. (Article 5)

1. To prepare plans, proposals and surveys for implementation of post-marketing surveys, etc.
2. To confirm that post-marketing surveys, etc. are conducted properly and smoothly in accordance with the standard operating procedures for duties for post-marketing surveys, etc. and the basic protocol on post-marketing surveys, etc. (instead the RMP, if available)
3. To provide notification in writing of the results of post-marketing surveys, etc. to the manufacturing/marketing authorization holder (instead the manufacturing/marketing authorization holder and the safety management supervisor, if the RMP is available)

Post-marketing surveys, etc. (Article 6)

1. The manufacturing/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.
2. The manufacturing/marketing authorization holder must instruct the supervisors on post-marketing surveillance and other post-marketing obligations to report in writing the conduct and outcomes of each drug-use results survey and post-marketing clinical studies to the safety management supervisor when the RMP is available for practice.

Drug use-results surveys (Article 6)

1. The manufacturing/marketing authorization holder must instruct the supervisor or other designated person to conduct drug use-results surveys according to the post-marketing surveillance SOP, etc.
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 items and method and other necessary matters must be established.

Post-marketing clinical studies (Article 7)

1. The manufacturing/marketing authorization holder must perform post-marketing studies by the post-marketing surveillance supervisor or other person designated by the manufacturing/marketing authorization holder based on the post-marketing surveillance, etc.
2. The studies must be conducted in compliance with GCP.

In-House inspections (Article 8)

1. The manufacturing/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.

Education and training (Article 9)

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 manufacturing/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.

Delegation of duties of post-marketing surveys, etc. (Article 10)

The manufacturing/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.

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. PAPER COMPLIANCE REVIEW AND ON-SITE GPSP SURVEYS OF DATA FOR REEXAMINATION AND REEVALUATION

Documents and data submitted for reexamination and reevaluation of a drug are subject to paper compliance review and on-site GPSP surveys in order to examine whether the materials for evaluation have been collected in accordance with the standards specified by the MHLW minister. Detailed procedures for the compliance review and on-site surveys are available as “the Guidelines on Compliance Paper Reviews on Approval Application Data for New Drugs” (Notification No. 1121-5 of the Evaluation and Licensing Division, PFSB dated November 21, 2014), and “the Guidelines for Implementation of GPSP On-site Surveys” (Notification No. 0330003 of the Evaluation and Licensing Division, PFSB dated March 30, 2005). Procedures for applying paper review and on-site surveys are specified in the “Application Procedures for Paper Review-Conformity Inspection and On-site GCP Inspection of Data for the Reexamination and Reevaluation of Drugs” (Notification No. 1121007 of the PMDA dated November 21, 2014).

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 68-10), 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 PFSB dated March 17, 2005 for enforcement of MHLW Ordinance for Partial Amendment of the Enforcement Regulations of Pharmaceutical Affairs Law (Reporting of Adverse Drug Reactions, etc.). 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 phase vigilance among adverse reactions of drugs other than drugs with new active ingredients for which early post-marketing phase vigilance 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 in Japan and overseas.

(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 the ICH E2D guideline were announced as “the Standards for expediting reporting of post-approval safety data” (Notification No. 0328007 of the Safety Division, PFSB 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. In July 2013, the Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs) (ICH E2B) was summarized and then its Japanese version was issued (Notification No. 0708-(5) of the Evaluation and Licensing Division and Notification No. 0708-(1) of the Safety Division, PFSB both dated July 8, 2013). Then, “ADR Reporting in Post-marketing Surveillance and Clinical Trials in accordance with the Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs) (E2B (R3))” (Notification No. 0917-(1) of the Evaluation and Licensing Division and Notification No. 0917-(2) of the Safety Division, PFSB both dated September 17, 2013) was issued for guiding principles on how to handle safety reporting and recommends reporting via internet to further promote electronic data processing and electronic database compilation.

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

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 (Article 77-(4)-2-2).

* The Pharmaceutical Affairs Law revised on June 14, 2006 (Law No. 69 enforced in 2009) also requests the registered manufacturing/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 (ARTICLE 68-14 and 68-24 in THE LAW)

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.

6. REEXISTAMINATION SYSTEM (ARTICLE 14-4 AND 23-29 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**

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 the 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. In May 2013, the PSUR system was replaced with the periodic benefit-risk evaluation report (PBRER) system following the release of ICH E2C (R2) guidelines.

As the base date for the reporting period of these reports, the concept of the international birth date in the PBRER 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 PBRER 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 PBRER 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; conclusion; 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 2-3 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 (ARTICLES 14-6 AND 23-31 OF THE LAW)

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 in Notification No. 610 of the PMSB dated July 7, 1971. 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 the "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, PMSB) and on November 24, 2006 (Notification No. 1124004 of the Evaluation and Licensing Division, PFSB) and February 29, 2012 (Notification No. 0229-(10) 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.
Post-marketing surveillance (PMS) system

- GVP, GPSP (GCP)
  - Adverse reaction and infectious disease reporting (ADR) system
    - Drug •medical device safety information reporting system by medical personnel
    - ADR and infectious disease reporting system by company
    - WHO international pharmaceutical monitoring system
  
- Reexamination system
  - Reexamination application
  
- Reevaluation system
  - Periodic safety reports - ICH PBRER

**Fig. 12** Pharmaceutical Post-marketing Surveillance System
Drug use-results surveys, special survey, and post-marketing clinical trials

