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## INFORMATION ON JAPANESE REGULATORY AFFAIRS

*Regulatory Information Task Force*  
*Japan Pharmaceutical Manufacturers Association*

# Pharmaceutical Administration and Regulations in Japan

Japan Pharmaceutical Manufacturers Association

# 2020

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<http://www.jpma.or.jp/about/issue/gratis/index2.html> (Japanese)

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## Pharmaceutical Administration and Regulations in Japan

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

Japan Pharmaceutical Manufacturers Association

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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) (Koseirodoshō 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, Director-General for Human Resources Development, 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 organization is the Central Labor Relations Commission (**Fig. 1** Organization of Ministry of Health, Labour, and Welfare (Health-related organizations only)).

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 Safety and Environmental Health Bureau (PSEHB) 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). 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 PSEHB 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 Safety and Environmental Health Bureau (PSEHB) and Pharmaceuticals and Medical Devices Agency (PMDA)).

## 1. PHARMACEUTICAL SAFETY AND ENVIRONMENTAL HEALTH BUREAU (PSEHB)

The Pharmaceutical Safety and Environmental Health Bureau (PSEHB) (except for the Department of Environmental Health and Food Safety) is one of the 11 bureaus of the MHLW. In addition to policies to assure the efficacy and safety of drugs, quasi-drugs, cosmetics, medical devices and cellular and tissue-based products, 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 Safety and Environmental Health Bureau (PSEHB) 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 Safety and Environmental Health Bureau
- 2) Matters related to pharmacists
- 3) Supervision of the PMDA (excluding areas under the control of the Pharmaceutical Evaluation Division, Medical Device Evaluation Division, Pharmaceutical Safety Division, and Compliance and Narcotics Division)
- 4) Issues related to PSEHB 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.)

#### • Office of International Regulatory Affairs

Overall coordinating activities for international affairs under the control of the Pharmaceutical Safety and Environmental Health Bureau.

### 1.2 Pharmaceutical Evaluation 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 (limited to approval to manufacture and market drugs, medical devices, etc.)

### 1.3 Medical Device Evaluation Division

- 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, or to market regenerative medicine products (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 PMDA (limited to work related to medical devices, extracorporeal diagnostic medicines and regenerative medicine products)
- 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

**1.4 Pharmaceutical Safety Division**

- 1) Planning and drafting of policies to assure the safety of pharmaceuticals and medical devices, etc.
- 2) Manufacturing/marketing business licenses to manufacture and market pharmaceuticals and medical devices, etc.
- 3) Review of the safety of pharmaceuticals and medical devices, etc. (excluding items handed by the Pharmaceutical Evaluation Division and Medical Device Evaluation Division)
- 4) Guidance and advice concerning preparation and storage of records of biological products and designated medical devices
- 5) Work related to the PMDA (limited to matters related to improve safety of pharmaceuticals and medical devices, etc. and excluding items handed by the Pharmaceutical Evaluation Division and Medical Device Evaluation Division)

**1.5 Compliance and Narcotics Division**

- 1) Control of poor quality or falsely labeled pharmaceuticals and medical devices, etc
- 2) Guidance and supervision related to advertising of pharmaceuticals and medical devices, etc
- 3) Testing and government certification of pharmaceuticals and medical devices, etc
- 4) Matters related to pharmaceutical inspectors, etc.
- 5) Control of narcotics and stimulants, etc
- 6) Duties of narcotics control officers and staff
- 7) Matters related to international cooperation concerning narcotics and stimulants, etc
- 8) Work related to the PMDA (limited to matters related to on-site inspection, etc. by the PMDA)

## 1.6 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 (excluding items handed by the Health Service Bureau)

## 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 PSEHB 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 PSEHB 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 PSEHB)
- 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 PSEHB)

### **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) in April 2004.

### **4. PHARMACEUTICALS AND MEDICAL DEVICES AGENCY, AN INDEPENDENT ADMINISTRATIVE ORGANIZATION**

In accordance with the special corporation rationalization plan passed by the Cabinet in December 2001, and enactment of the Pharmaceuticals and Medical Devices Agency Law in December 2002, the PMDA (KIKO) was established

in April 2004, through the integration of the Pharmaceutical and Medical Devices Evaluation Center in the National Institute of Health Sciences, the OPSR, and part of the Medical Devices Center, and the PMDA started handling all consultation and review work from the preclinical stage to approvals and post-marketing surveillance.

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

The PMDA consists of 28 offices, 4 groups, and the Kansai and Hokuriku branches as shown in Fig. 2, and, the duties are indicated below.

The PMDA is currently working to achieve goals under the Fourth Medium Range Plan (FY2019-FY2023), including maintaining the world's fastest review period while improving the quality of the work, seeking appropriate implementation of the SAKIGAKE Designation System and the Conditional Accelerated Approval System and improvement of the Regulatory Science Strategy Consultations and so on, and performing appropriate review and consultation in accordance with domestic and overseas guidelines in the review of new drugs.

#### **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 Pharmaceutical and Medical Device Act
- 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 Pharmaceutical and Medical Device Act

## 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 coordination of the matters related to review works, etc., commissioning of the members of expert meetings, and revision of charges, as well as tasks related to the receipt and management of various marketing approval application forms and notifications, etc.

### 4.2 Office of Review Management

This office handles tasks related to the planning and drafting of review works, etc., management of the protocol and reports of adverse reactions observed in clinical trials, and receipt and processing of clinical trial consultations on new drugs. The office also handles consultation on regulatory science strategy on drugs and medical devices mainly for universities, research institutes, and venture companies.

This office also handles tasks related to the preparation of draft Japanese Pharmacopoeia, standards on drugs, master file systems, and generic names (JAN).

### 4.3 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)

### 4.4 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.

### 4.5 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.

#### 4.6 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.

#### 4.7 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.

#### 4.8 Office of Cellular and Tissue-based Products

This office conducts reviews necessary for verification of clinical trial notifications and defects, approval, and 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, quality review of biological products, and reviews necessary for verification of clinical trial notifications and adverse drug reactions, and approval of biosimilar products.

#### 4.9 Office of Vaccines and Blood Products

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

#### 4.10 Office of OTC/Quasi-drugs

This office conducts reviews required for the approval, export certification, and quality

reevaluations of guidance-mandatory drugs non-prescription drugs, quasi-drugs, and cosmetics.

#### 4.11 Office of Generic Drugs

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

#### 4.12 Office of Non-clinical and Clinical Compliance

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

#### 4.13 Office of Medical Devices I

This office conducts reviews required for approval of medical devices intended for use in the fields of robots/information and communication technology (ICT)/others, ophthalmology/otorhinology, and cardiopulmonary circulation.

#### 4.14 Office of Medical Devices II

This office conducts reviews required for approval of medical devices intended for use in the fields of neurology/psychiatry, respiratory/cerebro/vascular systems, gastroenterology, reproductive systems, dentistry/oral cavity, and orthopedics/plastic and

reconstructive surgery.

#### **4.15 Office of Standards and Compliance for Medical Devices**

This office conducts works to investigate compliance of the documents related to applications for approval, reexamination, reevaluation, and use results evaluation of medical devices with the source documents, GLP, GCP, and GPSP, and the Criteria for Reliability of Application Data. This office also conducts works to investigate the criteria for certification and approval, etc. of medical devices, works to support acquisition of international standards such as ISO/IEC standards, works to manage the master files for raw materials of medical devices, and works to investigate compliance with the standards necessary for registration of third-party certification bodies.

#### **4.16 Office of In Vitro Diagnostics**

This office conducts reviews required for approval of in vitro diagnostics.

#### **4.17 Office of Manufacturing Quality and Vigilance for Medical Devices**

This office conducts works related to compliance inspections for QMS, etc., on-site inspection of manufacturing sites of medical devices, etc., and simple consultation on QMS. This office also conducts safety measures for medical devices and in vitro diagnostics.

#### **4.18 Office of Manufacturing Quality for Drugs**

This office conducts works related to compliance inspections for GMP and GCTP, etc.

#### **4.19 Office of Informatics and Management for Safety**

This office handles tasks related to contributions for safety measures, tasks related to receipt and organization of reports of adverse reactions and publication of the results of organization, and tasks related to provision of information for improvement of the quality, efficacy and safety of drugs and medical devices, etc.

#### **4.20 Office of Pharmacovigilance I**

This office conducts safety measures related to drugs in the fields under the jurisdiction of Office of New Drug I, Office of New Drug II, and Office of New Drug III (including generic drugs and OTC drugs), quasi-drugs, and cosmetics.

#### **4.21 Office of Pharmacovigilance II**

This office conducts safety measures related to drugs in the fields under the jurisdiction of Office of New Drug IV, Office of New Drug V, and Office of Vaccines and Blood Products (including generic drugs and OTC drugs) and cellular and tissue-based products.

#### **4.22 Office of International Programs**

This office makes plans and proposals concerning international activities and undertakes surveys and coordinations associated with this, coordinates the matters related to international conferences, international organizations, and foreign government organizations and groups, and conducts works related to the collection and analysis of overseas information and foreign public relations campaign.

#### **4.23 Office of International Cooperation**

This office makes plans and proposals concerning the works conducted by Asia Training Center for Pharmaceuticals and Medical Devices Regulatory

Affairs and undertakes surveys and coordinations associated with this.

#### **4.24 Office of Advanced Evaluation with Electronic Data**

This office conducts works related to collection of information on the use of various data related to application, planning, drafting, and investigation and analysis, etc. of the information regarding the quality, efficacy and safety of drugs and medical devices, etc. through the use of various data on planning, drafting, and application. This office also makes plans for education and training regarding access to and analysis of various data related to application.

#### **4.25 Office of Medical Informatics and Epidemiology**

This office conducts works related to investigation and analysis of the information regarding the quality, efficacy, and safety of drugs and medical devices, etc. using the technique of pharmacoepidemiology and other scientific techniques, as well as the works related to operation and management, etc. of MID—NET®.

#### **4.26 Kansai Branch**

This branch undertakes regulatory science strategy consultations and GMP and QMS inspections in the Kansai area.

#### **4.27 Hokuriku Branch**

This branch provides training on GMP inspections at manufacturing sites in Toyama prefecture held by Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC).

### **5. NATIONAL INSTITUTE OF BIOMEDICAL INNOVATION, HEALTH AND NUTRITION (NIBIOHN)**

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. JAPAN AGENCY FOR MEDICAL RESEARCH AND DEVELOPMENT (AMED)**

AMED was established on April 1, 2015 to promote integrated research and development in the field of medicine (medical R&D), from basic research to practical application; to ensure smooth application of the R&D outcomes to practices; and to establish and maintain an encouraging environment for medical R&D comprehensively and effectively.

By supporting research activities of universities and research institutions, AMED promotes R&D and furthermore establishes an encouraging environment for R&D.

### **7. PHARMACEUTICAL AFFAIRS AND FOOD SANITATION COUNCIL (PAFSC)**

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

The Council has as members experts in various

fields<sup>1)</sup> including the medical and pharmaceutical sciences.

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

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

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

Note 3) Categories of drugs for the Committee on Guidance-mandatory/Non-prescription Drugs to review: New guidance-mandatory/non-prescription drugs which are apparently different from existing guidance-mandatory/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.

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.pmda.go.jp/english/review-services/reviews/approved->

[information/drugs/0002.html](http://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0002.html))

## 8. NATIONAL INSTITUTE OF INFECTIOUS DISEASES

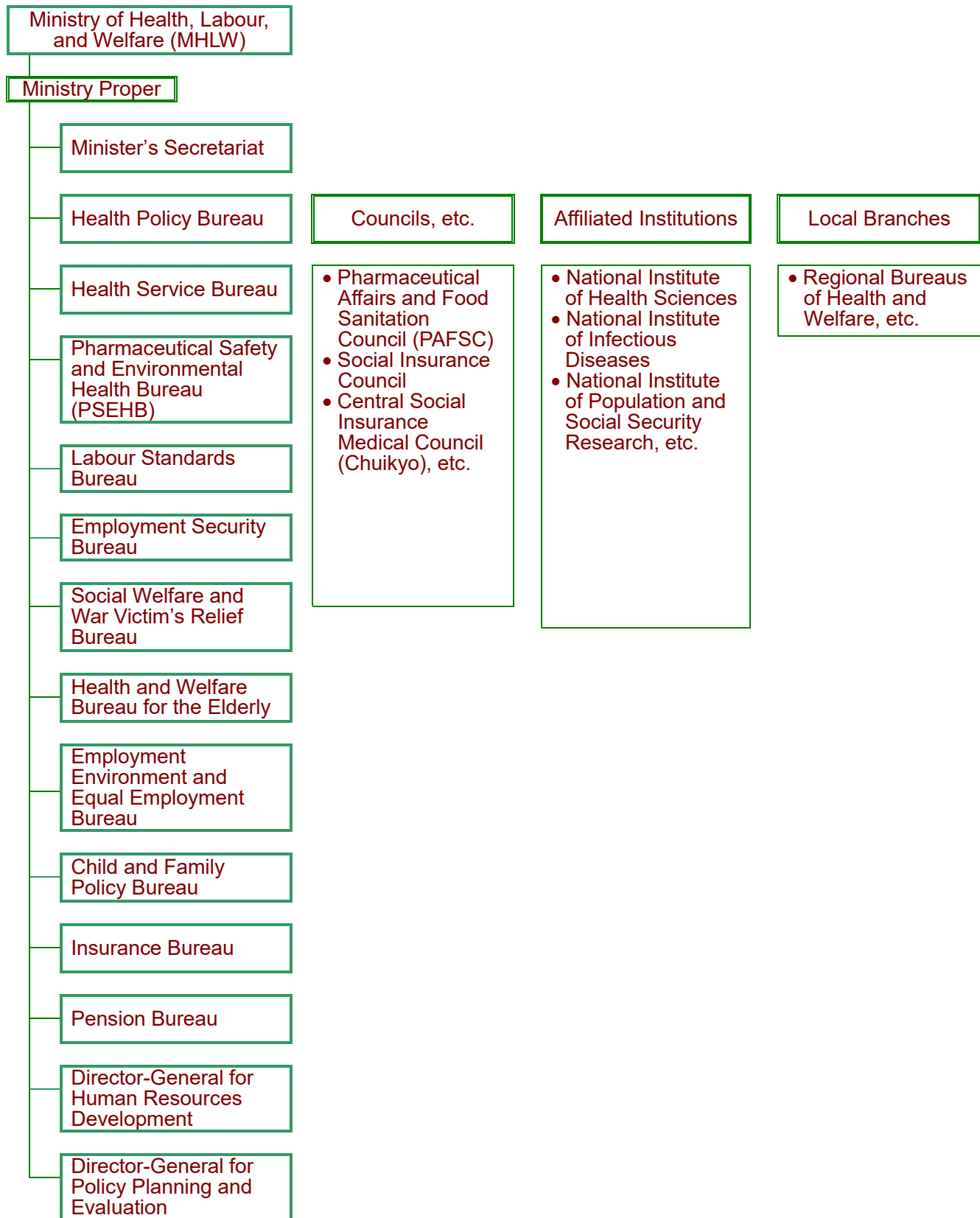
In April 1997, the name of the National Institute of Health was changed to the National Institute of Infectious Diseases. The institute undertakes basic and applied research, reference and surveillance activities, and collection, analysis, and supply of information pertaining to infectious diseases,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

- **Infectious Diseases Information Center**

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

- **AIDS Research Center**

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

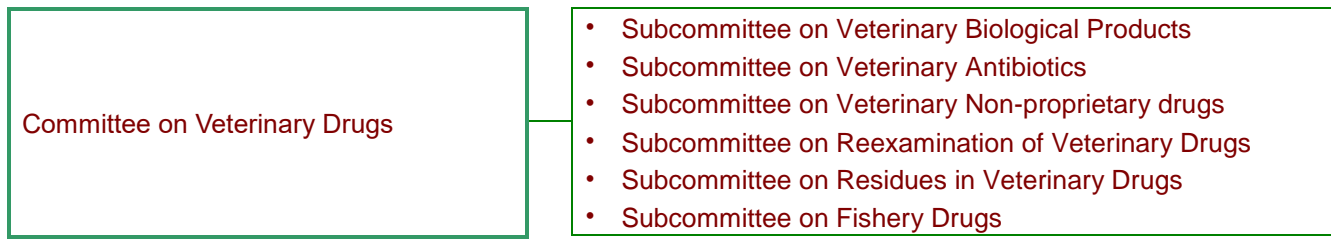


**Fig. 1 Organization of Ministry of Health, Labour, and Welfare (Health-related organizations only)**



**Fig. 2 Organization of Pharmaceutical Safety and Environmental Health Bureau (PSEHB) and Pharmaceuticals and Medical Devices Agency (PMDA)**

Committee on Japanese Pharmacopoeia	
First Committee on Judgment of Sufferers from Adverse Drug Reactions and Infections	<ul style="list-style-type: none"> <li>• Subcommittee on Evaluation of Adverse Drug Reactions of HPV vaccines</li> </ul>
Second Committee on Judgment of Sufferers from Adverse Drug Reactions and Infections	<ul style="list-style-type: none"> <li>• Subcommittee on Evaluation of Adverse Effects of Biological Products</li> </ul>
First Committee on New Drugs	
Second Committee on New Drugs	
Committee on Blood Products	<ul style="list-style-type: none"> <li>• Subcommittee on Safety of Blood Products</li> <li>• Subcommittee on Proper Use of Blood Products</li> <li>• Subcommittee on Blood Donation Promotion</li> </ul>
Committee on Medical Devices and <i>in vitro</i> Diagnostics	
Committee on Reevaluation of Drugs	
Committee on Handling Regulations for Regenerative Medicine Products and Biological Products	<ul style="list-style-type: none"> <li>• Subcommittee on Medicinal Products for Animals by Application of recombinant DNA Technology</li> </ul>
Committee on Guidance-Mandatory Drugs and Non-prescription Drugs	
Committee on Cosmetics and Quasi-Drugs	
Committee on Safety of Drugs	<ul style="list-style-type: none"> <li>• Subcommittee on Safety Measurements</li> </ul>
Committee on Safety of Medical Devices and Regenerative Medicine Products	<ul style="list-style-type: none"> <li>• Subcommittee on Safety Measurements</li> </ul>
Committee on Designated Substances	
Committee on Poisonous and Deleterious Substances	<ul style="list-style-type: none"> <li>• Subcommittee on Regulations for Handling Poisonous and Deleterious Substances</li> <li>• Subcommittee on Poisons and Deleterious Substances</li> </ul>
Committee on Safety of Chemical Substances	<ul style="list-style-type: none"> <li>• Subcommittee on Chemical Substances</li> <li>• Subcommittee on PRTR substances</li> <li>• Subcommittee on safety measures for household products</li> </ul>



**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) Pharmaceutical and Medical Device Act, (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 Pharmaceutical and Medical Device Act, and notifications issued by the Director General of the Bureaus or the directors of the Divisions in charge in the Ministry of Health, Labour, and Welfare.

## 2. PHARMACEUTICAL AND MEDICAL DEVICE ACT

The objectives of the Pharmaceutical and Medical Device Act 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 was completely revised in 1948 and 1960 (Law No. 145). 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 Pharmaceutical and Medical Device Act).

The revised Law, Pharmaceutical and Medical Device Act, 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: Manufacturing/Marketing Businesses of Drugs, Quasi-drugs and Cosmetics (Articles 12 to 23)

Chapter 5: Manufacturing/Marketing

Businesses, etc. of Medical Devices and in vitro Diagnostics  
Section 1 Manufacturing/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: Manufacturing/Marketing Businesses of Cellular and Tissue-based Products (Article 23-20 to 23-42)

Chapter 7: Retail Sellers, etc. of Drugs, Medical Devices and Cellular and Tissue-based Products  
Section 1 Retail Sellers of drugs (Articles 24 to 38)  
Section 2 Retail Sellers, Leasers and Repairers of Medical Devices (Articles 39 to 40-4)  
Section 3 Retail Sellers of Cellular and Tissue-based Products (Articles 40-5 to 40-7)

Chapter 8: Standards and Government Certification for Drugs (Article 41 to Article 43)

Chapter 9: Handling of Drugs  
Section 1 Handling of Poisonous and Deleterious Substances (Articles 44 to 48)  
Section 2 Handling of Drugs (Articles 49 to 58)  
Section 3 Handling of Quasi-drugs (Articles 59 and 60)  
Section 4 Handling of Cosmetics (Articles 61 and 62)  
Section 5 Handling of Medical Devices (Articles 63 to 65)  
Section 6 Handling of Cellular and Tissue-based Products (Articles 65-2 to 65-6)

Chapter 10: Advertising of Drugs, etc. (Articles

66 to 68)

Chapter 11: Safety of Drugs, etc. (Articles 68-2 to 68-15)

Chapter 12: Special Handling of Biological Products (Articles 68-16 to 68-25)

Chapter 13: Supervision (Articles 69 to 76-3)

Chapter 14: Handling of Designated Substances (Articles 76-4 to 77)

Chapter 15: Designation of orphan drugs, orphan medical devices and cellular and tissue-based orphan products (Articles 77-2 to 77-7)

Chapter 16: Miscellaneous Provisions (Article 78 to 83-5)

Chapter 17: Penal Provisions (Article 83-6 to 91)

### 3. OUTLINE OF PHARMACEUTICAL REGULATIONS

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

#### 3.1 Definition of Drugs

Drugs subject to the regulations in the Pharmaceutical and Medical Device Act 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 Classification of Drugs

Drugs (medicinal products) ("iyakuhin" in Japanese) can be classified as follows based on the regulatory provisions in the Pharmaceutical and Medical Device Act, 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 MHLW 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 Pharmaceutical and Medical Device Act or the Stimulants Control Law (**Table 1** List of Main Controlled Substances).

- (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) Psychotropic drugs (Narcotics and Psychotropics Control Law).
- (8) 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 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 Pharmaceutical and Medical Device Act 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 15, 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 Pharmaceutical and Medical Device Act 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 on February 8, 2008 (Notification No. 0208003 of the PFSB). On March 27, 2008, the manufacturing control and quality control of drugs and medical devices processed from human-derived (autologous) cells and tissues (Notification No. 0327027 of the Compliance and Narcotics Division, PFSB) 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 on September 12, 2008 (Notification No. 0912006 of the PFSB). 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).

For gene therapy products, etc., “Ensuring Quality and Safety of Gene Therapy Products, etc.” (Notification No. 0709-(2) of the Medical Device Evaluation Division, PSEHB) was issued on July 9, 2019.

### 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.

- (1) Type 1 drug manufacturing/marketing business license: Marketing of prescription drugs (Article 12 of the Law)
- (2) Type 2 drug manufacturing/marketing business license: Marketing of drugs other than prescription drugs (Article 12 of the Law)
- (3) Quasi-drug manufacturing/marketing business license: Marketing of quasi-drugs (Article 12 of the Law)
- (4) Cosmetic drug manufacturing/marketing business license: Marketing of cosmetics (Article 12 of the Law)
- (5) Type 1 medical device manufacturing/marketing business license: Marketing of specially controlled medical devices (Article 23-2 of the Law)
- (6) Type 2 medical device manufacturing/marketing business license: Marketing of controlled medical devices (Article 23-2 of the Law)
- (7) Type 3 medical device manufacturing/marketing business license: Marketing of general medical devices (Article 23-2 of the Law)
- (8) Manufacturing/marketing business license of in vitro diagnostics: Marketing of in vitro diagnostics (Article 23-2 of the Law)
- (9) Manufacturing/marketing business license of cellular and tissue-based products: Marketing of cellular and tissue-based

products (Article 23-20 of the Law)

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.

The licensing requirements for manufacturing/marketing businesses of medical devices include the appointment of a general marketing compliance officer of medical devices, etc., and compliance with the standards of manufacturing management and Quality Management System (QMS) and Good Vigilance Practice (GVP) for postmarketing safety surveillance. The licensing requirements for manufacturing/marketing businesses of cellular and tissue-based products include the appointment of a general marketing compliance officer, and compliance with the 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. Appropriate implementation of the activities of the triumvirate is required for the manufacturing/marketing business license holder, and a notification covering the points to consider to clarify the position and requirements of a general drug marketing compliance officer as well as the chain of command, roles and authority of the triumvirate, to ensure the human resources necessary for notifying them in the company and carrying out the activities, and to conduct quality management activities and safety assurance

activities, etc. was issued (Notification No. 0626-(3) of the PSEHB dated June 26, 2017).

### **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, labeling and storage

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.

After enforcement of the Law for Partial Amendment of the Pharmaceutical Affairs Law in November 2014, registration is required for manufacturing business of medical devices and extracorporeal diagnostic medicines, instead of previously required business licenses. Each manufacturing plant is required to register its

manufacturing business.

## 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.

Accreditation of overseas manufacturers is valid for a period of 5 years. Application for accreditation renewal has to be submitted at least 5 months before end of the valid period (Office Communication of the Evaluation and Licensing Division, PSEHB, dated March 29, 2016). "A List of Registered/Accredited Overseas Manufacturers" is shown on the PMDA homepage, and the overseas manufacturers that have not submitted an application for accreditation renewal even after 5 months after the end of the valid period are highlighted in yellow.

<https://www.pmda.go.jp/review-services/drug-reviews/foreign-mfr/0003.html>

After enforcement of the Law for Partial Amendment of the Pharmaceutical Affairs Law in November 2014, registration is also required for overseas manufacturing business of medical devices and extracorporeal diagnostic medicines, instead of previously required business accreditation. Each manufacturing plant is required to register its manufacturing business. The procedures for obtaining the accreditation of overseas manufacturers are described as follows in the "Q&A on Accreditation of Overseas Manufacturers" (Office Communication of the Evaluation and Licensing Division, PFSB dated February 14, 2006), etc. Refer to the PMDA homepage for reference.

Japanese HP:

<http://www.pmda.go.jp/review-services/drug-reviews/foreign-mfr/0010.html>

English HP:

<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 manufacture. 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 manufacturers). 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 the Evaluation and Licensing Division of PFSB 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 attached.
  - For executive officers, if a corporation, prima facie documents should be submitted to assure that they are not affected by psychosomatic disorder or intoxicated with narcotics, cannabinoids, opium or psychostimulants (Article 35-2 of the Enforcement Regulations).
- (4) On-site surveys for accreditation of overseas manufacturers  
When a GMP compliance survey is performed simultaneously with the accreditation, the structures and facilities are required for accreditation to be confirmed in the GMP compliance survey, as a rule.

### 3.5 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 (prefectural governor for non-prescription drugs for which approval standards are established) 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 compliance with the criteria in GMP 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 the criteria in GMP.

Approval items specified in the approval certificate are as follows: When a change is made on approval items except for brand name, a partial change application or slight modification notification has to be submitted.

- Brand name
- Ingredients and quantities, or nature
- Manufacturing process
- Dosage and administration
- Indications
- Storage condition and shelf life
- Specifications and testing methods
- Manufacturing plant of item to be marketed
- Manufacturing plant of the drug substance

### 3.6 Good Manufacturing Practice (GMP)

In manufacturing plants with manufacturing business license or overseas manufacturer accreditation, compliance with the criteria in GMP 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 the manufacturer of drug substances, etc. from marketing authorization holders, etc. and facilitating review work. Drug substance manufacturers, etc. (MF registrants) register the data on quality and the manufacturing method, etc. of drug substances, etc. to be used in drug products with regulatory authorities in the form of MF, thereby enabling applicants other

than MF registrants to quote the data in the approval review (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.

Items that 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 a drug substance in-country caretaker to handle the activities of the MF registrant in Japan (MF in-country caretaker). The MF in-country caretaker mediates communication between the MF registrant and the manufacturer or Japanese regulatory authority.

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 also must submit a partial change application or a slight modification notification for the MF depending on the contents of the change. When a minor MF modification notification is submitted, however, a procedure for changing the approval certificate is not required. In either case, the MF registrant must notify the manufacturing/marketing authorization holder of the change(s) in advance through the MF in-country caretaker.

Information of chemicals, drug substances, drug products, etc. registered under the MF system is publicly available at the following PMDA homepages. <http://www.pmda.go.jp/review-services/drug-reviews/master-files/0008.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: Operations in which guidance-mandatory drugs or non-prescription drugs are marketed or provided at a store
- (2) Drug sellers by household distribution: Operations in which non-prescription drugs are marketed or provided through distribution
- (3) Drug sellers wholesale distribution: Operations in which drugs are marketed or provided to proprietors of pharmacy, pharmaceutical manufacturing/marketing authorization holders, manufacturers or distributors, or hospitals, clinics or other parties specified under the MHLW Ordinance

Marketing business license is valid for a period of 6 years.

At pharmacies and store-based drug sellers, pharmacists can market guidance-mandatory drugs or type 1 non-prescription drugs, and pharmacists or registered 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.

For drug sellers by wholesale distribution, a pharmacist must be allocated to each sales office and thereby assigned to management of the office.

### 3.9 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 enforced on June 1, 2009 (Law No. 69 dated June 14, 2006) mandates non-prescription drugs to be classified into one of type 1, type 2, and type 3 according to the risk and to bear a label indicating the type.

In addition, barcode labeling of prescription drugs (excluding extracorporeal diagnostic medicines) was partially mandated in July 2015 to prevent medical accidents due to misunderstandings, ensure traceability, and improve the efficiency in prescription drug distribution (Notification No. 1 of the Economic Affairs Division, HPB and No. 1 of the Safety Division, PFSB both dated June 29, 2012). Moreover, it has been requested to increase the range of essential labeling, to take more rapid and reliable measures to identify and manage batch numbers, etc. in the distribution process, and to carry out important responsibilities in taking safety measures by April 2021 (or by April 2023 in special circumstances) (Notification No. 0830-(1) of the Economic Affairs Division, HPB, Notification No. 0830-(1) of the Safety

Division, PSEHB, and Notification No. 0830-(1) of the Compliance and Narcotics Division of PSEHB all dated August 30, 2016)

Furthermore, 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. 0630001 of the Safety Division, PFSB dated June 30, and No. 0331-1 of the Safety Division, PFSB and No. 0331-8 of the Compliance and Narcotics Division, PFSB both dated March 31, 2014).

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, before initiation of manufacturing/marketing or amendment, they must submit to the PMDA the package insert that covers all the required information such as precautions for use and handling. The package insert must be published on the PMDA homepage immediately after submission of the notification.

The guidelines on preparation of package inserts were revised into the guidelines which are easier to understand and use. They were applied from April 1, 2019. The package inserts for the drugs which have already been approved and the drugs for which application for approval has already been filed as of this date must be revised as soon as possible according to the revised guidelines on preparation of package inserts by March 31, 2024 (Notification No. 0608-(1) of the PSEHB dated June 8, 2017)

### 3.10 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. The standards shall be applied to advertisements on all media including newspapers, magazines, TV, radio, website, and social network services. 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. 0929(4) of the PSEHB dated September 29, 2017, and Notification No. 0929(5) of the Compliance and Narcotics Division of PSEHB dated September 29, 2017).

Appropriateness of advertisement of drugs shall be judged based on the following requirements: the advertisement clearly intend to attract customers (enhances purchase motivation of customers); it present the commercial name and class clearly such as specified drug; and it be accessible to general public (Notification No. 148 of the Inspection and Guidance Division, PMSB dated September 29, 1998).

With the 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).

Furthermore, behaviors which are unlikely to leave evidence (oral explanation, etc.), behaviors which are not regarded as obviously false and deceptive but are likely to facilitate inappropriate use, and behaviors to provide information for which it is difficult to immediately detect involvement of the company and

difficult to judge whether it should be regarded as advertisement (such as research papers) are conducted in activities to provide sales information on prescription drugs, and their effects on the proper use of prescription drugs are concerned. Under such circumstances, "Guidelines on Activities to Provide Sales Information on Prescription Drugs" (Notification No. 0925-(1) of the PSEHB dated September 25, 2018) and the Q&As (Office Communication dated February 20, 2019, Office Communication dated March 29, 2019, and Office Communication dated September 6, 2019) were issued to improve public health by properly conducting advertising or advertising-like behaviors in the activities to provide sales information.

### 3.11 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" dated June 13, 2008 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).

### 3.12 Good Clinical Practice (GCP)

"Clinical trials" refer to studies with the objective of

collecting data on clinical trial results from among the data attached to drug approval application forms. In Japan, clinical trials are conducted in accordance with the GCP which was implemented to assure scientific quality and reliability of clinical study data. This GCP was replaced by the Standards for the Conduct of Clinical Studies (MHW Ordinance No. 28, dated March 27, 1997) based on the ICH-GCP Guidelines (E6) (see Chapter 3 for details). Operating procedures of the implementation of the New GCP were issued as Notification of the Pharmaceutical Affairs Bureau (Notification No. 430 of the PAB dated March 27, 1997) and Notification of the Pharmaceuticals and Cosmetics Division/Safety Division, Pharmaceutical Affairs Bureau (Notification No. 445 of PAB/PCD/Notification No. 68 of PAB/SD dated May 29, 1997).

Since then, standards intended to activate clinical trials have been established for utilization of site management organizations (SMOs), training of clinical research coordinators (CRCs), and implementation of a site monitoring system. In 2003, a system of investigator-initiated clinical trials was officially introduced (Ministerial Ordinance No. 106 dated June 12, 2003). Even after that, discussion has been held for measures to ensure reliability of clinical trials and safety of study subjects as well as smooth and transparent conduct of clinical studies. Consequently, the GCP has been often revised in addition to the ministerial ordinances and notifications for implementation.

Other: Enforcement Notification of major changes in GCP Ordinance, etc.:

- 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 dated March 31, 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 (Notification No. 1221002 of the Research and Development Division of HPB dated December 21, 2007; revised by Notification No. 0326-(1) of the Research and Development Division of HPB and Notification No. 0326-(1) of the Evaluation and Licensing Division of PFSB dated March 26, 2013, and Notification No. 0710-(4) of the Research and Development Division of HPB, Notification No. 0710-(2) of the Pharmaceutical Evaluation Division, PSEHB, and Notification No. 0710-(2) of the Medical Device Evaluation Division, PSEHB dated July 10, 2018) was issued 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 dated February 29, 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 dated February 29, 2008).