Planning of early post-marketing phase vigilance

Visits of MRs to physicians to provide safety information and to ask cooperation

Marketing

6 months

Early post-marketing phase vigilance

Promotion of proper use of drugs by means of periodic visits, sending letters, faxes, and E-mails to physicians by marketing authorization holders and wholesalers

ADR and other safety information

Pharmaceutical safety information reporting system

Safety reporting system by pharmaceutical companies

Fig. 13 Post-marketing Collection and Reporting of Pharmaceutical Safety Information
Fig. 14  Collection and Reporting of Pharmaceutical Safety Information
Fig. 15  Reexamination System
Fig. 16  Reevaluation System
CHAPTER 5
Supply and Dissemination of Drug Safety Management Information

Manufacturing/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 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 Law. The Law specifies items which must be included in package inserts or containers/wrappers (package insert information), points to consider in preparing package inserts and items which are not allowed to be included in package inserts. The revised Law enacted on November 25, 2014 included the provisions that package insert information should be based on scientific knowledge and information obtained in latest literatures, etc. and that brand names and precautions for usage and handling should be noticed prior to initiation of manufacturing/marketing or amendment followed by prompt publication. 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 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 special committees 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 PMSB dated May 15, 2003) and “the Guidelines for Entries in Package Inserts of Biological Products” (Notification No. 0520004 of the Safety Division, PMSB dated May 20, 2003). These notifications came into effect from July 2003.

Labeling was changed with the amendment of the Law in April 2005. “Manufacturer and importer” was changed to “marketing authorization holder” (Notification No. 0331008 of the Compliance and Narcotics Division, PFSB dated March 31, 2005, “Handling of Labeling of Drugs in the Amended Pharmaceutical Affairs Law”). “Drug requiring a prescription” was changed to “prescription drug” and “Caution: Use under prescription from a physician, etc.” was to be entered based on Notification No. 0210001 of the PFSB dated February 2005, “Designation of prescription drugs.”

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.

The notification entitled “Enforcement of The Law for Partial Amendment of the Pharmaceutical Affairs Law” (Notification No. 0806-(3) of PFSB dated August 6, 2014) specified that precautions for usage and handling (package insert information) based on the latest scientific knowledge and information should be prepared to promptly reflect essential cautions, etc. based on outcome from evaluation of safety information including adverse drug reactions collected according to the provisions in the Law.
and the MHLW Ordinance on GVP. Package inserts must include the package insert information based on latest findings, nonetheless package inserts prior to amendment may be attached in the following exceptional amendment case:

(1) When the products had already been manufactured and distributed prior to amendment of package insert information (post-marketing products),
(2) When all of the following requirements were met:
   i. The products are manufactured and distributed within 6 months after the amendment date (within 1 year in cases of amendment of package insert information of products requiring testing or multiple products, which cannot be manufactured and marketed promptly with the amended package insert information),
   ii. The amended package insert information are published on the PMDA website, and
   iii. The manufacturing/marketing authorization holder of the product may promptly notify users including physicians or pharmacists of information on amendment of package insert information.

For submission of notifications, it was specified in the “Points to consider for notification of package insert information” (Notification No. 0901-(1) of the Safety Division, PFSB dated September 1, 2014) that notifications should be submitted on the web page for notification via the PMDA website before initiation of manufacturing/marketing in cases of notifications for products to be newly manufactured/marketed including new drugs (nonetheless, when information provision to medical institutions, etc. is started prior to initiation of manufacturing/marketing, the notification should be submitted in advance preferably), or before the initiation date of information provision of the amendment or the initiation date of manufacturing/marketing of products with the amended package insert, whichever is earlier, in cases of amendment of package insert information. It was also specified that package insert information should be published on the PMDA website promptly upon submission of the notification to the PMDA. Nonetheless, when there is a certain time between the notification date and the amendment date of package insert information, publication may be made in line with the scheduled amendment date.

Of note, it is possible that information provision of the amended package insert information may be initiated upon submission of the notification to the PMDA, however it is recommended that such information is provided upon confirmation of PMDA’s acceptance, because some modification may be needed when any inadequacy was found at confirmation from the PMDA (Office Communication of the Safety Division, PFSB dated September 1, 2014).

1.1 Guidance on the Style and Format of Package Inserts

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 Heads 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 PMSB and Notification No. 0520004 of the Safety Division, PMSB). 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.

* Heads and Their Sequence in Package Inserts
  1) Date of preparation and/or revision(s) of the package insert
  2) Standard Commodity Classification No. of
1.3 Precautions

Reference: Age classification for pediatric use (basic standards)
- Children: under 15 years of age
- Small children: under 7 years of age
- Infants: under 1 year of age
- Newborns (neonates): under 4 weeks of age
- Low birth weight infants (premature infants): body weight of less than 2,500 g (according to the WHO recommendation)

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 PMSB and Notification No. 0520004 of the Safety Division, PMSB) for details concerning the contents of Precautions.

* Headings used with precautions
1) "Warning" (in red letters and encased in red at the beginning of "Precautions")
2) "Contraindications" (in black letters and encased in red following "Warning" in principle. However, at the beginning of the Precautions when there is no "Warning")
   (1) Contraindications ("This product is contraindicated in the following patients.")
   (2) Relative contraindications ("As a general rule, this product is contraindicated in the following patients. If the use of this product is considered essential, it should be administered with care.")
3) Precautions related to indications (In the event of such precautions, they are entered under the heading "Indications" in the package insert.)
4) Precautions related to dosage and administration (In the event of such precautions, they are entered under the heading "Dosage and Administration" in the package insert.)
5) Careful administration ("This product should be administered with care to the following patients.")
6) Important precautions
7) Drug interactions
   (1) Contraindications for coadministration ("This product should not be coadministered with the following drugs.") (in black letters and encased in red, with simple explanation provided under "Contraindications" above.)
(2) Precautions for coadministration
The MHW issued an office communication stressing that the Drug Interaction section must be based on the most recent scientific findings [office communication dated December 25, 2000 as a supplement of Notification No. 607 of PAB, MHW].

8) Adverse reactions (incidence shown in numerical values whenever possible)
* A key to the frequency of adverse reactions should be provided at the beginning.
(1) Clinically significant adverse reactions
(2) Other adverse reactions

9) Use in the elderly
10) Use during pregnancy, delivery, or lactation
11) Pediatric use (low birth weight infants, newborns, infants, small children, children)

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 1, 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. FPMAJ Notification No. 165 was canceled by the above voluntary agreement, and the above Office Communication of the Safety Division, PAB dated June 3, 1991 was also canceled by Notification No. 0409001 of the Safety Division, PMSB 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 for handling
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. The notifications issued jointly by directors of the Evaluation and Licensing Division and the Safety Division, PFSB specified handling of brand names of prescription combination drugs and heparin preparations (injection) and labeling of solutions attached to injection (Notification No. 0922002 of the Evaluation and Licensing Division, PFSB and No. 0922002 of the Safety Division, PFSB dated September 22, 2008) and handling of brand names of insulin preparations (Notification No. 0331001 of the Evaluation and Licensing Division, PFSB and No. 0331001 of the Safety Division, PFSB dated March 31, 2012). Handling of brand names of prescription combination drugs and insulin preparations was partially amended in Notification No. 0710-(7) of the Evaluation and Licensing Division, PFSB and No. 0710-(5) of the Safety Division, PFSB dated July 10, 2014. The brand name of generic drugs is required to be a name based on the Japanese Accepted Name as directed in Notification No. 0922001 of the Evaluation and Licensing Division, PFSB and No. 0922002 of the Safety Division, PFSB dated September 22, 2005 and the brand name of biosimilar products as directed in Notification No. 0214-(1) of the Evaluation and Licensing Division, PFSB dated February 14, 2013.

For generic drugs of combination drugs, unified brand names had been discussed, and since August 2013, these have been managed in accordance with voluntary consensus that unified brand names may be retained by Japan Society of Generic Medicines as trade names and used by companies on a license basis.

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 drugs prepared by manufacturing/marketing authorization holders in Japan is available on the following JPMA homepage:

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 of use to provide more detailed information about pharmaceutical products.

#### 2.1 Outline of Prescription Pharmaceutical Product Information

The Outline of Prescription Pharmaceutical Product Information is prepared by the manufacturing/marketing authorization holders with the objective of providing accurate and appropriate information to health professionals to assure proper use of their drugs. The brochure is available in two types: the general outline version explaining the entire description of the product (containing information under all headings of package insert) and property-specific version (containing information under certain headings of package insert such as clinical studies and clinical pharmacology).

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 (revised in June 2013), but the contents also follow the MHLW notification on the Guidelines for Preparation of Package Inserts. The document must also comply with the JPMA Promotion Code for Prescription Drugs.

New drugs that are approved after October 2001 are marked with a logo indicating that the drug is subject to early post-marketing phase vigilance for such a period of time as specified in labeling (refer to Chapter 4, 1. 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 April 2013, and interview forms (IF) are being prepared in the new format for new drugs approved from October 2013.

### 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 these are 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 November 25, 2014. This flowchart is posted on the webpage for supply of information on drugs and medical devices.

http://www.info.pmda.go.jp/iyaku/file/h261126-003_1.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 advice meeting 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) advice meeting, convening a meeting of experts, and taking measures (refer to Fig. 18 and Fig. 19).

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/bunyosoudan.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. Practices for disseminating such information are specified in Notification No. 1031-(1) of the Safety Division, PFSB dated October 31, 2014.

(1) Situations

- Situations where cases of deaths, disabilities, events that may lead to 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) 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.

Of note, for drugs of which package insert information are subjected to be notified, manufacturing/marketing authorization holders must notify the PMDA of details of amendment in package inserts prior to publication on the website of companies or the like.

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 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. 1031-(1) of the Safety Division, PFSB dated October 31, 2014.

2) Format and content

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.

3) Methods of information dissemination

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. 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.

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.

Of note, for drugs of which package insert information are subjected to be notified, manufacturing/marketing authorization holders must notify the PMDA of details of amendment in package inserts prior to publication on the website of companies or the like.

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.

3.3 Distribution of Information by 'Notices of Revision of Precautions'

1) Preparation criteria

1) Cases where the Director of the Safety Division of PFSB 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 content

The paper must not be yellow or blue.

3) Methods of information 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) Distribution

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
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 disseminates 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 50,000 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 phase vigilance for such a period of time as specified in labeling (refer to Chapter 4, 3. GVP).

4. ELECTRONIC INFORMATION DISSEMINATION

The MHLW received a report from its special committee on policies to supply drug information to health professionals, etc. using the Internet, which was established in 1997, 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 Yellow Letters (formally-called Dear Doctor Letters)/Blue 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.

The PMDA is providing services free (via PMDA medi-navi) to distribute safety-related information such as revisions to precautions in use of drugs, which has been
placed on the Agency’s homepage, to medical personnel who have registered their e-mail address with the Agency. As of the end-November 2014, approximately 110,000 reports are accessible via the navi.