- 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.

- 2016

The GCP Ordinance was revised on January 22, 2016 according to the “Ministerial Ordinance to Partially Revise the Ordinance on Standards for Conduct of Clinical Trials (GCP)” (MHLW Ordinance No. 9). The major points of revision were associated with the implementation of expanded trials (see 3.13 Trial Conducted from a Compassionate Viewpoint (expanded trial)).

### 3.13 Trial Conducted from a Compassionate Viewpoint (expanded trial)

For “unapproved drugs and drugs of off-label use with high medical needs,” discussion was held on introduction of a program for enhanced access of patients not eligible for ongoing trials of these drugs to a trial (trial conducted from a compassionate viewpoint or expanded access trial), while the development and process for approval are continued. The program came into operation on January 25, 2016 (Notification No. 0122-7 of the Evaluation and Licensing Division, PSEHB, dated January 22, 2016).

An expanded access trial is conducted after conduct of a trial at the final development phase in Japan (pivotal trial) in which patients are highly likely

to benefit from an unapproved drug or off-label use as expected, or while such trial is ongoing (after completion of the enrollment). Applicable investigational products have to be used for serious life-threatening diseases for which no effective conventional treatment is available.

To enforce expanded access trials, the GCP Ordinance was revised (MHLW Ordinance No. 9 dated January 22, 2016). More specifically, the revisions included: (1) a trial conducted from a compassionate viewpoint is defined as an “expanded access trial”; (2) a part of matters to be described on the investigational product are to be exempted if it is an investigational product used outside of Japan or a commercially available approved drug; and (3) a drug to be used in the expanded access trial is required to be quarantined from the other drugs appropriately (investigational product control/accountability) (Notification No. 0122-2 of thePSEHB, dated January 22, 2016).

Information on the clinical trials being conducted as pivotal trials and expanded access trials is placed on the homepage of the PMDA.

<http://www.pmda.go.jp/review-services/trials/0019.html>

### 3.14 Patient-requested Therapy System

This system was enforced in April 2016 to allow patients to receive an unapproved drug as an uninsured concomitant therapy at a local medical institution as accessible to him or her as possible with the safety and efficacy being monitored. It is intended to collect data that may lead to application of insurance and scientific evidences.

Medical care potentially supported by the patient-requested therapy system is one that is expanded from “advanced medical care” under the uninsured concomitant therapy expense system and is intended to be covered by insurance in the future. In addition, it has to be originated by the request from a patient to the MHLW. If the medical care has not been used as a patient-requested therapy, a clinical research

central hospital shall judge the feasibility, and submit an application form to the MHLW with attached documents such as protocol. If it has been used previously, a clinical central hospital shall review the application, and judge whether it can be used or not before the clinical use.

When a patient requests for use of an unapproved drug that has been already used in clinical trials or in advanced medical care, firstly participation in a clinical trial, and if there is no relevant clinical trial, participation in advanced medical care should be considered. If no relevant trial can be found in spite of the consideration, patient-requested therapy should be considered.

### 3.15 Good Post-marketing Study Practice (GPSP)

The GPMSO 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 GPMSO was divided into Good Vigilance Practice (GVP) and Good Post-marketing Study Practice (GPSP). The GPSP ordinance was enforced from April 1, 2005. The ordinance was revised on October 26, 2017 to add the “post-marketing database survey” to the “drug use-results survey” and the “post-marketing clinical study,” which had been prescribed as the surveys to be conducted after marketing. The ordinance was enforced on April 1, 2018 (refer to Chapter 4).

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

### 3.16 Reexamination

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.

The drugs to be reexamined are the drugs which have been designated by the Minister of Health, Labour and Welfare at the time of marketing approval as the drugs obviously different from existing approved drugs in terms of active components, contents, administration method, dose levels, indications, and so on.

The concept of the risk management plan has been incorporated in reexamination. At the same time, a notification regarding the documents to be attached to application for reexamination was revised in 2017 to cope with the above-described revision of the GPSP ordinance (Notification No. 1128-(2) of the Pharmaceutical Evaluation Division, PSEHB, dated November 28, 2017).

Refer to Designation for Reexamination in Chapter 4 for the timing of reexamination.

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

### 3.17 Reevaluation

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.

The Minister of Health, Labour and Welfare will hear the opinions of the Pharmaceutical Affairs and Food Sanitation Council regarding the drugs to be reevaluated, and publicly announce the drugs which are judged to necessitate reevaluation. In public announcement, the scope of the drugs to be reevaluated, documents to be submitted, and due date for submission of documents will be presented. If necessary documents are not submitted before the due date, the approval of the drug will be cancelled or other necessary measures will be taken according to the provision in Article 74-2, Paragraph 3 of the Law.

### 3.18 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.

Any serious adverse drug reaction that cannot be expected from the investigator's brochure of the currently ongoing trial should be reported, whenever it occurs. In addition, adverse drug reactions must be periodically reported through Development Safety Update Report (DSUR) on an annual basis.

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.). The reports are required to be sent to the PMDA from April 1, 2004. (Notification No. 0325013 of PFSB dated March 25, 2004)

### 3.19 Risk Management Plan (RMP)

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.

In addition, "Partial Revision of 'Formulation of the Risk Management Plan'" (Notification No. 1205-(1) of the Pharmaceutical Evaluation Division, PSEHB and Notification No. 1205-(1) of the Safety Division, PSEHB dated December 5, 2017) and "Formulation of the RMP Questions and Answers" (Office Communication dated December 5, 2017) were issued to show details about formulation of the Risk Management Plan.

A list of the items for which a risk management plan has been submitted is shown on the homepage of the PMDA.

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

### 3.20 Dissemination of Information

Marketing authorization holders of drugs, medical devices, or cellular and tissue-based products, wholesalers, distributors, etc. of medical devices, distributors of cellular and tissue-based products and overseas restrictive approval holders are asked to collect and examine information on efficacy, safety, and proper use of drugs, medical devices, and cellular and tissue-based products and supply such information to pharmaceutical and health professionals such as physicians and pharmacists. (Article 68-2, Paragraph 1 of the Law)

### 3.21 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) (currently PSEHB). 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.

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.

Review reports and summaries of data for applications are placed in the homepage of the PMDA.

Japanese HP:

<http://www.pmda.go.jp/PmdaSearch/iyakuSearch/>

English HP:

<https://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0001.html>

### 3.22 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 (submission date of clinical trial plan) 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** Flowchart of Patent-Life Extension).

Generic drugs will not be approved until the substance patent or the application patent has expired and production of the active ingredient becomes possible. 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 HP of the Patent Office:

<https://www.jpo.go.jp/index.html>

English HP:

<https://www.jpo.go.jp/e/index.html>

### 3.23 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 Pharmaceutical and Medical Device Act 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 (MHLW Ordinance No. 14 dated February 28, 2007). On February 28, 2007, the Guidelines on Monitoring of Import of Designated Drugs were issued (Notification No. 0228009 of the PFSB, partially amended by Notification No. 0218-5 of the PSEHB dated February 18, 2016). On February 20, 2013, MHLW Ordinance No. 19 was revised and issued to implement comprehensive control of controlled drugs/substances.

In the Law for Partial Amendment of the Pharmaceutical Affairs Law enacted on April 1, 2014 (Law No. 103 dated December 13, 2013), new provisions have been added for possessing, using, purchasing and receiving such designated drugs.

Furthermore, in the Law for Partial Amendment of the Law enacted on December 17, 2014 (Law No. 122 dated November 27, 2014), additional measures were established for prevention of public health risk caused by “dangerous illegal drugs”, i.e., the inspection order and the sales-suspension order should apply more widely, goods subjected to the sales-suspension order must not be sold in a wide area, and advertisement should be restricted more strictly.

In August 2018, the Fifth Five-Year Drug Abuse Prevention Strategy was formulated to reinforce the measures for coping with smuggling, to intensify the counter measures for smuggling crimes which are becoming more and more shrewd and latent, to cope with the drugs which are not regulated in Japan or the

drugs which are used in different forms, and to carry out monitoring and crackdown to prevent vicious crimes improperly using psychotropic drug.

### 3.24 Countermeasures for Counterfeit Prescription Drug

Safety, stability, and efficiency are required in distribution of drugs because shortage of the products can directly endanger life. Under such circumstances, it was found in 2017 that a counterfeit drug was distributed and dispensed at a pharmacy. In response to this event, "Ordinance for Partially Modifying the Enforcement Regulations for the Law for Ensuring Quality, Efficacy, and Safety of Drugs and Medical Devices" (MHLW Ordinance No. 106 of 2017), "Ordinance for Partially Modifying Regulations for Buildings and Equipment of Pharmacies, etc." (MHLW Ordinance No. 107 of 2017), and "Ordinance for Partially Modifying the Ministerial Order to Determine the System for Pharmacies, Store-Based Distribution, and Household Distribution" (MHLW Ordinance No. 108 of 2017) were promulgated on October 5, 2017 and enforced on January 31, 2018 (a part of them on July 31, 2018) to take necessary measures for the matters which need to be coped with immediately to prevent distribution of the counterfeit drug. At the same time, "Handling of Sealing of Drugs" (Notification No. 0801-(1) of the PSEHB dated August 1, 2018) and the Questions and Answers (Q&As) (Office Communication dated March 29, 2019) were issued from the point of view of prevention, etc. of recurrence of distribution of counterfeit drugs, etc., and "Guidelines on Good Distribution Practice (GDP)" (Office Communication dated December 28, 2018) was formulated in the Health, Labour and Welfare Policy Research.

## 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 for non-prescription drugs for which approval standards are established) reviews the name, quality, dosage and administration, indications, ADRs, etc. of the product in an application submitted by a person with a marketing business license. A GMP compliance review is performed to assure that the plant manufacturing the product complies with the manufacturing control and quality control standards. Marketing approval is granted to products meeting these standards. This approval system is the essential basis for ensuring good quality, efficacy, and safety of drugs and related products, which is the principal objective of the Pharmaceutical and Medical Device Act.

### 4.2 Marketing Approval Reviews

The entire process of approval review from review-related inspections and clinical trial consultation to review works for the drugs approved by the Minister of Health, Labour and Welfare is undertaken by the PMDA.

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.

The ordinary evaluation process followed by the PMDA is as follows (see the PMDA homepage). 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, Notification No. 1003001 of the PMDA dated October 3, 2016).

<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 (until 6 months before the anticipated date of approval)
- (5) Review report (1)
- (6) Expert review meeting (includes at least three clinical specialists as experts)
- (7) Review report (2)
- (8) Report to the Pharmaceutical 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 homepage 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 Pharmaceutical and Medical Device Act, “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
- (9) Prescription combination drugs with similar formulations
- (10) Other prescription drugs

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

These guidelines consist of five parts: Module 1

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

For the generic products, their application has come to require submission of CTD, in principle, since March 1, 2017 (Notification No. 0311-3 of the Evaluation and Licensing Division, PSEHB dated March 11, 2016).

Regarding the review period for new drugs from application to approval, the Fourth Medium Range Plan (FY2019-FY2023) of PMDA has set a goal to process 80% of the products to be approved in the relevant year within 9 months for priority review products and within 12 months for ordinary review products, and all the products subject to the SAKIGAKE Designation System within 6 months. In addition, “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” sets out the policy of conducting preliminary interviews for planned reviews and indicates 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 is also indicated (Administrative Notice of the Evaluation and Licensing Division 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 HP :

<http://www.pmda.go.jp/review-services/outline/0002.html>

English HP :

<http://www.pmda.go.jp/english/review-services/reviews/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 No. 0527-(4) of the Evaluation and Licensing Division, PFSB) (Partially modified by Notification No. 0825-(1) of the Evaluation and Licensing Division, PFSB dated August 25, 2008, and Notification No. 0707-(3) of the Evaluation and Licensing Division, PFSB dated July 7, 2009).

For products for which marketing application will be made since October 1, 2016, clinical trial data should be submitted in accordance with the specifications in the Clinical Data Interchange Standards Consortium (the CDISC standards), so that PMDA 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.

When clinical study data are submitted as electronic data at the time of application for approval, an agreement should be reached with PMDA in a clinical trial consultation regarding the range of the electronic data for application to be submitted. Concerning specific electronic data to be submitted, necessary issues should be discussed with PMDA in the consultation related to submission of electronic data for application, and final confirmation should be made with PMDA regarding the scope of the electronic data to be submitted in a preliminary interview for planned reviews for approval of a new

drug .

In line with submission of electronic data of clinical studies, 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)

Documents for manufacturing/marketing approval application are to be submitted via gateway system, in principle, to improve efficiency of information processing between the applicant and PMDA, share information between them, and manage progress of review-related paperwork.

Japanese HP :

<http://www.pmda.go.jp/review-services/drug-reviews/about-reviews/p-drugs/0003.html>

English HP :

<http://www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0002.html>

#### **4.4 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, ones covered by the SAKIGAKE Designation System and the other ones 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. This system is also applied to the drugs subjected to the Conditional Accelerated Approval System. With this system, applications for specified drugs are reviewed on a priority basis (Notification No. 0122-(12) of the Evaluation and Licensing Division, PSEHB / Notification No. 0122-(2) of the Medical Device Evaluation Division entitled "Handling of Priority Review" dated January 22, 2016).

##### **(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) Standpoint 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 Pharmaceutical Evaluation Division decides whether or not to apply the priority review. The Pharmaceutical Evaluation Division notifies this decision to the applicant and the PMDA. The Pharmaceutical Evaluation 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**

It is possible to obtain priority interview advice on indications and other items concerning the products designated for priority interview advice. Orphan drugs and drugs covered by the SAKIGAKE

Designation System are handled as the products designated for priority interview advice. Consultation regarding eligibility for the Conditional Accelerated Approval System for Pharmaceuticals will be subjected to the products designated for priority interview advice, but it will not apply if characteristics of the disease and the results of clinical trials conducted suggest that the requirements for Conditional Accelerated Approval System for Pharmaceuticals are not satisfied.

#### 4.5 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 (Article 14-3 of the law).

#### 4.6 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 (except for intractable diseases specified by the national agency) indicated for the drug concerned and excellent usefulness of the drug from the medical standpoint. The designation is conducted after deliberation by PAFSC.

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

drug designated as an orphan drug has obtained a marketing approval, new drug creation premium will be applied at the time of calculation of drug price for the product.

A list of the products designated as orphan drugs is published on the homepage of the National Institutes of Biomedical Innovation, Health and Nutrition.

<http://www.nibiohn.go.jp/en/activities/research-development.html>

A list of specified intractable diseases is available on the homepage of MHLW.

<http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000084783.html>

#### 4.7 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 the results of special drug use-results surveys or post-marketing clinical studies during the reexamination period (Notification No. 1324 of the PMSB dated December 27, 2000).

Guidance on Clinical studies on Drugs in Pediatric Populations was issued as a guideline for implementation of clinical studies in the pediatric population (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.

A supplement was issued to supplement the contents of the guidance, and to propose a new way of thinking necessary for development of pediatric drugs (Notification No. 1227-5 of the Evaluation and Licensing Division, PSEHB dated December 27, 2017).

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.

#### **4.8 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 88 items, and the clinical development of 15 unapproved items or those off-label use was started in sequence one after the other. In the third recruitment, the development request was issued for 50 items, and developing companies were recruited for the 5 items. In the fourth recruitment, the development request was issued for 10 items, and developing companies were recruited for 2 items (the latest version of the drug list is available at the following site). The fourth recruitment of requests for unapproved or off-label use drugs was started in July 2015, and requests have been received as needed. Recruitment is still ongoing. From July 2015 and onward, not only development requests for

unapproved drugs in Japan but also those for unapproved drugs overseas are discussed. Development of unapproved drugs and those of off-label use in requests is discussed within the Scheme for prompt practical use of unapproved drugs under the Packaging Strategy for World-first Products (Strategy of Sakigake). (Notification No. 0701-2 of the Evaluation and Licensing Division, PFSB and Notification No. 0701-2 of the Research and Development Division, HPB both dated July 1, 2015)

Contents of previous discussion meetings are available on homepage of the MHLW.

<http://www.mhlw.go.jp/stf/shingi/other-iyaku.html?tid=128701>

In August 2010, a new approach has started 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.

#### 4.9 Packaging Strategy for World-first Products

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. It includes, 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

This strategy is intended to designate drugs expected to be highly effective against life-threatening serious diseases by mechanism of action different from that of approved drugs in principle. The PMDA will assign a review coordinator as a concierge to strengthen cooperative relationship among relevant divisions of the MHLW and PMDA and to manage the progress to accelerate the development. Preliminary consultation will be improved with consultations on SAKIGAKE comprehensive assessment and will be subjected to priority review, with the aim of reducing the review period to 6 months. (Notification No. 0906-(1) of the Pharmaceutical Evaluation Division, PSEHB dated September 6, 2019)

For designation, a drug has to meet all of the following 4 requirements.