5. PACKAGE INSERTS OF NON-PRESCRIPTION DRUGS

The MHW established a special committee 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 issued 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. For non-prescription Chinese herbal preparations with the established approval criteria, items to be included in Precautions in package inserts, etc. were presented in Notification No. 1014-(7) of the Safety Division, PFSB and No. 1014-(8) of the Evaluation and Licensing Division, PFSB dated October 14, 2011, and partially amended in Notification No. 0327-(1) of the Safety Division, PFSB and No. 0327-(1) of the Evaluation and Licensing Division, PFSB dated March 27, 2013.

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, PMSB dated April 9, 2002.

For the background of labeling of drug excipients, refer to Section 1.4 on pharmaceutical excipients.

The revised Law enacted on November 25, 2014 specified that package insert information should be based on scientific knowledge and information obtained in latest literatures, etc. as is the case for prescription drugs. Nonetheless, the exceptions for package insert information to be attached to products may be applicable also as is the case in prescription drugs (refer to 1. PACKAGE INSERTS).

6. PACKAGE INSERTS OF GUIDANCE-MANDATORY DRUGS

For guidance-mandatory drugs (refer to CHAPTER 2, 3.2 Classification of Drugs), as is the case for prescription drugs, package inserts should be based on scientific knowledge and information obtained in latest literatures, etc., and brand names and precautions for usage and handling should be noticed prior to initiation of manufacturing/marketing or amendment followed by prompt publication on the PMDA website (Notification No. 0806-(3) of PFSB dated August 6, 2014).

For notification, the specified notification format should be submitted to the PMDA with package insert information (copy) attached (Notification No. 0901-(1) of the Safety Division, PFSB dated September 1, 2014).

 Nonetheless, the exceptions for package inserts to be attached to products may be applicable also as is the case in prescription drugs (refer to 1. PACKAGE INSERTS).
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.

Note: A case with “Warnings” (with a red bracket in the right margin)

(PMS Subcommittee, Drug Evaluation Committee, JPMA)  Note: Sections in refer to Precautions
Fig. 18 Standard procedures for revision of package insert (1)
Fig. 19  Standard procedures for revision of package insert (2)
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 (NHI) 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 industry-managed employees’ health insurance programs or locally-based health insurance programs. At this point, "health insurance covering the entire population" was established.

Increasing efforts were made thereafter to improve the structure/scope of medical benefits given under various health insurance programs. In addition, under the Welfare Law for the Elderly, all medical costs for the elderly have been provided free of charge since 1973, and additional health care services became available for patients with intractable diseases to alleviate their economic burden. These, special health insurance programs have been implemented to reduce high medical costs for special populations.

On the other hand, because of the long-term deficit in the health insurance system, not only temporary financial measures but also radical measures have been successively introduced to counteract the deficit.

As medical services for the elderly had been concentrated on financial support and provided free, the cost of their medical treatment sharply increased every year, seriously affecting the financial status of the NHI program.

In addition, the financial support for the elderly created an imbalance in the amount of medical costs of the elderly and hence burden of insured persons between the different industry-managed and locally-based 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 enforced in 1983.

This law encourages general health related projects for the elderly, including the prevention and treatment of diseases and rehabilitation training. The law also introduced a new system 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 among the people concerning home care of elderly people 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 health insurance system, and a reform of the health-care insurance system together with the introduction of a new social security system was debated. The Long-Term Care Insurance Law was passed together with the third revision of the Medical Care Law on December 19, 1997 and it was enforced from April 1998. It is amended every 5 years.

The health-care insurance reform concurrently studied in 1997 brought a change in 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.

The law to reform the health insurance system was discussed from 2005 and was enacted in June 2006. From October 2006, persons aged 70 years or older with similar regular income as during their working years were subject to a copayment of 30% and limits on copayments and food/housing costs for inpatients of nursing home increased. From April 2008, a healthcare system for very old people was initiated.

2. MEDICAL BENEFITS OFFERED UNDER HEALTH INSURANCE PROGRAMS

As mentioned above, there are various types of health insurance programs in Japan and medical benefits available vary from one program to another. Medical benefits available for the insured person can also differ depending on the type of insurer, type of insurance program, and presence of family members (non-working dependents). 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 (the original coverage was stipulated to be 80% in the law but it was 90% until a notification of the Minister of Health and Welfare issued on a day after April 1986 after approval by the Diet). From September 1997, the 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. From October 2002, the burden on elderly patients aged 70 years or older was set at 10% and at 20% for those with a certain level of income, latter of which was revised to 30% from October 2006.

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For family members of insured persons, regardless of type of health insurance program, at least 70% of actual costs are covered by the 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 medical treatments and to support specified medical care coverage 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 listed in the NHI system 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 (in Yen) 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 DPC classifications. The medical bill includes 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 (days) 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 increased to 2,873 as of April 2014 and the application of this billing system has been extended to 1,585 hospitals (about 490,000 beds) as of April 2014.

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) Price List.

4. NATIONAL HEALTH INSURANCE PRICE LIST

The National Health Insurance (NHI) 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 Price List.

5. PRICING FORMULA FOR REIMBURSEMENT PRICE REVISIONS OF DRUGS LISTED IN THE NHI PRICE LIST

The difference in the purchase price by medical institutions and the NHI reimbursement price (price discrepancy), which provides extra 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, taking an opportunity of an attempt 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 in anticipation that the NHI 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 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.

In brief, 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 the “specified 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%. However, 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 problems, and a Chuikyo recommendation was issued to deal with the problems 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) than 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. 0212-(7) of the Health Insurance Bureau dated February 12, 2014, “Drug Pricing Standards.”

### 6. RECENT REVISIONS OF THE NHI 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 Price List using the weighted average pricing formula from 1992.

The actual reimbursement price revisions cover the drugs sold in the month of September of a previous year. A survey of all products in the NHI 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).

**Formula**

\[
\text{New drug price} = \text{weighted average value of market price in survey} \times (1 + \text{consumption tax rate}) + \text{current reimbursement price} \times R/100 \quad (\text{however, the new price shall not exceed the current reimbursement price}).
\]

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 class and same indication.

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 new drugs), the Central 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 2014.

Drug prices listed in the NHI Price List were revised to include additional 3% consumption tax in April 2014 as the tax rate was raised from 5% to 8% in the month.

The results of reimbursement price revisions from 1992 through 2014 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, 1996, 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 launch of the first drug or within three drugs with the same pharmacological action) was set at a lower price for a daily dose. The rule for coordinating prices with foreign reimbursement prices was also clarified (maximally twice the foreign price).

The seven premium rates as of February 2014 were set at 70-120%, 35-60%, 5-30%, 5-20%, 10-20%, 5%, and 10% for innovation, usefulness I and II, pediatric use, market size I and II, and world’s first registration in Japan, 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...
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. 0212-(7) of the Health Insurance Bureau dated February 12, 2014, “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. 0212-(8) of the Health Policy Bureau dated February 12, 2014, “Handling of Entries of Prescription Drugs in the NHI Price List”). Methods for submission of requests for inclusion of new drugs in the price list were most recently revised in Notification No. 0212-(4) of the Health Policy Bureau dated February 12, 2014.

A drug pricing organization was established to undertake scientific surveys concerning selection of products for price 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 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. 20 (Reimbursement Pricing Flow-sheet for New Drugs).

(Entries of new drugs in the NHI Price List are made as a rule four times a year.)

8. ENTRY OF GENERIC DRUGS IN THE NHI PRICE LIST

In the past, generic drugs have been entered in the NHI 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. 0212-(7) of the Health Insurance Bureau dated February 12, 2014, “Drug Pricing Standards.”) Procedures for calculation of reimbursement prices were specified in detail in September 2000 (most recent revisions: Notification No. 0212-(8) of the Health Policy Bureau dated February 12, 2014, “Handling of Entries of Prescription Drugs in the NHI Price List” and Notification No. 0212-(4) of the Health Policy Bureau dated February 12, 2014 “Method for Submission of Requests for Entry in the NHI Price List for Prescription Drugs”).

1) When a generic drug identical to the brand drug is entered in the price list for the first time, the price of the generic drug is obtained by multiplying the brand drug price by a factor of 0.6. The factor is 0.5 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 a 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. The Ministry of Health, Labour and Welfare 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 new 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 new 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 new 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.
Marketing approval based on Pharmaceutical Affairs Law

Request by manufacturer/marketing authorization holder for entry in NHI Price List

Hearing for manufacturer/marketing authorization holder (Economic Affairs Division)

Examination of data submitted at hearing by authorities (Medical Economics Division; preparation of pricing draft)

First meeting of drug pricing organization
  • Direct expression of opinion by manufacturers/marketing authorization holder (upon request)
  • Hearing of opinions of experts on pricing draft and examination of the following points:
    - Presence of similar drugs
    - Suitability of similar or optimally similar drugs
    - Necessity of applying premiums
    - Evaluation of cost price, etc.
    Note) Requests by manufacturer/marketing authorization holder are distributed.
  • Decision concerning pricing draft based on majority opinion of members

Notification of pricing draft to manufacturer/marketing authorization holder

<No problems arise>

Submission of dissenting opinion by manufacturer/marketing authorization holder

Second meeting of drug pricing organization
  • Direct expression of opinion by manufacturer/marketing authorization holder
  • After manufacturer/marketing authorization holder leaves, investigation of necessity of draft revision and revised pricing draft; decision on pricing draft based on majority opinion of members.

Notification of results after hearing opinions to manufacturer/marketing authorization holder

Report of pricing draft to Chuikyo and its approval

Entry in NHI Price List

Fig. 20 Reimbursement Pricing Flow-sheet for New Drugs

(Note 1) The parts in the double box show parts involving the drug pricing organization
(Note 2) Time clock (agreed on at MOSS conferences)
Entry in price list 4 times per year. Listing within 60 days as a rule or 90 days at the longest
### 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 (Approval indicated with ★ means 4 times/year of approval of drugs that requires price listing procedures).
- ★/★: Special entry in the year of NHI price revision (every 2 years)
- ★: The entry in February in the year of NHI price revision (year of “special entry”) is actually made in April (based on the 90-day rule).