- (1) Designation requirement 1: innovativeness of the therapeutic drug  
In principle, the following drugs are applicable: a drug has to have a mechanism of action different from that of any approved drug; a drug that has the same mechanism of action as that of approved drug, but is developed to have different indications; and a drug that is to use an innovative drug delivery system.
- (2) Designation requirement 2: Seriousness of the disease targeted by the drug  
The drug has to be indicated for any of the following diseases.
  - Life-threatening serious diseases
  - Diseases presenting persistent symptoms (in a state hard to maintain social life) and without radical treatment
- (3) Designation requirement 3: Considerably high efficacy on the target disease  
The drug has to have no competing approved drugs, or has to have the efficacy expected to be considerably higher than that of conventional therapeutic drugs /therapies (or expected to have the considerably improved

safety)

- (4) Designation requirement 4: Intention /system of world's leading early development and application in Japan

The drug has to be planned to be applied for approval in Japan before anywhere in the world (or applied concurrently in multiple regions including Japan) with great importance attached to the development initiated in Japan, and the drug has to have the appropriate system for application for approval. Drugs of which steadily advanced development in Japan can be demonstrated are desirable. That is, therapeutic drugs applicable to both of the following conditions are desirable.

- Drugs of which a First In Human (FIH) study has been conducted in Japan.
- Drugs of which a Proof Of Concept (POC) study has been conducted in Japan.

When an application is to be filed for a drug which needs to be used together with companion diagnostics, etc., there should be a system for concurrently filing an application for approval of the diagnostic drug (including cooperation with other companies).

A list of the products subject to this system is available on the homepage of PMDA.

<http://www.pmda.go.jp/review-services/drug-reviews/0003.html>

## 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. If there are companies involved in development of these drugs in Japan, such companies would be requested to proceed with the development and to conduct clinical trials. If there is a drug candidate developed by a venture company outside of Japan, but it takes time to match with a company potentially involved in the development, the scheme will encourage clinical research central hospitals and National Centers to conduct investigator-initiated clinical trials or provide advanced medical care, and thereby to obtain data potentially used in drug approval application actively. As described the above, the scheme will support the research and development intensively to ensure the environment in which companies can readily initiate the development. (Notification No. 0701-(2) of the Evaluation and Licensing Division, PFSA and Notification No. 0701-(2) of the Research and Development Division, HPB entitled "Expansion of the Targets of Demand among Unapproved Drugs and Drugs Off-label Use Urgently Required for Healthcare dated July 1, 2015)

## 4.10 Regulatory Science Strategy Consultations for Regenerative Medicine Products (former Regulatory Strategy Consultations)

It is specified in the notifications that safety- and quality-related issues on drugs, etc. processed from cells and tissues, drugs for gene therapy, and recombinant live vaccines are to be discussed with PMDA through regulatory science strategy consulting from the early stage of research and development (Notification of No. 0630-(2) of PFSA entitled "Modifications of Handling of Medicinal Products and Medical Devices Utilizing Cells and Tissues to Comply with Implementation of Regulatory Strategy Consultation" dated June 30, 2011 and Notification of No. 0701-(13) of PFSA entitled "Abolition of the

Verification Application System for Products for Gene Therapy" dated July 1, 2013). Procedures for requesting and holding a regulatory science strategy consultation are available in Notification No. 0322050 of PMDA entitled "Guidelines for Regulatory Science Strategy Consultations" dated March 22, 2018. For regenerative medicine products, clinical trials should be initiated after a regulatory science strategy consultation for quality and safety with PMDA.

#### **4.11 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.

#### **4.12 Conditional Accelerated Approval System for Pharmaceuticals**

For the drugs for treating serious diseases which occur in a small number of patients, for which effective treatment methods are limited, and for which a clinical trial is difficult to conduct or requires long-period, a conditional accelerated approval system was established in which the results of confirmatory clinical trials are not required, but the conduct of necessary post-marketing surveys, etc. is required as a condition for marketing approval. (Notification No. 1020(1) of Pharmaceutical Evaluation Division, PSEHB entitled "Implementation of conditional

accelerated approval system for pharmaceuticals" dated October 20, 2017).

The drugs to be subjected to this system must meet all of the following conditions from (i) to (iv).

- (i) The drug is indicated for serious diseases.
- (ii) The medical usefulness is high.
- (iii) Confirmatory clinical trials are difficult to conduct.
- (iv) The results of clinical trials, etc. other than confirmatory clinical trials suggest some efficacy and safety.

For the approval of the drugs subjected to this system, surveys, etc. necessary for reconfirmation of the efficacy and safety become a condition for approval. Medical information databases and patient registries, etc. can be used for such surveys.

If it is appropriate to define the requirements for institutions, etc. from the point of view of ensuring proper use of the drugs, implementation of the measures, etc., necessary for ensuring the requirements may be included in the conditions for approval.

The drugs covered by this system will be subject to the priority review.

#### **4.13 Guidelines for Promoting Optimal Use**

A drug with a new innovative mechanism of action may have obviously different pharmacological actions or safety profiles as compared with existing drugs. Thus, it is important that the drug is used at medical institutions satisfying certain requirements and having the ability to promptly take necessary measures for coping with any adverse drug reactions for a period until sufficient efficacy and safety information is accumulated. Therefore, it is necessary to formulate the guidelines for promoting the optimal use at the same time with the reviews related to the approval for innovative drugs with new mechanisms of action from the point of view of promoting the optimal use on the basis of the latest scientific findings with the aim of presenting the requirements for the patients and

medical institutions, etc. that are to use the drug as well as the points to consider. (Notification No. 0915(1) of Pharmaceutical Evaluation Division, PSEHB, Notification No. 0915(1) of Medical Economics Division, HIB entitled "Handling of Guidelines for Promoting Optimal Use" dated September 15, 2017).

The drugs to be subjected to the guidelines must meet any of the following conditions from (i) to (iii).

- (i) The drugs that have a mechanism of action different from that of existing drugs available for treatment of the disease
- (ii) The drugs that have the same mechanism of action as a drug which has already been subjected to the guidelines
- (iii) The drugs that meet the condition (i) or (ii) and have already been subjected to the guidelines, and for which new indications are added

Concerning the drugs falling under (i), eligibility for the target drug will be judged globally considering the following points.

- The pharmacological action differs significantly from that of existing drugs.
- The safety profile differs significantly from that of existing drugs, and special precautions are required for the use.
- The efficacy is significantly higher than that of existing drugs.
- The clinical positioning differs from that of existing drugs, and the drug may be usable for a wider range of patients.
- It may be possible to increase the users through development for other diseases (addition of indications, etc.).

The guidelines for promoting the optimal use are available on the homepage of the PMDA.

<http://www.pmda.go.jp/review-services/drug-reviews/review-information/p-drugs/0028.html>

#### 4.14 Biosimilar Products

For biological products, it is difficult to prove the equivalence of active ingredients with those of existing drugs unlike with chemically synthesized drugs, but with the advances made in technology, biosimilars (or follow-on biologics) have been developed in foreign countries as products with equivalence to and the same quality as existing biological products. WHO and major countries 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 No. 0304011 of the Evaluation and Licensing Division, PFSB dated March 4, 2009, Notification No. 0214-(1) of the Evaluation and Licensing Division, PFSB, Office Communication dated February 14, 2013), and Questions and Answers on Policies to Verify the Quality, Efficacy, and Safety of Biosimilar Products (Office Communication dated July 21, 2009, Office Communication dated March 31, and Office Communication dated December 15, 2015) were issued.

#### 4.15 Combination Products

A "combination product" is defined as a drug that was approved to be manufactured/marketed with other components including devices or equipments 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) and has been applied since November 25, 2014. Subsequently, it was revised by Notification No. 0915-(1) of the Pharmaceutical Evaluation Division, PSEHB / Notification No. 0915-(1) of the Medical Device Evaluation Division, PSEHB / Notification No. 0915-(3) of the Safety Division, PSEHB / Notification No. 0915-(3) of the Compliance and Narcotics Division of PSEHB dated September 15, 2016, and Notification No. 1122-(4) of the Pharmaceutical Evaluation Division, PSEHB / Notification No. 1122-(10) of the Medical Device Evaluation Division, PSEHB / Notification No. 1122-(7) of the Safety Division, PSEHB / Notification No. 1122-(4) of the Compliance and Narcotics Division of PSEHB dated November 22, 2016. After this revision, a medical device which cannot be separated from the drug and which is generally referred to as a container according to the definition of the general term for the medical device has come to be regarded as a container, and is no longer regarded as a combination product. However, the category of the “prefilling syringe,” which used to be regarded as a container according to the definition of general terms of medical devices, was changed to an ordinary medical device. Therefore, a “prefilled syringe product” will continuously be handled as a combination product.

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).

#### 4.16 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.

#### 4.17 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.

Transfer of marketing approvals of products that have been marketed only for shorter than 1 year

since the approval is not accepted except for that due to business merger. For transfer in association with disposition of the business unit, however, whether or not it is acceptable will be judged as an evaluation result of the individual content, if the specified requirements are met. Consultation with the regulatory authority to which the notification is to be submitted should be done in advance to obtain the acceptance (Office Communication from the Evaluation and Licensing Division / Compliance and Narcotics Division dated March 29, 2016).

#### 4.18 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.

#### 4.19 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 Pharmaceutical and Medical Device Act 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 availability of certification in advance, if the form of certificate designated by the requesting country is different from that specified in the notification (Notification No. 1125-(12) of the PFSB dated November 25, 2014, Partial revision of Notification No. 1011-(1) of the PSEHB dated October 1, 2015).

The certificates are also issued, when final products manufactured in an overseas plant are exported to a third country (Notification No. 0604-(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) for aseptic chemical pharmaceuticals (such as tablets, capsules, and external preparations). 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. In April 2016, Japan-Europe certification system became applicable to all the EU countries (Notification No. 0426-3 of the

Compliance and Narcotics Division of PSEHB dated April 26, 2016). From July 17, 2018, the drugs subject to GMP mutual recognition system were expanded to the drug substances (active ingredients), aseptic drugs, biological products including vaccines (except for the products originating from the samples collected from a large number of unspecified donors, such as human blood, cells, and tissues), and most drug products came to be covered. 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).

In preparation for the situation in which the MRA between Japan and the European Union (EU) becomes no longer applicable to the relationship between Japan and the United Kingdom (UK) after the withdrawal of the UK from the EU (Brexit), the Mutual Recognition Agreement (MRA) between Japan and the UK was concluded in September 2019 (Notification No. 0920-(2) of the Compliance and Narcotics Division, PSEHB).

## 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 Pharmaceutical and Medical Device Act 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 HP:

<http://www.pmda.go.jp/rs-std-jp/standards-development/jp/0001.html>

English HP:

<http://www.pmda.go.jp/english/rs-sb-std/standards-development/jp/0009.html>

The 17th edition of the JP was notified with Notice No. 64 issued by the MHLW on March 7, 2016, and applied on April 1, 2016. Supplement 1 was notified with Notice No. 348 issued by the MHLW on December 1, 2017, and applied on the day. Supplement 2 was notified with Notice No. 49 issued by the MHLW on June 28, 2019, and applied on the day.

The basic compilation policies of the 18th edition were announced as shown below with Office Communication dated October 19, 2016.).

#### (1) 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.

The JP is compiled by utilizing the knowledge and experience of many pharmaceutical professionals specialized in pharmaceutical administration and regulations, pharmaceutical companies, medical care, pharmaceutical research, pharmacological education, and so on. 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 provide a list of

drugs which are important for public health and medical care in Japan, and to undertake the role of and achieve an expected level of contribution to the maintenance and assurance of advanced and global harmonization on drug product quality in the international community.

## (2) Five major policies of 18th Edition of Japanese Pharmacopoeia

- 1) Complete entries of all drugs important in healthcare
- 2) Improvement of quality by introduction of the latest scholarship and technology
- 3) Further promotion of internationalization for coping with globalization of drugs
- 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.

## (3) Policies for entry

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 US Pharmacopoeia (USP) and European Pharmacopoeia (EP) and are globally in wide use. Approved drugs which are important from the point of view of insurance and the drugs approved as generic drugs are examined for entry as soon as possible. New drugs to be approved in the future will be entered after a certain period has passed after approval. For example, entry of such drugs will be considered as soon as it becomes possible to collect a certain amount of information about quality, safety and efficacy.

- Date of enforcement

The 18th edition of the JP is expected to be enacted in April, 2021. Revision of Supplement and partial revision of the 17th edition of JP will be

made as needed, considering the situation of review, etc.

## • 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 Kansai 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 on the basis of the guidelines for preparation of the JP draft. The draft is reviewed by the JP Expert 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 (**Fig. 7** Flowchart of Drug Listing in Japanese Pharmacopoeia).

## 5.2 Standards Based on Article 42 of the Pharmaceutical and Medical Device Act

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

### 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.

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 dated March 27, 2009.

In line with the revised Pharmaceutical Affairs Law enacted on November 25, 2014 (Law No. 84 dated November 27, 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. Gelatin (including collagen) derived from wool, milk, bone and skin was classified as “low-risk raw materials,” and the scope of countries of origin excepted from the restriction was expanded. Previously, fatty acids, glycerin, fatty acid esters, amino acids, synthetic

oligopeptides and materials processed by heat and alkali treatment were excluded from the scope of the Standards for raw materials of ruminant origin. In addition, with this notice, materials processed by appropriate treatment are to be excluded, such as those that have been assessed to ensure the safety of the final products on the basis of clearance data of prion potentially present in raw materials.

#### 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 (Article 43 of the Law).

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

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

### 6.2 Product Recalls

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 or manufactured 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 Pharmaceutical and Medical Device Act

or approved condition, and all recall information is published on the PMDA homepage by class as below. Also 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 countries of applicants, member companies of the European Economic Area (EEA), cooperating global organization (World Health Organization; WHO), The European Directorate for the Quality of Medicines and Healthcare (EDQM), and European Commission.

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, partially revised by Notification No. 0208-(1) of the PSEHB dated February 8, 2018)

### 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.

For new replacement approval applications for changes in brand names as a measure to prevent accidents, 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. After that, BSE infection was confirmed in Canada and the United States of America, and measures were taken after each onset.

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.

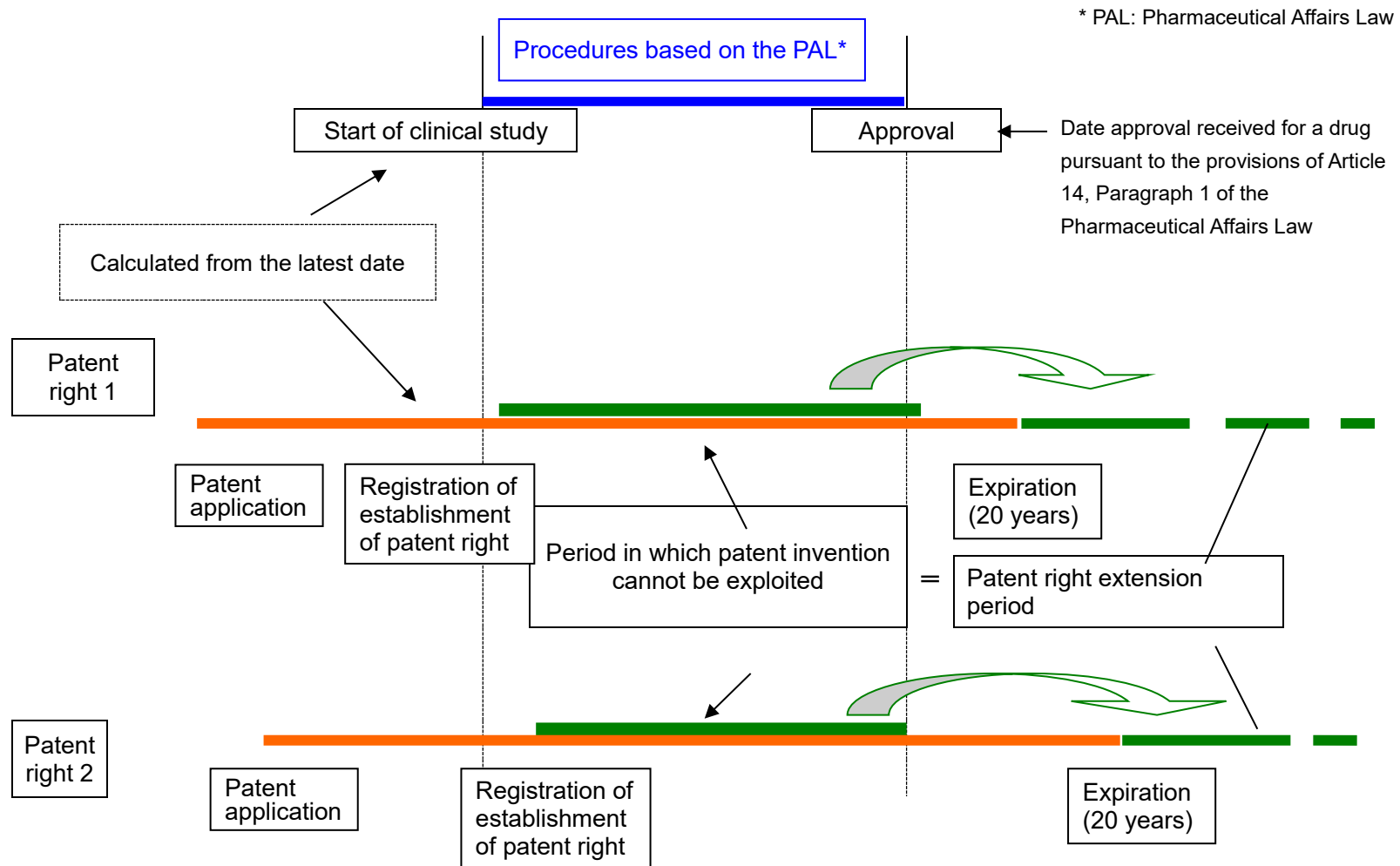
It has been considered necessary to adopt quality and safety assurance measures based on current scientific levels for drugs manufactured using raw materials of human or animal origin. Companies have been requested to undertake voluntary inspections and make adjustments in approval documentation.

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.

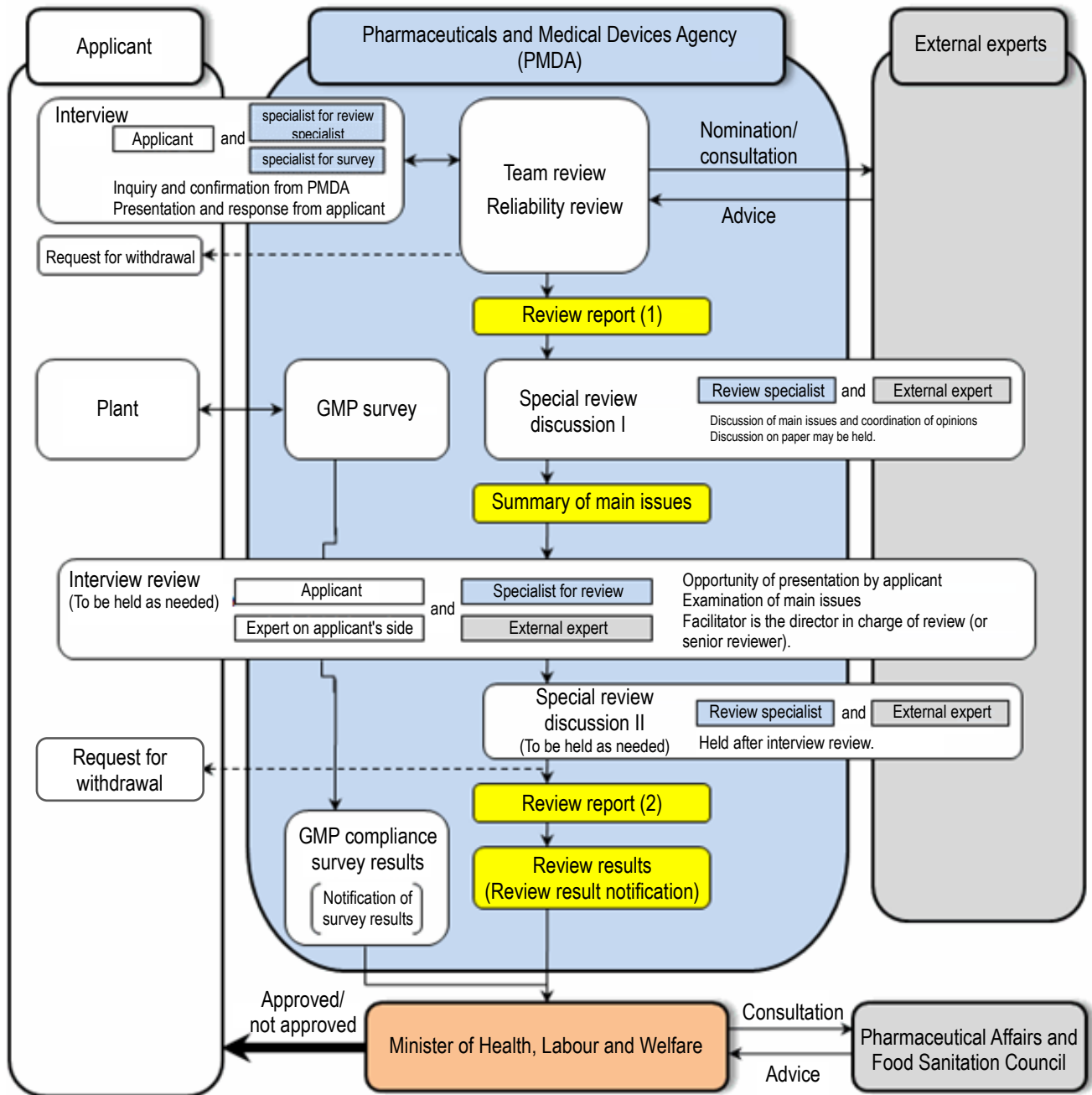
In an office communication of the Compliance and Narcotics Division, PFSB dated September 5, 2006 entitled "Self-checking of Drugs, etc. Using Raw Materials Derived From Cattle Produced in the United States," instructions are given to verify by self-check forms (self-check points) as an additional preventive measures since it was clear that products in some lots were manufactured using raw materials derived from cattle produced in the United States even after the deadline for changing raw materials. In 2007, the removal of Chile from the list of countries free from where biological materials can be imported for medical use was notified, and the industry was requested again 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.

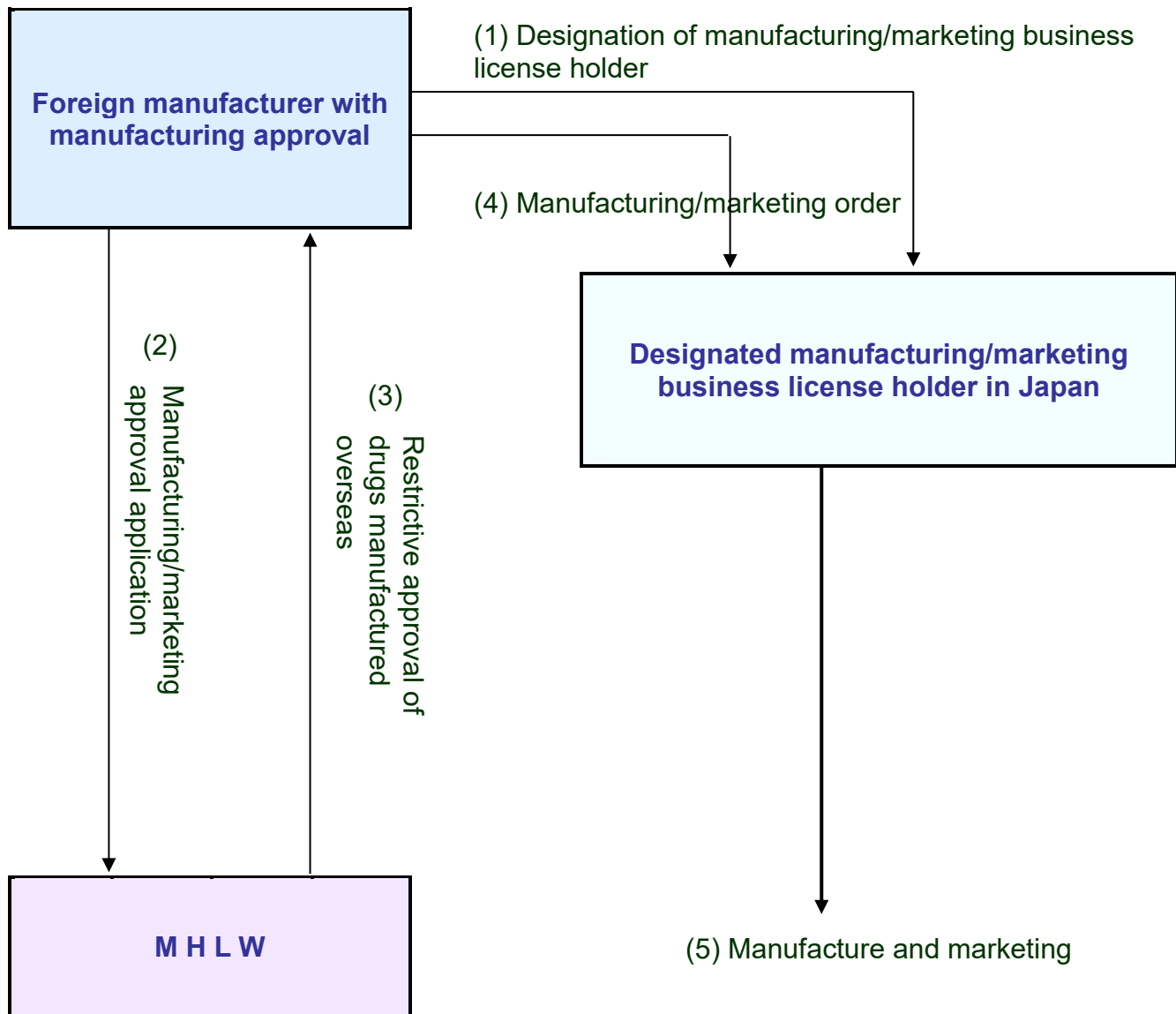
The Standards for Biological Materials were partially revised by Notice No. 375 of the MHLW in September 2014, the countries which were evaluated as having negligible risks according to the BSE risk status of the Office International des Epizooties (OIE) were added to the list of countries of origin of raw materials originating from cows and other ruminants that can be used as raw materials.



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



**Fig. 5 Flowchart of Approval Review**



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

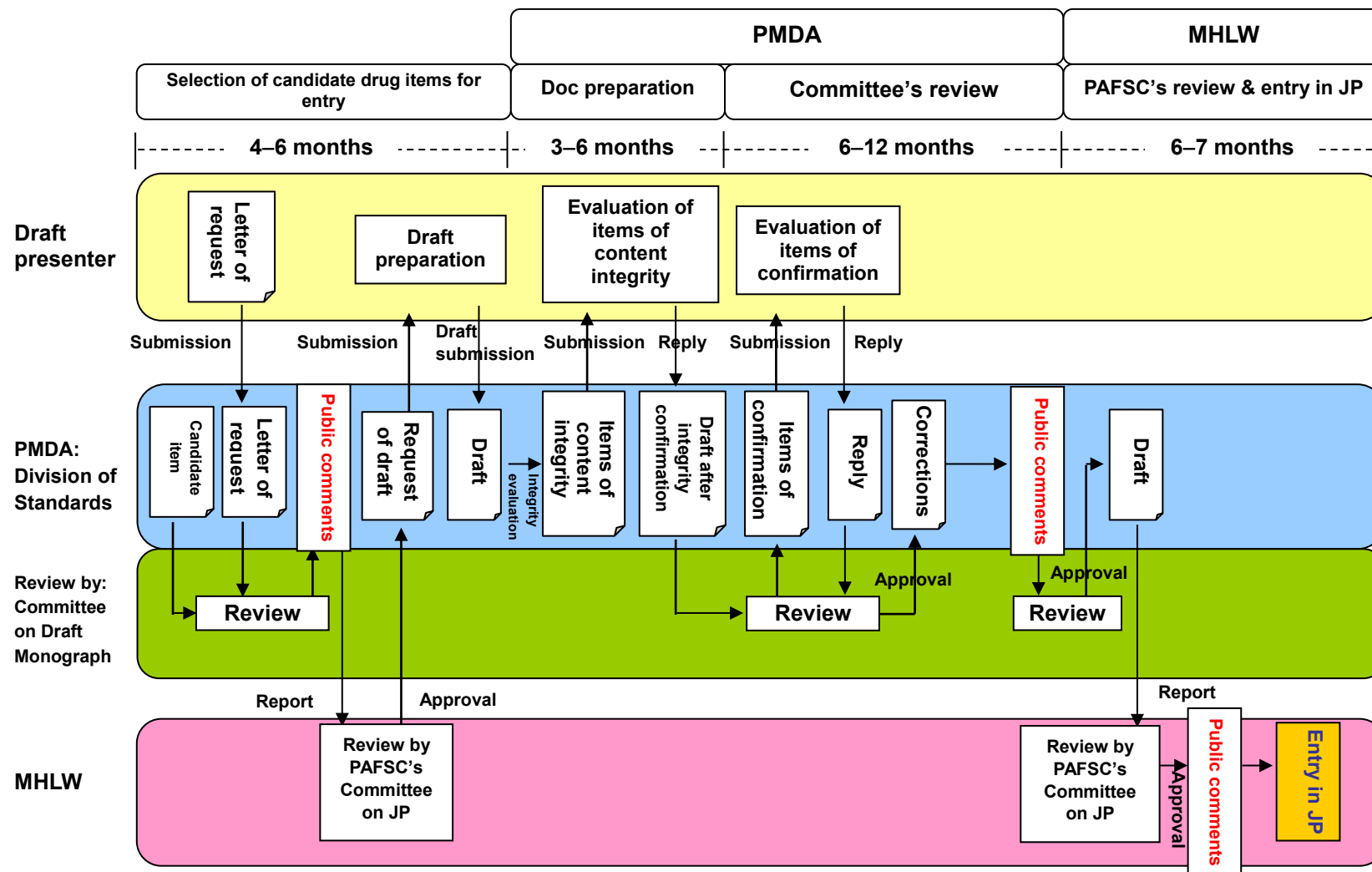


Fig. 7 Flowchart of Drug Listing in Japanese Pharmacopoeia

**Table 1 List of Main Controlled Substances**

Category	Topics
Poisonous and deleterious substances	Poisonous and deleterious substances are designated by the MHLW as drugs which cause or might cause damage to the functions of humans or animals when injected and absorbed or applied externally to humans or animals because the effective dose is close to the lethal dose, cumulative effects are potent or the pharmacological effects are intense.
Prescription drugs	Prescription drugs are designated by the MHLW as drugs which may be sold or supplied only under the prescription of a physician, dentist or veterinarian.
Habit-forming drugs	Habit-forming drugs are drugs designated by the MHLW as habit-forming.
Drugs for designated diseases	Drugs for designated diseases are drugs intended for the treatment of cancer and other diseases designated by cabinet order, which might cause damage to patients unless used under the guidance of a physician or dentist.
Narcotics	Narcotics are drugs designated by the MHLW as drugs which affect psychological function by their effects on the central nervous system, are habit forming and can cause severe damage when abused. The narcotics specified in the Narcotics and Psychotropics Control Law include morphine, codeine, pethidine and cocaine.
Psychotropics	Psychotropics are drugs designated by the MHLW, as drugs which affect psychological function by their effects on the central nervous system, are habit forming and cause less severe damage than narcotics or stimulants when abused. The psychotropics specified in the Narcotics and Psychotropics Control Law include hypnotics such as barbital, anxiolytics such as diazepam, and analgesics such as pentazocine.
Opium	Opium and powdered opium obtained by concentration and processing of the liquid extract from the opium poppy. Opium and powdered opium processed as drugs are not controlled by the Opium Law but regulated as narcotics under the narcotics and psychotropics classification.
Stimulants	Stimulants are drugs specified as drugs which are habit-forming, can cause severe damage when abused and have potent stimulant effects. The stimulants specified in the Stimulants Control Law include phenylaminopropanes (amphetamines), phenylmethylaminopropanes (methamphetamines), their salts and products containing any of them.
Raw materials for stimulants	Raw materials for stimulants are specified in the Attached Table of the Stimulants Control Law” and “Government Ordinance on Specifications of Raw Materials for Stimulants.”

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

Division	Certification Item
Pharmaceutical Evaluation Division	<ol style="list-style-type: none"> <li>1. Items related to business licenses for manufacturing of drugs, quasi-drugs, etc.</li> <li>2. Items related to manufacturing/marketing approvals (notification) for drugs, quasi-drugs, etc.</li> <li>3. Items related to attached documentation for new drug manufacturing/marketing approval applications</li> <li>4. Items related to compliance of drugs with GLP Ordinance (Standards for Conduct of Nonclinical Studies on the Safety of Drugs)</li> <li>5. Items related to certification of pharmaceutical products (drugs)</li> <li>6. Items related to statements of approval and licensing status of pharmaceutical products</li> <li>7. Items related to clinical trial protocol notifications for drugs</li> </ol>
Medical Device Evaluation Division	<ol style="list-style-type: none"> <li>1. Items related to business registrations for manufacturing of medical devices</li> <li>2. Items related to manufacturing/marketing approvals (notification) for medical devices</li> <li>3. Items related to business registrations and licenses for manufacturing of extracorporeal diagnostic medicines and regenerative medicine products</li> <li>4. Items related to manufacturing/marketing approvals (certification/notification) for extracorporeal diagnostic medicines and regenerative medicine products</li> <li>5. Items related to attached documentation for manufacturing/marketing approval applications for regenerative medicine products</li> <li>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)</li> <li>7. Items related to certification of pharmaceutical products (extracorporeal diagnostic medicines and regenerative medicine products)</li> <li>8. Items related to statements of approval and licensing status of pharmaceutical products (extracorporeal diagnostic medicines and regenerative medicine products)</li> </ol>
Pharmaceutical Safety Division	<ol style="list-style-type: none"> <li>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.)</li> </ol>
Compliance and Narcotics Division	<ol style="list-style-type: none"> <li>1. Items related to compliance of drugs and quasi-drugs with GMP requirements (except for items related to certification of pharmaceutical products)</li> <li>2. Items related to compliance with requirements of Ministerial Ordinance on QMS for Medical Devices and In Vitro Diagnostics</li> <li>3. Items related to compliance with requirements of Ministerial Ordinance on GCTP for Regenerative Medicine Products</li> <li>4. Items related to compliance of drug manufacturing plants with GMP requirements for investigational products</li> </ol>

## CHAPTER 3

# DRUG DEVELOPMENT

### 1. PROCESS FROM DEVELOPMENT TO APPROVAL

The provisions of Article 14 of the “Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices” (Law No. 145, 1960; hereinafter referred to as the Law) after revision according to the Law for Partial Amendment of the Pharmaceutical Affairs Law (Law No. 84, 2013) stipulate that, when a person with an intention to manufacture and market a drug has filed an application for approval of the manufacture and marketing of the drug, designated reviews should be conducted for the drug to be applied regarding the components/contents, dosage and administration, and indications of, and adverse reactions, etc., and the Minister of Health, Labour and Welfare shall give an approval for each product. When an application for approval is filed, evidence sufficient for proving the quality, efficacy, and safety of the application-related drug need to be presented using the documents with ethical and scientific validity and reliability on the basis of the medical and pharmaceutical academic standards at that time point (PFSB Notification No. 1121-(2) dated November 21, 2014).