### Fig. 21 Correlation between the Time of Marketing Approval Based on Pharmaceutical Affairs Law and the Time of Entry in the NHI Price List
### Table 7  Methods of Previous Reimbursement Price Revisions

<table>
<thead>
<tr>
<th>Year</th>
<th>Survey</th>
<th>R zone</th>
<th>Special items</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>June 1991</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>1994</td>
<td>June 1993</td>
<td>13%</td>
<td>Repricing</td>
</tr>
<tr>
<td>1996</td>
<td>June 1995</td>
<td>11%</td>
<td>Repricing</td>
</tr>
<tr>
<td>1997</td>
<td>Sept. 1996</td>
<td>10% (Long listed products)</td>
<td>Repricing Long listed products</td>
</tr>
<tr>
<td>1998</td>
<td>Sept. 1997</td>
<td>5% (Long listed products)</td>
<td>Repricing Long listed products</td>
</tr>
<tr>
<td>2000</td>
<td>Sept. 1999</td>
<td>Range adjusted, 2%</td>
<td>Repricing Range adjusted: 2%</td>
</tr>
<tr>
<td>2002</td>
<td>Sept. 2001</td>
<td>Range adjusted, 2%</td>
<td>Long listed products (Special adjustment: 4, 5, 6%)</td>
</tr>
<tr>
<td>2004</td>
<td>Sept. 2003</td>
<td>Range adjusted, 2%</td>
<td>Long listed products (Special adjustment: 4, 5, 6%) 1/2: JP products entered by brand name</td>
</tr>
<tr>
<td>2006</td>
<td>Sept. 2005</td>
<td>Range adjusted, 2%</td>
<td>Long listed products (Special adjustment: additional 2%, new 8%) 5%: JP products entered by brand name</td>
</tr>
<tr>
<td>2008</td>
<td>Sept. 2007</td>
<td>Range adjusted, 2%</td>
<td>Long listed products (Special adjustment: 4, 5, 6%) 1/2: JP products entered by brand name</td>
</tr>
<tr>
<td>2010</td>
<td>Sept. 2009</td>
<td>Range adjusted, 2%</td>
<td>Long listed products (Special adjustment: additional 2.2%, new 6%) 1/2: JP products entered by brand name</td>
</tr>
<tr>
<td>2012</td>
<td>Sept. 2011</td>
<td>Range adjusted, 2%</td>
<td>Long listed products (Special adjustment: additional 0.86%, new 6%) 1/2: JP products entered by brand name  Long listed generic products: 0.33%</td>
</tr>
<tr>
<td>2014</td>
<td>Sept. 2013</td>
<td>Range adjusted, 2%</td>
<td>Long listed products (Special adjustment for original product which replacement rate with generic products is less than 60% at 5 years after their entry is permitted: 2% to 1.5%) 1/2: JP products entered by brand name</td>
</tr>
</tbody>
</table>

### Table 8  Revision Rates of Reimbursement Prices

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of products with price decrease</th>
<th>Number of products with price increase</th>
<th>Number of products with price unchanged</th>
<th>Total</th>
<th>Revision rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>7,681</td>
<td>2,121</td>
<td>3,771</td>
<td>13,573</td>
<td>-8.1%</td>
</tr>
<tr>
<td></td>
<td>-8.5%</td>
<td>0.4%</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994</td>
<td>8,613</td>
<td>2,083</td>
<td>2,679</td>
<td>13,375</td>
<td>-6.6%</td>
</tr>
<tr>
<td></td>
<td>-6.8%</td>
<td>0.2%</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1996</td>
<td>9,568</td>
<td>1,697</td>
<td>1,604</td>
<td>12,869</td>
<td>-6.8%</td>
</tr>
<tr>
<td></td>
<td>-7.0%</td>
<td>0.2%</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>7,718</td>
<td>3,394</td>
<td>862</td>
<td>11,974</td>
<td>*-3.0%</td>
</tr>
<tr>
<td>1998</td>
<td>9,921</td>
<td>6</td>
<td>1,765</td>
<td>11,692</td>
<td>-9.7%</td>
</tr>
<tr>
<td></td>
<td>-9.7%</td>
<td>0.0%</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>8,935</td>
<td>61</td>
<td>2,291</td>
<td>11,287</td>
<td>-7.0%</td>
</tr>
<tr>
<td></td>
<td>-7.5%</td>
<td>0.5%</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 drug price revision implemented in 2014 is outlined below:
- The revision rate is -2.65% (+2.99%) on the drug price basis and -0.58% (+0.64%) on the medical care expenditure basis.
- Figures in parenthesis are costs for 3% consumption tax raised on April 1, 2014.

1. “Premiums for the promotion of innovative drug discovery and resolution of off-label use issue, etc.”

(1) Products covered

1) Premium is added to the price of a new drug calculated based on current market prices of drugs in class if the new drug meets all of the following conditions:
   i. The drug was listed in the NHI Price List less than 15 years ago and no generic drug has not been available on the market yet.
   ii. The discrepancy between the NHI price and current market price of the drug is not larger than that averaged for all drugs available in the NHI Price List.
   iii. The drug is manufactured and marketed by a company engaged in the development of a new drug(s) upon request by the MHLW or application for public recruitment or a company conducting R&D activities for the development of “new drugs that could truly contribute to the improvement of medical care quality.”
   iv. The drug is not subject to repricing.

2) Number of active ingredients and products that met requirements for premiums (a drug reformulated (old and new formulations) was counted once)

<table>
<thead>
<tr>
<th></th>
<th>Oral</th>
<th>Injection</th>
<th>Topical</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of active ingredients</td>
<td>185</td>
<td>149</td>
<td>63</td>
<td>397</td>
</tr>
<tr>
<td>Number of products</td>
<td>346</td>
<td>292</td>
<td>120</td>
<td>758</td>
</tr>
</tbody>
</table>

Of these, 4 ingredients and 10 products were given premium for pediatric indication, etc. and 3 ingredients and 5 products for orphan indication, etc. (additionally to the premium for the promotion of innovative drug discovery and resolution of off-label use issue, etc.).