When an application for approval of a drug is filed, the data of the results of clinical trials and other data must be attached (Article 14, Paragraph 3 of the Law).

This section explains the outline of the matters related to the drug development including procedures for clinical trials, interview advice meetings and approval review

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.

### 1.1 Development of New Drugs

It is important to collect evidence sufficient for proving the quality, efficacy and safety 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 Pharmaceutical and Medical Device Act 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 MHLW Ordinance No. 9 dated January 22, 2016; 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 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) 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 (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 (Notifications No. 0531-(8) of the Evaluation and

Licensing Division of PFSA 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

In response to issuance of the guideline of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), "Assessment and Control Of DNA Reactive (mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (ICH-M7)," the protocol notifications submitted on January 15, 2016 or later have to include "Document on assessment and control of DNA reactive (mutagenic) impurities" as an attachment in addition to those of the above a. to e. (Notification No. 1110-(3) of the Evaluation and Licensing Division, PSEHB dated November 10, 2015, partially modified with Notification No. 0627-(1) of the Pharmaceutical Evaluation Division dated June 27, 2018).

When a protocol notification of a protein drug manufactured from established cell line is submitted for the first time, reference documents on the quality of the investigational product covering the following information have to be attached separately (Office Communication dated December 14, 2015).

- Manufacturing flow chart of the investigational product
- Whether the cell line is contaminated with infectious agents or not
- Whether conditioned culture medium before purification is contaminated with pathogens such as bacteria, mycoplasma and aberrant virus or not

- Conformity to the Standard for Biological Ingredients if a human or animal-derived raw material is used
- Virus safety of the investigational product if animal cells or biological raw material is used in its manufacture
- Removal states of impurities and transient specifications for safety-related test parameters under specification tests of the drug substance and drug product

Concerning the protocol notifications to be submitted on October 1, 2019 or later, attachment of the final reports of the nonclinical safety studies (toxicity study and safety pharmacology study) used as the rationale for creation of the investigators' brochure has become necessary for the protocols for the clinical trials using a drug that is administered to humans for the first time (Office Director's Notifications No. 0620003 and No. 0620004 of PMDA dated June 20, 2019).(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. 0531-(8) of the Evaluation and Licensing Division, PFSB dated May 31, 2013).

In view of an 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).

When the plan of a trial of a product deemed as a combination product at the time of marketing is submitted, a phrase, "trial of a combination product," shall be stated on the space for remarks, and a plan of a clinical trial shall be submitted either as a drug, device, processed cells, etc. (Notification No. 1024-(2) of the Evaluation and Licensing Division, PFSB, Notification No. 1024-(1) of the Medical Devices Division, PFSB, Notification No. 1024-(9) of the Safety Division, PFSB, and Notification No. 1024-(15) of the Compliance and Narcotics Division, PFSB all dated October 24, 2014, revised by Notification No. 1122-(4) of the Pharmaceutical Evaluation Division, PSEHB, Notification of No. 1122-(10) of the Medical Device Evaluation Division, PSEHB, Notification No. 1122-(7) of the Safety Division,

PSEHB, and Notification No. 1122-(4) of the Compliance and Narcotics Division of PSEHB dated November 22, 2016).

### 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 "Clinical Safety Data Management" (Notification No. 227 of the Evaluation and Licensing Division, PAB dated March 20, 1995; ICH-E2A).

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, PFBSB dated December 28, 2012: ICH E2F)

Any manufacturer or marketing authorization holder who has submitted plan of a trial of a product deemed as a combination product at a market shall be obligated to report any malfunction of a part of device or equipment in the combination product as specified for malfunction reports of medical devices

(Notification No. 1024-(2) of the Evaluation and Licensing Division, PFBSB, Notification No. 1024-(1) of the Medical Devices Division, PFBSB, Notification No. 1024-(9) of the Safety Division, PFBSB, and Notification No. 1024-(15) of the Compliance and Narcotics Division, PFBSB all dated October 24, 2014, revised by Notification No. 1122-(4) of the Pharmaceutical Evaluation Division, PSEHB, Notification of No. 1122-(10) of the Medical Device Evaluation Division, PSEHB, Notification No. 1122-(7) of the Safety Division, PSEHB, and Notification No. 1122-(4) of the Compliance and Narcotics Division of PSEHB dated November 22, 2016).

#### 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 July 1, 2019). Main items of the interview advice meeting 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 homepages of the PMDA. <http://www.pmda.go.jp/review-services/f2f-pre/consultations/0007.html>

Preparatory consultation is also available to assure smooth interview advice.

##### (1) Clinical trial consultation

- Consultations on procedures
- Consultations before start of expanded trials

of drugs

- 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 plans of post-marketing clinical studies of drugs, etc.
- Consultation at completion of post-marketing clinical studies of drugs, etc.
- Additional consultations on drugs
- Consultations on plans to use drug registry

## **(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 for priority review and conditional accelerated approval for new drugs**

In consultations on eligibility for priority review, eligibility for priority review is evaluated and a report is prepared for new drugs other than the drugs covered by the SAKIGAKE designation system or orphan drugs for which the applicant desires priority review before application for approval. In consultations on eligibility for conditional

accelerated approval, eligibility for conditional accelerated approval is evaluated and a report is prepared for new drugs for which the applicant desires conditional accelerated approval before application for approval.

Procedures for handling priority review are available in Notification No. 0122-(12) of the Evaluation and Licensing Division, PSEHB and Notification No. 0122-(2) of the Medical Device Evaluation Division, PSEHB dated January 22, 2016.

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)
- Consultations on the applicability of conditional accelerated approval status
- Consultations on the applicability of conditional accelerated approval 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 epidemiological surveys**

- Consultations on the procedure of epidemiological surveys of drugs
- Consultations on the plan of epidemiological surveys of drugs
- Additional consultation on epidemiological surveys of drugs

## **(6) Consultations for preliminary confirmation of the revision of package inserts and**

**consultations on the revision of package inserts**

**(7) Consultations on the use of drug registries**

**(8) Consultations on surveys of reliability of drug registries**

**(9) Consultations on generic drugs**

- Consultations on bioequivalence of generic drugs
- Consultations on quality of generic drugs

**(10) 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

**(11) Consultations on GCP/GLP/GPSP of a drug**

**(12) 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
- Quasi drugs
- Drugs for controlling harmful insects and animals
- New drugs
- GCP/GLP/GPSP inspection of a drug
- GMP/QMS inspection
- GCTP inspection
- Simple consultation for preliminary confirmation of drug change notification
- Simple consultation for preliminary confirmation of generic drug change notification

**(13) Post-interview consultations on drugs**

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.

**(14) 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.

**(15) Consultations on compliance review 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”.

**(16) Consultations on compliance review for drug reexamination**

Guidance and advice are provided to the applicant concerning compliance of the following documents with the reliability standards: applicable documents are planned to be attached in the application for drug reexamination and are related to the previously completed post-marketing clinical study, drug use-results survey or special drug use-results survey.

**(17) Consultations on compliance review for data used as the rationale for revision of package inserts of drugs**

Guidance and advice are provided to the applicant concerning reliability of the documents regarding clinical trials used as the rationale for revision of package inserts of drugs according to the reliability standards.

**(18) Regulatory science general consultations / Regulatory science strategy consultations (former 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 R&D period from the final stage of lead compound or candidate medical device selection mainly until the early phase of clinical development [Phase IIa]). Preparatory consultations and main consultations are held as "regulatory science strategy consultations," and individual consultations are held as "regulatory science general consultations." In addition, guidance and advice for quality and safety may be provided from an early development phase 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.

**(19) Consultations on SAKIGAKE comprehensive assessment**

Consultations on drugs covered by the SAKIGAKE Designation System (prior data assessment of planned application documents on the following fields to organize issues and tasks to be addressed before the review)

- Quality data
- Non-clinical data
- Clinical data
- Reliability
- GMP/GCTP/QMS

**(20) Consultations on electronic data submission for application**

Consultations to investigate the details for specific products before application and to ensure smooth preparation of approval application and subsequent review with respect to the matters associated with submission of electronic data for application for approval of new drugs (including biosimilar products) for which attachment of electronic data to the approval application is anticipated. They can be classified into the

following categories.

- Consultations for confirming submission of electronic data for pharmaceutical application
- Consultations on the procedure of submission of electronic data for pharmaceutical application
- Consultations for exemption of submission of electronic data for pharmaceutical application

**(21) Preparatory consultation on minor change notification of drugs**

Consultation on issues that generally require prior data assessment for appropriateness of items to be included in a minor change notification

**(22) Consultations for preliminary confirmation of changes and management of generic drugs**

Consultations to give guidance and advice on appropriateness of the policies for preliminary evaluation of changes and sufficiency, etc. of the materials related to management of prior changes and completion of approval documents concerning generic drugs except for biological products for which application for approval of partial changes will be submitted in the future

**(23) Consultation on the system for changing approved matters using PACMP for drugs**

Consultation will be held when an applicant desires to use the system for changing approved matters using the Post-Approval Change Management Protocol (PACMP) based on the notification entitled "Handling, etc. of Changes in Approved Matters Related to Drug Quality," (Notification No. 0309-(1) of the Pharmaceutical Evaluation Division and Notification No. 0309-(1) of the Compliance and Narcotics Division, PSEHB dated March 9, 2018).

- Pharmaceutical PACMP quality consultation
- Generic drug PACMP quality consultation
- PACMP GMP consultation

**(24) Consultations related to Cartagena Protocol (Interview advice/preparatory consultation)**

Consultations confined to the matters for which application, etc. is anticipated and for which the Minister of Health, Labour and Welfare serves as the competent minister.

- Consultations before preliminary reviews of the application for approval of Type 1 Use regulations
- Consultations before preliminary reviews of the application for verification of containment measures in Type 2 Use, etc.
- Consultations related to Cartagena Protocol

Preparatory consultations are conducted to organize consultation items in advance to smoothly conduct interview advice. The records will be prepared for a fee if requested by the applicant.

## 1.5 Approval review

The documents to be attached at the time of application are designated for each application category (PFSB Notification No. 1121-(2) entitled "Approval Applications for Drugs" dated November 21, 2014). See the "Points to Consider for Approval Application Data for New Drugs" (Notification No. 1121-(12) of the Evaluation and Licensing Division of PFSB dated November 21, 2014), etc. for the matters to be kept in mind in preparation of the documents. Related notifications are available on the PMDA homepages.

Japanese HP: <http://www.pmda.go.jp/review-services/drug-reviews/about-reviews/otc/0001.html>

The recommended standard format for the quality and clinical safety information on CTD is presented by PMDA (Office Communication entitled "Format for Preparing the Common Technical Document for Submission of New Drug Applications to Reduce Total Review Time" dated January 17, 2011).

PMDA is mainly in charge of the activities related to an approval review of a new drug. Once the application form is received by PMDA, a detailed team review is performed by the review staff.

Moreover, compliance review (certification from source data) and GCP on-site inspection are conducted to confirm the reliability of application data (Refer to Section 4.2: Marketing Approval Reviews of Chapter 2). As the points to consider in the review of new drugs, 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 homepages:

Japanese HP:

<http://www.pmda.go.jp/files/000157674.pdf>

English HP:

<http://www.pmda.go.jp/files/000153830.pdf>

After the review by PMDA is completed, the application is then discussed (reported) 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.

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

<http://www.pmda.go.jp/review-services/drug-reviews/user-fees/0001.html>

The timeline after application for approval of a new drug is shown in the notice "Timeline for Completing the New Drug Application Review under the Standard Process" (Office Communication dated January 30, 2015) (See **Fig. 9** Timeline of the standard process of new drug approval (ordinary review products) and **Fig. 10** Timeline of the standard process of new drug approval (priority review products)).

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.

For the purpose of improving predictability of approvals, "Handling of approval application for increased predictability of approval of new drugs and concept on total review period" (Notification No.

1006-(1) of the Evaluation and Licensing Division, PFSSB and Notification No. 1006-(1) of the Compliance and Narcotics Division, PFSSB both dated October 6, 2014) requires that PMDA holds a preparatory meeting with a potential applicant. The procedure is described in "Implementation Guidelines for Preparatory Consultations Expecting New Drug Approval Review" (Notification No. 1006001 of the PMDA dated October 6, 2014).

## 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. Subsequently, in association with the start of submission of electronic data from October 1, 2016 on the basis of the "Notification on Practical Operations of Electronic Study Data Submissions" (Notification No. 0427-(1) of the Evaluation and Licensing Division of PFSSB dated April 27, 2015),

"Pharmaceuticals and Medical Devices Agency: Procedures for Implementation of Document-based Assessment and GCP On-site Inspection for Drug Application" (PMDA Notification No. 0511005 dated May 11, 2016) was revised.

- **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 revision No. 1121-(5) dated November 21, 2014 of the Evaluation and Licensing Division, PFBS) 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").

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 27, 2013).

- **On-site reviews**

In these reviews, the PMDA review staff examines the data at the sites where it was collected or compiled. The guideline for on-site GCP compliance reviews is 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, PFBS dated January 31, 2006, revised by Notification No. 1121-(1) of the Evaluation and Licensing Division, PFBS dated November 21, 2014).

The reviews are generally performed in the applicant's offices and facilities and medical institutions performing the clinical study (approximately four facilities as a rule for ordinary review products; approximately two facilities for priority review products). 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.

Checklists and management sheets for paper reviews and on-site reviews are available at the following PMDA homepage as a reference for self-inspections. On March 1, 2017, the "GCP Management Sheet" to be used by companies for document-based inspection and GCP on-site inspection was officially published by PMDA. The companies that wish to use it should submit it to PMDA as the document to be used immediately before the inspection.

<http://www.pmda.go.jp/review-services/inspections/gcp/0002.html#r=s&r=s>

## 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 (prefectural governor for non-prescription drugs for which approval standards are established) 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

When an application is submitted for a new drug manufacturing and marketing approval, the plant will be evaluated by the authorities to determine if it actually complies with the GMP standards. ("Establishment/abolishment of the Ministerial Ordinances and Notices on Good Manufacturing Practice and Quality Management System (GMP/QMS) of drugs and medical devices, etc. in association with enforcement of the Law for partial amendment of the Pharmaceutical Affairs Law and the Blood Collection and Donation Service Control Law" Notification No. 0330001 of the Compliance and Narcotics Division, PFSB dated March 30, 2005.)

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

#### 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, evaluation is conducted 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: The number of 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 evaluations 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 agreement of drug GMP (MRAs) with the EU countries was firstly concluded in May 2003, and in April 2016, Japan-Europe MRA became applicable to all the 28 EU countries (Notification No. 0426-(3) of the Compliance and Narcotics Division of PSEHB dated April 26, 2016). In July 2018, the scope of the drugs to be subjected to mutual approval was expanded to newly include drug substances and aseptic preparations for chemical pharmaceuticals, and to newly include drug substances and aseptic products (such as vaccines), other than the products for which equivalence of GMP to be applied has not been confirmed, for biological pharmaceuticals (Notification No. 0718-(1) of the Compliance and Narcotics Division of PSEHB dated July 18, 2018).

Positive utilization of the internationally recognized GMP rules contained in Pharmaceutical Inspection Cooperation Scheme was recommended 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. ("Concepts of Utilization of GMP Guidelines of PIC/S," Office Communication dated February 1, 2012, partially revised on August 9, 2017).

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 regulations for 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. Major regulations including the matters to be agreed upon with the manufacturer in foreign country by the importer, the fact that the importer must confirm that the drug to be imported is manufactured under appropriate manufacturing control and quality control, and that the reception and shipping, storage and testing of the products must be conducted in accordance with standards, etc. are taken over in "Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs" (MHLW Ordinance No. 179 dated December 24, 2004).

In addition, 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.

From April 1, 2005, a manufacturer/marketing authorization holder or manufacturer had to submit an import certificate before custom clearance when importing drugs as business, but this regulation was abolished in December 2015. No import certificate is currently required. Instead, from January 2016,

the custom clearance procedure requires presentation of business license and marketing approval certificate of a product to be imported.

## 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 revision: Notification No. 0525003 of the Evaluation and Licensing Division, PFSB dated May 25, 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 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 on companion diagnostics and associated drugs; and PFSB Notification No. 0612-(6) 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 ; Notification No. 1020002 of the Evaluation and Licensing Division, PFSB dated October 20, 2008 for partial amendment on non-prescription drugs;

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. 0705-(4) of the Pharmaceutical Evaluation Division of PSEHB dated July 5, 2017) 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. In the notification of partial revision dated February 2, 2017, the procedure to describe "Benefits and Risks Conclusions" was completely reconsidered.

For electronic specifications of the CTD (eCTD), "Electronic Specifications of the Common Technical Document" (Notification No. 0604001 of the PFSB dated June 4, 2003, partially revised by Notification No. 0707-(3) of the Evaluation and Licensing Division, PFSB dated July 7, 2009). Version 3.2.2 was enforced from October 1, 2009. Handling of submissions of electronic data is shown in the Handling of Electronic Specifications for Common Technical Documents (Notification No. 0527004 of the Evaluation and Licensing Division, PFSB dated May 27, 2004, partially revised by Notification No. 0824-(3) of the Pharmaceutical Evaluation Division, PSEHB dated August 24, 2016).

On July 5, 2017, "Approval Applications using Electronic Common Technical Documents (eCTD)" (Notification No. 0705-(1) of the Pharmaceutical Evaluation Division of PSEHB) and Q&As (Office Communications) was issued and mentioned the partial revisions on preparation of eCTD according to eCTD Version 4.0 ICH agreement. The date of application of this partial revisions will be separately notified.

It was decided that, with the start of submission of electronic clinical study data from October 1, 2016, data attached to approval applications will, as a general rule, be in eCTD format. (The period until March 31, 2020 will be the transitional measure period.)

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), its partial revision (Notification No. 0124-(1) of the Pharmaceutical Evaluation Division, PSEHB dated January 24, 2019), and its Q&A (Office Communication dated January 24, 2019) were issued. Moreover, "Notification on Practical Operations of Electronic Study Data Submissions" (Notification No. 0427-(1) of the Evaluation and Licensing Division of PFSB dated April 27, 2015), its partial revision (Notification No. 0124-(4) of the Pharmaceutical Evaluation Division, PSEHB dated January 24, 2019), and the Q&As (Office Communication dated January 24, 2019) were issued, and the range of submission of electronic data is explained by these notifications and Q&A, etc. Furthermore, submission of electronic data through gateway was started on October 1, 2016. Applicable clinical trial data should be submitted in the formats according to the specifications in Clinical Data Interchange Standards Consortium.

Concerning submission of electronic data, the period of transitional measures for submission of electronic data for application will end in March 31, 2020, and it will become necessary to submit electronic data for all studies and analyses in the designated scope for submission from April 1, 2020.

In principle, the items for which submission of electronic data become necessary are the prescription drugs listed in the Notification by the Director-General ((1) to (7), (9), and (9-2) in Attached Table 2-(1) of Application for Approval of Drugs, PFSB Notification 1121-(2) dated November 21, 2014).

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

- (1) Application documentation table of contents (including Module 1)
  - (i) Table of contents of application document including Part 1

- (ii) Synopsis
- (2) Approval application (copy)
- (3) Certificates (Declarations of those responsible for collection and compilation of data for approval applications, GLP and GCP related data, contracts for codevelopment [copies], etc., 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) Risk management plan (RMP) (draft):
- (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)]  
Laboratory target and set values to be entered in the manufacturing method column of the application form for drugs other than biological products should be tabulated and the list be attached to the application

document as directed in “CTD Format for Reducing Total Review Time for New Drugs” (Office Communication of the Evaluation and Licensing Division, PFSB dated January 17, 2011).

Review data on new additives, if any, should be included in the application dossier (copies) as directed in the “Submission of Review Data on New Additives” (Notice of the PMDA dated June 23, 2017).

<5> Points to consider in formatting the eCTD

## 2) Module 2: Data summaries or CTD “Gaiyo”

- (1) Modules 2 to 5 (CTD) table of contents
- (2) CTD introduction
- (3) Quality overall summary
- (4) Nonclinical overview
- (5) Clinical overview
- (6) Nonclinical summary (text and tables)
  - <1> Pharmacology
  - <2> Pharmacokinetics
  - <3> Toxicity
- (7) Clinical summary
  - <1> Summary of biopharmaceutics and associated analytical methods
  - <2> Summary of human pharmacology
  - <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
- (See **Fig. 11** Organization of ICH Common Technical Documents).

Separately from CTD, submission of the following documents is required at the time of application for approval.

- FD application document (sample), document of FD contents
- Marketing license (copy)
- Application for examination for drug approval review
- Import contract or equivalent document
- MF registration certificate (copy) if MF is used
- Contract with MF registrant regarding the use of MF (copy)
- List of persons involved in compilation of attached data
- List of competitive products and companies
- List of persons involved in competitive products

It is necessary to submit a "list of persons involved in compilation of attached data," a "list of competitive products and companies," and a "list of persons involved in competitive products" immediately after application submission, prior to the expert meeting, and prior to meeting of the Committee on Drugs.

It was decided that the applicant should submit the conversion factor, etc. for calculating the maximum daily use of drug additives during the process of application for marketing approval (including application for a change) in order to enable appropriate management of the maximum daily use of drug additives by the regulatory authority. (Notification No. 1007001 of the Office of Review Management, PMDA dated October 7,

2016, partially revised by Notification No. 0927001 of the Office of Review Management, PMDA dated September 27, 2017).

## 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). The application dossier is 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.

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, MHLW 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.

As globalization of drug development progresses and numerous global joint clinical trials have come to be planned and conducted, "General Principles for Planning and Design of Multi-

Regional Clinical Trials" (Notification No. 0612-(1) of the Pharmaceutical Evaluation Division, PSEHB dated June 12, 2018: ICH-E17) was notified. This notification shows the general principles for planning and design of global joint clinical trials to make global joint clinical trials more acceptable in various regions in the world.

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 Quality and 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 guidelines shown in Table 6 have been revised or established concerning physicochemical properties, specifications, and tests methods.

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

Concepts concerning simplification of stability tests on a scientific basis have also been specified in Application of Bracketing and Matrixing Methods in Stability Tests on Drug Substances and Drug Products (ICH Q1D) (Notification No. 0731004 of the Evaluation and Licensing Division, 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 guidelines shown in Table 7 have been revised or established, and the Guidelines for Toxicity Studies of Drugs have been replaced by these guidelines.

Data on the following studies that are required for the review and evaluation of a new drug application by the Ministry **should be prepared and submitted in accordance with the above guidelines (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) has been issued. For infection prophylactic vaccines, the guideline “Nonclinical safety evaluation of prophylactic vaccines (Notification No. 0527-(1) of the Evaluation and Licensing Division, PFSB dated May 27, 2010) has been issued, and for anti-malignant tumor agents, the guideline

“Nonclinical safety evaluation of anti-malignant tumor agents (Notification No. 0604-(1) of the Evaluation and Licensing Division, PFSB dated June 4, 2010) and its Q&As (Office Communication dated March 27, 2019) have been issued.

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

All toxicity tests conducted to support applications for new drug manufacturing and marketing approval and reexamination must be in accordance with the Good Laboratory Practice Standards for Safety Studies on Drugs (GLP). (MHW Ordinance No. 21 dated March 26, 1997, partially revised by MHLW Ordinance No. 114 dated June 13, 2008) (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.). Handling of the ministerial ordinance for partial revision is noticed in “Guidance on the Implementation of the Ministerial Ordinance on the Good Laboratory Practice for Nonclinical Safety Studies of Drugs as Revised by the Ministerial Ordinance for Partial Revision of the Ministerial Ordinance on the Good Laboratory Practice” (PFSB Notification No. 0613007 dated June 13, 2008).

This ordinance consists of eight chapters and 19 articles as 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

Study facilities in which studies have been conducted under the GLP ordinance (GLP-compliant studies) must be inspected for compliance with the GLP ordinance by PMDA under contract with MHLW for approval review in principle (item review). However, this inspection can be omitted if the trial is conducted at a GLP-compliant facility according to the following survey of GLP compliance by facilities conducted by PMDA (facility review).

This facility review is conducted on the basis of “the System of Guidelines for On-site Reviews Based on the Pharmaceutical GLP and Medical Device GLP” (Notification No. 0620058 of PMDA dated June 20, 2008, Notification No. 0815007 of PMDA dated August 15, 2008, and Notification No. 1121005 of PMDA 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 this review, the results of the tests performed in the facility will be accepted, in principle, for use as review data if the trial is started and completed within 3 years after the date of issuance 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) issued by the Councillor, PFSB dated November 21, 2014).

## 5) Guidelines for general pharmacological studies

The results of primary pharmacodynamics studies, secondary pharmacology studies, safety pharmacology studies, and studies of drug interactions may be required if necessary.

The guidelines shown in Table 8 have been issued on pharmacology 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 preparing data related to pharmacodynamic drug interactions, 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”.

## **6) Guidelines for pharmacokinetic studies**

The guidelines shown in Table 9 have been issued on pharmacokinetic studies.

Pharmacokinetic data is useful in determining doses and other conditions for toxicity and pharmacological tests in animals. Moreover, the assessment and understanding of these data may provide very useful information for the assessment of efficacy and safety in humans. The Guidelines on Nonclinical Pharmacokinetic Studies (Notification No. 496 of the Evaluation and Licensing Division, PMSB dated June 26, 1998)

were issued requiring applicants to study the absorption, distribution, metabolism, and excretion of test drugs in animal and in vitro study systems to clarify their pharmacokinetic profile. The above guidelines have instructed the applicant to evaluate the distribution in a single-dose study in principle and to use the Guideline for Repeated Dose Tissue Distribution Studies (Notification No. 442 of the Evaluation and Licensing Division, PAB dated July 2, 1996; ICH S3B) for reference in terms of circumstances requiring repeated dose studies and actual conduct of the studies.

Concerning the points to consider in the population pharmacokinetic analysis and pharmacokinetic/pharmacodynamic analysis for evaluating clinical pharmacokinetics, the basic concept is presented in “Clinical Pharmacokinetic Studies on Drugs” (Notification No. 796 of the Evaluation and Licensing Division, PMSB dated June 1, 2001). Subsequently, “Guidelines for Population Pharmacokinetic/Pharmacodynamic Guidelines” (Notification No. 0515-(1) of the Pharmaceutical Evaluation Division, PSEHB dated May 15, 2019) was issued based on overseas guidelines and accumulated clinical trial data.

## **7) Guidelines for bioequivalence studies**

Although no guidelines are available for formulation changes during development, the guidelines shown in Table 10 may be applied where necessary, depending on timing and content of a change. In general, investigational drug products for late phase II clinical studies and subsequent ones are required to be equivalent to the commercial ones.

### **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. 9 dated January 22, 2016) was issued with the aims of specifying the requirements for the planning, conduct, monitoring, auditing, records, analysis, and reports of clinical studies performed to collect data to be submitted with applications for approval to manufacture and market drugs; to protect the human rights, safety, and welfare of study subjects; and to assure the scientific quality of the study and the reliability of its results.

The 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. 0219-(4) issued by the Evaluation and Licensing Division of PFSB dated February 19, 2010: ICH M3R(R2), and Office Communication (Q&A on the guidelines) dated August 16, 2012).

### (i) Safety studies

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

### (ii) Pharmacological studies

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

- (1) Pharmacological basis of principal effects (mechanism of action).
- (2) Dose-response or concentration-response relationships and duration of action.
- (3) Study of the potential clinical routes of administration.
- (4) Systemic general pharmacology, including pharmacological effects on major organ systems and physiological processes.
- (5) Absorption, distribution, metabolism, and excretion

## 2.2) Quality of investigational products

Products used in clinical studies should be well characterized, with information on bioavailability wherever feasible. The product should be appropriate for the stage of drug development.

Ideally, the preparation should be adequate to allow testing in a series of studies that examine a range of doses.

For investigational products, on July 9, 2008, the Investigational Product GMP was revised to allow the quality assurance of an investigational product according to the phase of a clinical trial in consideration of characteristics of the trial, including ones at an early exploratory stage (Notification No. 0709002 of PFSB). Subsequently, the Q&A on the Investigational Product GMP was released (Office Communication of Compliance and Narcotics Division, PFSB dated July 2, 2009).

## 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 close but variable correlations between the development phase and study type are shown in [Fig. 12](#) Correlation between Development Phases and Types 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, and partially revised in Notification No. 1225-(1) of the Pharmaceutical Evaluation Division, PSEHB dated December 25, 2019).

**(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 studies conducted in the phase IV include all studies conducted after drug approval (except for routine post-marketing surveillance) pertaining to the approved indications. The studies in the phase IV must have appropriate scientific objectives. The studies conducted commonly include additional drug interaction studies, dose-response studies, safety studies, and the studies for supporting the use for the approved indications (such as studies to investigate mortality or prevalence and epidemiological studies).

**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.

Guidelines for clinical evaluation of drugs classified by therapeutic category, guidelines for clinical evaluation in general, and other guidelines have been issued as shown in Table 11.

### **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 (newest revision: MHLW Ordinance No. 9 dated January 22, 2016), 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. Furthermore, for smooth implementation of the clinical trials compliant with the GCP Ministerial Ordinance, the

“Ordinance on Standards for Conduct of Clinical Trials (GCP) (Notification No. 1228-(7) of the Evaluation and Licensing Division of PFSB dated December 28, 2012) was issued. Subsequently, since ICH-E6-(R2) was compiled, the GCP Guidance was revised based on the revision, etc. of the GCP Ordinance (Notification No. 0705-(3) of the Pharmaceutical Evaluation Division, PSEHB dated July 5, 2019). In association with them, “Basic Concept of Quality Management in Clinical Trials” (Notification No. 0705-(5) of the Pharmaceutical Evaluation Division, PSEHB dated July 5, 2019), “Basic Concept of Monitoring Based on Risks” (Notification No. 0705-(7) of the Pharmaceutical Evaluation Division, PSEHB dated July 5, 2019), and “Documents or Records Related to Clinical Trials” (Office Communication dated July 5, 2019) were issued.

A compassionate use system making unapproved drugs available for patients not eligible for ongoing trials of these drugs was introduced (Notification No. 0122-(7) of the Evaluation and Licensing Division, PSEHB dated January 22, 2016).

The system is established on the following premises: the applicable unapproved drugs are to be indicated for diseases for which no effective conventional treatment is available; they are clinically used in consideration of balance between the relevant risk and expected therapeutic benefit; and such use does not interfere with development of the concerned drug.

By this system, an investigational product after conduct of a trial at the final development phase in Japan (which is regularly intended to verify the efficacy and safety after the indications as well as dosage and administration have been set through a series of development operations, or called as a pivotal trial) or while such trial is ongoing (but after completion of the enrollment) is made available in a

framework of a trial in patients with the above diseases.

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

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, partially revised on August 1, 2019).

## 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. After that, the above notifications were reconsidered on the basis of marked advancement of gene recombinant technology, cell culture technology and other scientific technology as well as the knowledge of quality, safety and efficacy of biological products accumulated to date, and “Approval Application Category of Biotechnology Products and Procedure for Preparation of Attached Documents Necessary for Approval Application” (Notification No. 0705-(5) of the Pharmaceutical Evaluation Division, PSEHB dated July 5, 2017) was issued.

Various guidelines have been issued for biotechnology products on the basis of discussion at ICH ([Table 12](#)). 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 ([Table 3-xx](#)).

### 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 of the PMSB dated December 26, 2000). In addition, various notifications have been issued, manufacturers have been requested to undertake self-inspection and coordinate application documents, and safety measures have been specified. For ingredients of bovine origin in particular, notifications have been issued as required in accordance with worldwide risk conditions and measures to assure quality and safety have been strengthened (refer to “Safety Measures for Bovine Spongiform Encephalopathy [BSE]” in Section 6.4, Chapter 2). Biological products and specified biological products were newly defined in the revised Pharmaceutical Affairs Law dated July 31, 2002 and measures to assure safety when there is a risk of infection have been designated. The Standards for Biological Materials were specified in May 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 were designated (Notice No. 210 issued by the MHLW in 2003).

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 in addition to the above, the Standards for Biological Materials were partially amended (Notice No. 375, issued by MHLW in 2014).

### 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 (Office Communication dated July 21, 2009, Office Communication dated March 31, 2010, and Office Communication dated December 15, 2015). 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). 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 draft in the application dossier.

#### **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, PMSB dated November 11, 1999), and New Drug Approval Information Packages containing summary reviews prepared by the MHLW and nonclinical and clinical data submitted by the applicant have been published. Thereafter, the methods of submitting data for application were changed as specified in “Disclosure of Information Concerning Approval Reviews of New Drugs” (Notification No. 0529003 of the Evaluation and Licensing Division, PMDA dated May 29, 2002). Basic procedures for submission and disclosure have also been specified (Notification No. 0422001 of the Evaluating and Licensing Division, PFSB dated April 22, 2005, Notification No. 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 homepages:

Japanese:

<http://www.pmda.go.jp/PmdaSearch/iyakuSearch/>,

English (part of product items):

<http://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0001.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 JAPIC Clinical Trial Information (JapicCTI) (<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.