3) Premium rate
   0 – 4.94%

4) The proportion of products which NHI price was maintained the same by obtaining premium (revised price = price before revision × 108/105)
   **83.1% (630 out of 758 products)**

5) The proportion of original products that received premiums whereby generic products are not available
   Approximately 37%

(2) Number of products which premiums were abolished

1) The price of a new drug that has become not compliant with Requirements i) or iii) above is reduced by a premium(s) given in a preceding price revision from the price calculated by referring to current market price.

2) Number of active ingredients and products which premiums were abolished
2. Special price reduction for original products for which the entry of generic products is slow

1) The price of an original drug which replacement rate with generic products does not exceed 60% over 5 years after the entry of the first generic product in the NHI Price List is lowered by the following rate from the price calculated by referring to current market price.

   i. Replacement rate of < 20%:  2.00%
   ii. Replacement rate of ≥ 20% - < 40%:  1.75%
   iii. Replacement rate of ≥ 40% - < 60%:  1.50%

2) Number of active ingredients and products that were subject to special price reduction

<table>
<thead>
<tr>
<th>Price reduction (%)</th>
<th>Oral</th>
<th>Injection</th>
<th>Topical</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of active ingredients</td>
<td>2.00</td>
<td>52</td>
<td>25</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>1.75</td>
<td>116</td>
<td>16</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>1.50</td>
<td>64</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>232</td>
<td>67</td>
<td>80</td>
</tr>
<tr>
<td>Number of products</td>
<td>2.00</td>
<td>126</td>
<td>106</td>
<td>129</td>
</tr>
<tr>
<td></td>
<td>1.75</td>
<td>323</td>
<td>39</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>1.50</td>
<td>210</td>
<td>87</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>659</td>
<td>232</td>
<td>227</td>
</tr>
</tbody>
</table>

3. Price recalculation based on expanded market size and revised dosage/administration

1) Number of active ingredients and products that were subject to the price recalculation

<table>
<thead>
<tr>
<th></th>
<th>Repricing based on expanded market size</th>
<th>Repricing based on revised dosage and administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral</td>
<td>Injection</td>
</tr>
<tr>
<td>Number of active ingredients</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Number of products</td>
<td>17</td>
<td>5</td>
</tr>
</tbody>
</table>

4. Premiums for pediatric indication, orphan indication, and innovative clinical usefulness (therapeutic benefits)

1) Number of active ingredients and products that received premiums for additional pediatric indication

<table>
<thead>
<tr>
<th></th>
<th>Oral</th>
<th>Injection</th>
<th>Topical</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of active ingredients</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Number of products</td>
<td>5</td>
<td>13</td>
<td>3</td>
<td>21</td>
</tr>
</tbody>
</table>

2) Number of active ingredients and products that received premiums for additional orphan indication

<table>
<thead>
<tr>
<th></th>
<th>Oral</th>
<th>Injection</th>
<th>Topical</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of active ingredients</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Number of products</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

3) Number of active ingredients and products that received premiums for innovative clinical usefulness (therapeutic benefits)

   None

5. Price recalculation based on unprofitable trade of products

1) Number of active ingredients and products that were repriced due to unprofitable trade
Number of active ingredients: 34  
Number of products: 196

2) Main active ingredients repriced

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Unit</th>
<th>Current price</th>
<th>Revised price</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atractylodes lancea rhizome</td>
<td>10g</td>
<td>12.60-14.30</td>
<td>25.20</td>
<td>Crude drug</td>
</tr>
<tr>
<td>Uncaria hook</td>
<td>10g</td>
<td>14.10-14.40</td>
<td>25.00</td>
<td>Crude drug</td>
</tr>
<tr>
<td>Glucose inj</td>
<td>5% 100mL/botl</td>
<td>103</td>
<td>113</td>
<td>Saccharide prep</td>
</tr>
<tr>
<td>Isotonic Na-Cl sol</td>
<td>145</td>
<td>8.30-9.10</td>
<td>149</td>
<td>Blood substitute</td>
</tr>
<tr>
<td>Cataplasms</td>
<td>8.30-9.10</td>
<td></td>
<td>9.60</td>
<td>Nonsteroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>Saponated cresol sol</td>
<td>10g</td>
<td>9.20-9.40</td>
<td>12.90</td>
<td>Disinfectant</td>
</tr>
<tr>
<td>Purified lanolin</td>
<td>21.30</td>
<td></td>
<td>32.00</td>
<td>Ointment base</td>
</tr>
</tbody>
</table>

6. Other

Number and market share of products by the category of drugs in the NHI Price List (source: Drug price survey conducted in September 2013) (The number of products was obtained by the survey conducted in April 2014 and the market share in sales quantity and amount in September 2013.)

<table>
<thead>
<tr>
<th></th>
<th>Number of products</th>
<th>Share in sales quantity</th>
<th>Share in sales amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original drugs</td>
<td>2,074</td>
<td>18.2%</td>
<td>49.3%</td>
</tr>
<tr>
<td>Generic drugs not available</td>
<td>1,562</td>
<td>31.2%</td>
<td>31.7%</td>
</tr>
<tr>
<td>Generic drugs (A)</td>
<td>8,038</td>
<td>27.6%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Other drugs (JP standard drugs, crude drugs, etc.)</td>
<td>3,629</td>
<td>23.0%</td>
<td>8.0%</td>
</tr>
</tbody>
</table>

Share in sales quantity* (new index) = (B) / [(A) + (B)] = 46.9%

*Source: “Roadmap for Further Promoting the Use of Generic Drugs” (MHLW April 2013)

Note 1) Generic drugs are defined as any drugs other than those approved as new drugs by the Pharmaceutical Affairs Law (excluding “drugs in other classes”)

Note 2) “Drugs in other classes” are defined as JP standard drugs, crude drugs, biologicals (including vaccines, blood products), and drugs approved in or before 1967.

Note 3) Figures are rounded to one decimal place: the total does not add up to 100%.

Number of products included in the NHI Price List as of April 2014.

<table>
<thead>
<tr>
<th></th>
<th>Oral</th>
<th>Injection</th>
<th>Topical</th>
<th>Dental</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>9,092</td>
<td>3,721</td>
<td>2,465</td>
<td>25</td>
<td>15,303</td>
</tr>
</tbody>
</table>

Table 9  Requirements for Applying Premiums

<Types, requirements and rates of premiums>

(1) Premium for innovativeness (rate: 70-120%)
  Applied to new drug products in the NHI Price List 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) Premium for usefulness I (35-60%)
  Applied to new drug products in the NHI Price List that meet two of the three requirements listed above.
<table>
<thead>
<tr>
<th>(3)</th>
<th>Premium for usefulness II (5-30%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Applied to new drug products in the NHI Price List that meet one of the following requirements (excluding products to which the innovativeness premium or usefulness premium (I) is applied):</strong></td>
<td></td>
</tr>
<tr>
<td>1) The newly entered drug has a clinically useful new mechanism of action.</td>
<td></td>
</tr>
<tr>
<td>2) The newly entered drug has been shown objectively to be more effective and safe than existing (comparator) drugs in the same class.</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>4) The newly entered drug has been shown objectively to improve treatment of the indicated disease or trauma.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(4)</th>
<th>Premium for pediatric use (5-20%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Applied to new drug products in the NHI Price List meeting all of the following requirements:</strong></td>
<td></td>
</tr>
<tr>
<td>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).</td>
<td></td>
</tr>
<tr>
<td>2) The premiums for pediatric use must not have been given to comparator drugs available in the NHI Price List.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(5)</th>
<th>Premium for marketability (I) (10-20%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Applied to new drug products in the NHI Price List meeting all of the following requirements:</strong></td>
<td></td>
</tr>
<tr>
<td>1) Orphan drugs pursuant to the provisions of Article 77-2 of the Pharmaceutical Affairs Law in the NHI Price List for which the orphan indications for the disease or trauma are the main indications of the drugs concerned.</td>
<td></td>
</tr>
<tr>
<td>2) The premium for marketability (I) must not have been given to comparator drugs available in the NHI Price List.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(6)</th>
<th>Premium for marketability (II) (5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Applied to new drug products in the NHI Price List meeting all of the following requirements (excluding products to which marketability premium (I) is applied):</strong></td>
<td></td>
</tr>
<tr>
<td>1) New drugs in the NHI Price List 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.</td>
<td></td>
</tr>
<tr>
<td>2) The premium for marketability (I) or (II) must not have been given to comparator drugs available in the NHI Price List.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(7)</th>
<th>Premium for the world’s first registration in Japan (10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Applied to new drug products in the NHI Price List meeting all of the following requirements (the price of a comparator drug should be free of the premium for the world’s first registration in Japan, when the price of a new drug is calculated by the Similar Efficacy Comparison-Based Price Setting Method I or II comparing with the price of the comparator to which the premium for the world’s first registration in Japan was applied):</strong></td>
<td></td>
</tr>
<tr>
<td>1) A new drug with novel action mechanism different from that of any drugs already approved in foreign countries (specifically in the US, UK, Germany, and France) and Japan</td>
<td></td>
</tr>
<tr>
<td>2) A new drug first approved in Japan</td>
<td></td>
</tr>
<tr>
<td>3) A new drug ascertained not to be marketed solely in Japan based on foreign clinical development status (including R&amp;D plan), clinical trial notification, etc.</td>
<td></td>
</tr>
<tr>
<td>4) A new drug for which premium for innovativeness or usefulness I is applicable</td>
<td></td>
</tr>
</tbody>
</table>
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<td>Global harmonization of GMP</td>
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<td>53</td>
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Participating Company List

Under the supervision of Ministry of Health Labour and Welfare Japan, this publication has been updated regularly with the cooperation of the enthusiastic editors below.

Leader: Katsunori KURUSU

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<td>Regulatory Affairs: Katsunori INUI</td>
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<td>New Drug Regulatory Affairs: Yoshiyuki HATTORI Regulatory Development Department: Kazuhiro SASAKI</td>
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<td>Pharmacovigilance and Quality Assurance: Hiroyuki OHTSUKA</td>
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<tr>
<td>(Chapter 5)</td>
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<td>Quality &amp; Regulatory Compliance: Yuichi TAKIDO</td>
</tr>
<tr>
<td>(Chapter 6)</td>
<td>Otsuka Pharmaceutical Co, Ltd</td>
<td>Regulatory Affairs Department: Toshio SATO</td>
</tr>
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Contact:

<table>
<thead>
<tr>
<th>Administrative Office</th>
<th>JAPAN PHARMACEUTICAL MANUFACTURERS ASSOCIATION</th>
<th>Office of International Affairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-3-11 Nihonbashi-Honcho, Chuo-ku, Tokyo 103-0023, Japan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e-Mail address:</td>
<td>international @ jpma.or.jp</td>
<td></td>
</tr>
<tr>
<td>Phone</td>
<td>81-3 (3241) 0326</td>
<td></td>
</tr>
<tr>
<td>Fax</td>
<td>81-3 (3242) 1767</td>
<td></td>
</tr>
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