Moreover, a notification regarding the matters to be considered at the time of registration of the status of implementation of the clinical trial was issued, and registration of the trial-related information on the Japan Registry of Clinical Trials (JRCT), JapicCTI, and the Clinical Trials Registry of the Japan Medical Association is required after submission of a notification of the clinical trial plan.

(Notification No. 0326-(3) of the Pharmaceutical Evaluation Division, PSEHB dated March 26, 2018).

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 registered on the homepage of the Pharmaceuticals and Medical Devices Agency (PMDA) with the aim of establishing an environment to provide the trial personnel with easy access to the information regarding institutional review boards and making the information widely known to the public. (Notification No. 0515-(5) of the Evaluation and Licensing Division, PFSB dated May 15, 2013, partially revised by Notification No. 0331-(9) of the Pharmaceutical Evaluation Division, PSEHB dated March 31, 2017).

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

ICH was established in April 1990 by six parties, i.e., regulatory authorities and industry groups of Japan, the United States, and Europe, with the aim of promptly supplying safe and effective new drugs to the patients who need them. The ICH Steering Committee consists of six original parties of EU, EFPIA, MHLW, JPMA, FDA, PhRMA as well as Swissmedic and Health Canada. In addition, WHO and IFPMA participate as an observer and a member (without the vote), respectively. To discuss issues on an individual basis, expert working groups (EWGs) consisting of specialists and government officials from organizations were established. Furthermore, in an attempt to cope

with increasingly globalized drug development and regulations, organizational reform took place in October 2015, and a new ICH corporation was established as an international nonprofit corporation under the SWISS ACT to enhance further international harmonization of pharmaceutical affairs.

At present, it is made up of the general assembly which consists of all members and serves as the main body of the organization, the management committee responsible for preparation for discussion in the general assembly as well as for operation of the organization, and working groups in which specialists discuss the guidelines.

New ICH harmonization is conducted by the following five steps.

- Step 1: Selection and analysis of topics to be addressed, analysis of issues, establishment of EWGs, and preparation of draft ICH guidelines
- Step 2a: Consensus of regulatory authorities and industry groups regarding technical documents
- Step 2b: Consensus among regulatory authorities regarding 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 **Table 13** (ICH topics and guidelines - Progress of harmonization).

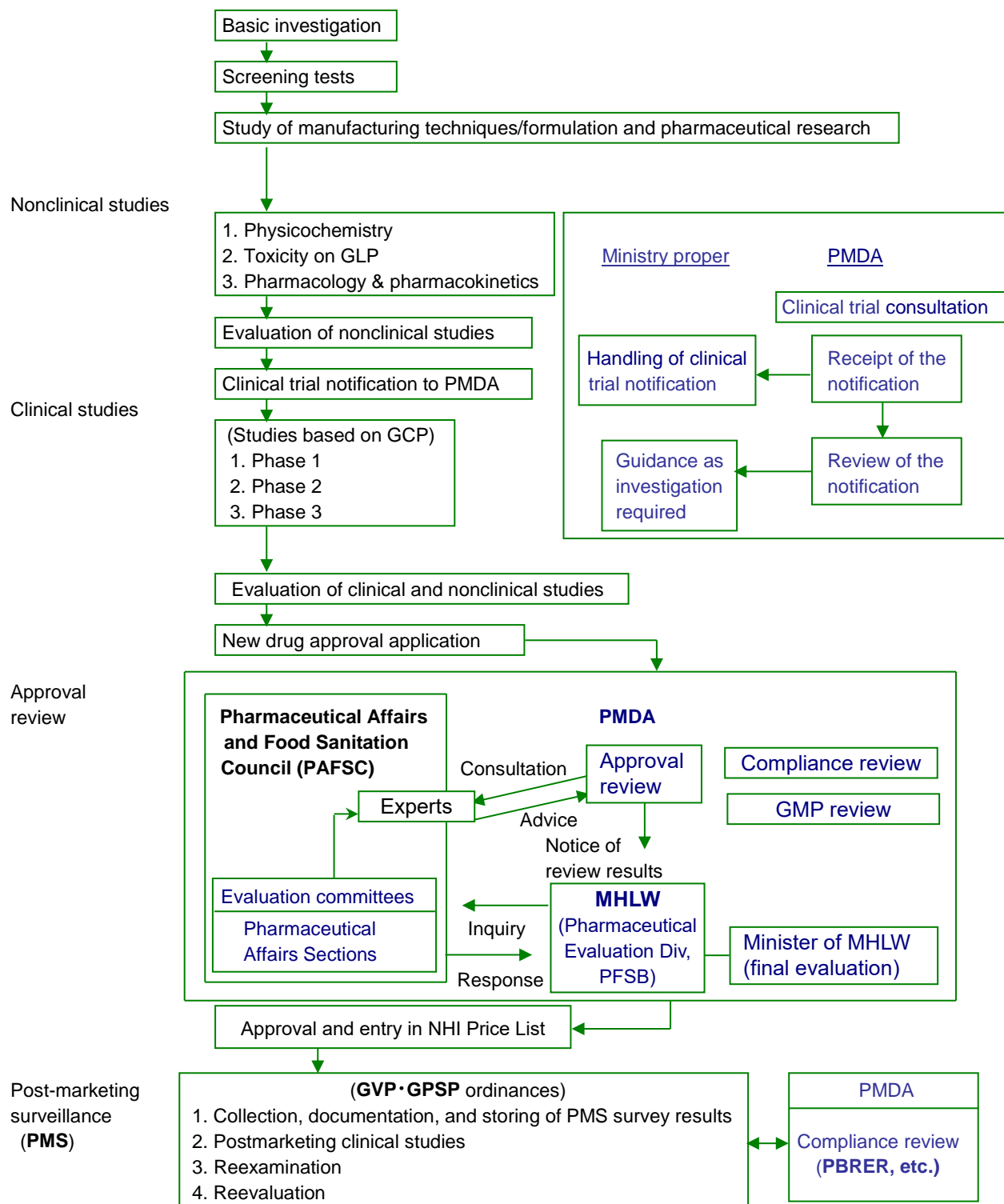
Visit the following homepage for details of ICH guidelines.

Japanese:

<https://www.pmda.go.jp/int-activities/int-harmony/ich/0014.html>

English:

<http://www.ich.org/home.html>

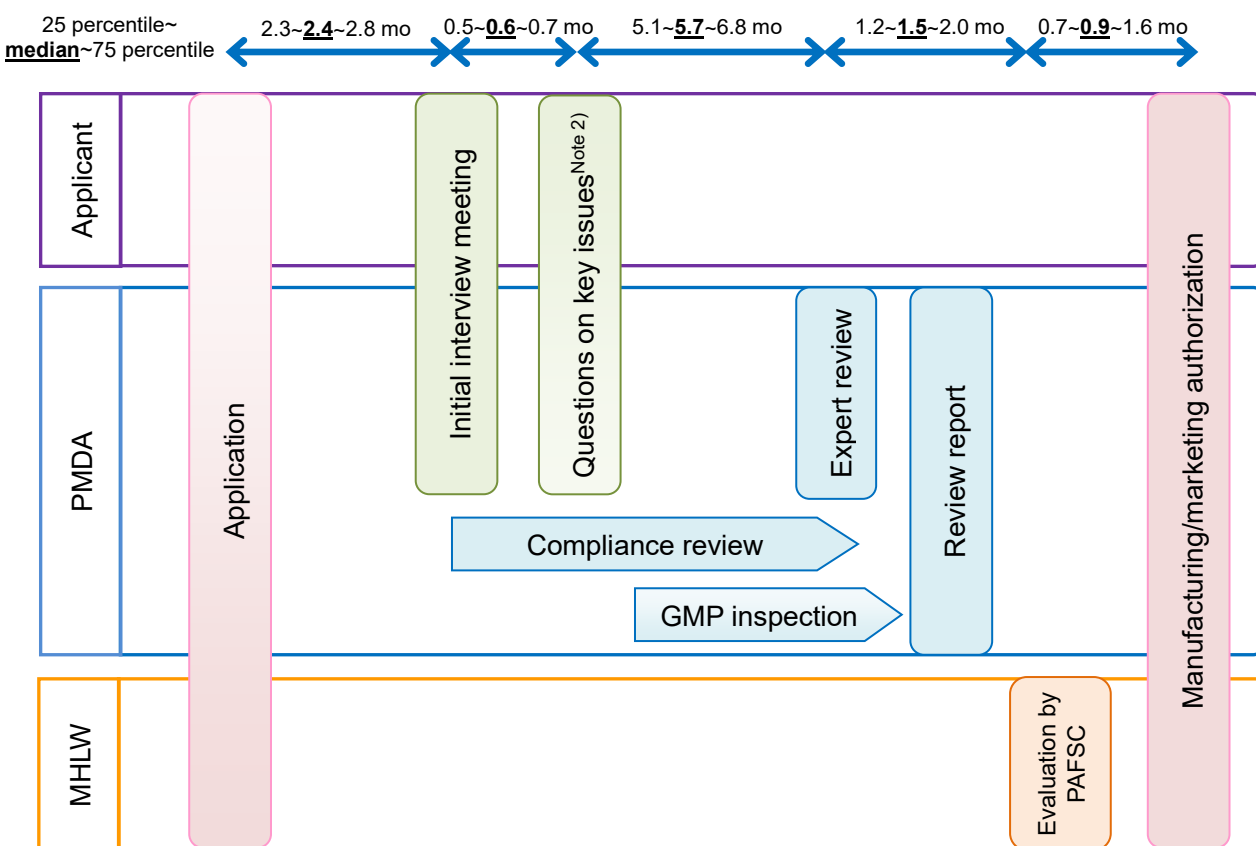


**Fig. 8 Flowchart of New Drug Development and Approval**

### Timeline of the standard process of new drug approval (ordinary review products)

The following timeline shows a rough indication of review time<sup>Note 1)</sup> for individual review process, according to the past records of approval reviews, to achieve the target total review time of 12 months (ordinary review products) 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.

Rough indication of review time



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.

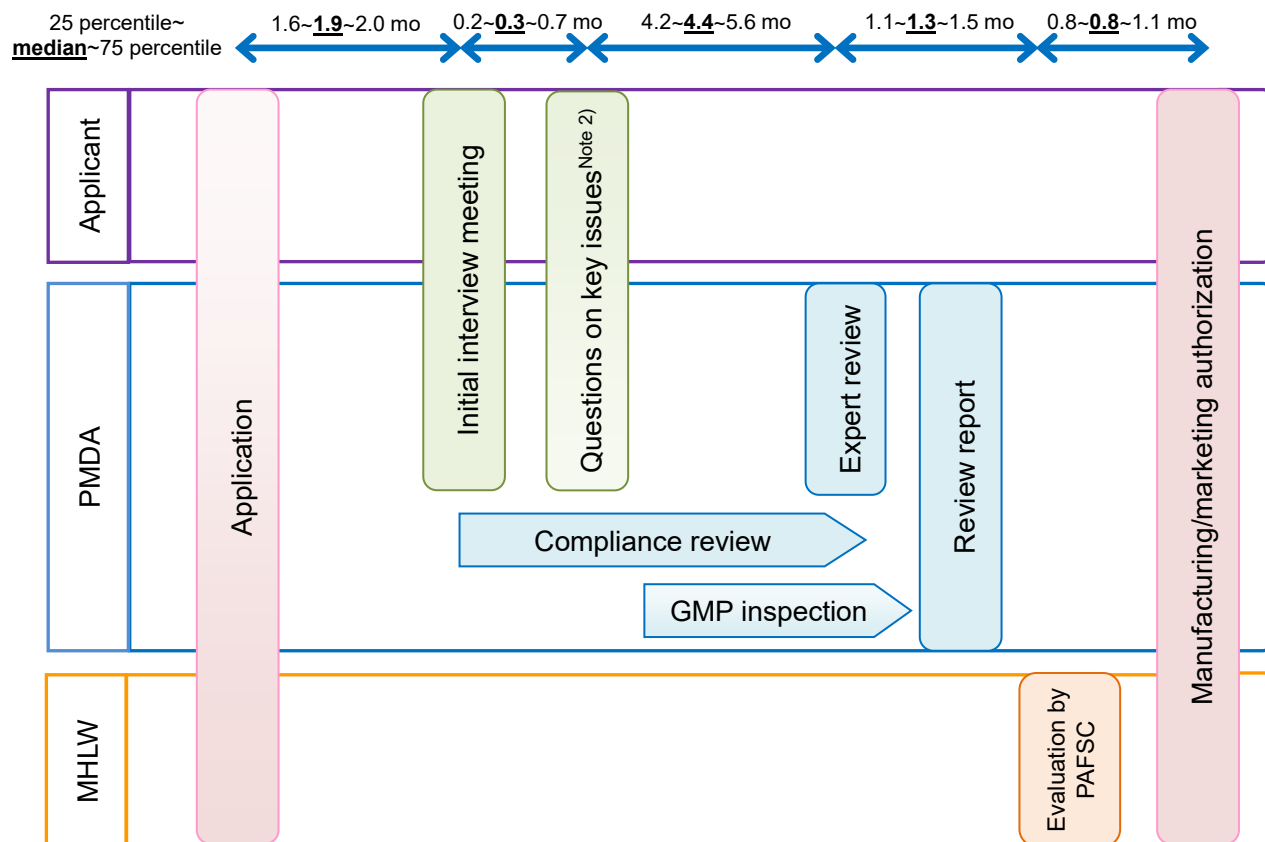
Note 2) Questions on key issues: First questions issued following the initial interview

**Fig. 9 Timeline of the standard process of new drug approval (ordinary review products)**

### Timeline of the standard process of new drug approval (priority review products)

The following timeline shows a rough indication of review time<sup>Note 1)</sup> for individual review process, according to the past records of approval reviews, to achieve the target total review time of 9 months (ordinary review products) 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.

Rough indication of review time



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: 12, Questions on key issues: 12, Expert review: 34, Evaluation by PAFSC: 30, Manufacturing/marketing authorization: 31.

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

**Fig. 10 Timeline of the standard process of new drug approval (priority review products)**

**Table 3 Data to be Submitted with an Application for Approval to Manufacture/Market: A New Prescription Drug**  
**(Attached Table 2-1 in PFSB Notification No. 1121-(2) dated November 21, 2014)**

Left Column	Right Column							
	A 1 2 3	B 1 2 3	C 1 2 3	D 1 2 3	E 1 2 3 4 5 6	F 1 2 3 4 5 6 7	G	H
(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 (during reexamination period)	○ ○ ○	× ○ ○	△ △ ○	× × ×	× × × × ○ ×	× × × × × × ×	×	○
(8-2) Prescription drugs with additional dosage forms (not during reexamination period)								
(9) Prescription combination drugs with similar formulations (during reexamination period)	○ ○ ○	× ○ ○	○ ○ ○	△ △ ×	× × × × × ×	○ △ × × × △ ×	○	○
(9-2) Prescription combination drugs with similar formulations (not during reexamination period)								
(10) Other prescription drugs (during reexamination period)								
(10-2) Other prescription drugs (Same with (10), changes in manufacturing method of biological products, etc.)	× × ×	× △ ○	× × ○	× × ×	× × × × ○ ×	× × × × × × ×	×	○ 1)
(10-3) Other prescription drugs (not during reexamination period)								
(10-4) Other prescription drugs (Same with (10-3), changes in manufacturing method of biological products, etc.)								

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

- 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 drugs not classified into any of the above (1) to (9). Changes of manufacturing method of biological products are classified into 10-2 or 10-4. Biological products refer to vaccines and blood products entered in the Biological Product Standards; recombinant DNA technological drugs, cell culture drugs and other biotechnological drugs or drugs derived from living organisms.

A	Origin or background of discovery, conditions of use in foreign countries	1. Origin or background of discovery 2. Conditions of use in foreign countries 3. Special characteristics, comparisons with other drugs, etc.
B	Manufacturing methods, standards and test methods	1. Chemical structure and physicochemical properties, etc. 2. Manufacturing methods 3. Standards and test methods
C	Stability	1. Long-term storage tests 2. Tests under severe conditions (stress tests) 3. Accelerated tests
D	Pharmacological action	1. Tests to support efficacy 2. Secondary pharmacology, Safety pharmacology 3. Other pharmacology
E	Absorption, distribution, metabolism, and excretion	1. Absorption 2. Distribution 3. Metabolism 4. Excretion 5. Bioequivalence 6. Other pharmacokinetics
F	Acute, subacute, and chronic toxicity, teratogenicity, and other types of toxicity	1. Single dose toxicity 2. Repeated dose toxicity 3. Genotoxicity 4. Carcinogenicity 5. Reproductive toxicity 6. Local irritation 7. Other toxicity
G	Clinical studies	Clinical trial results
H	Information in the attached data, etc. provided for in Article 52, Paragraph 1 of the Law	Information in the attached data, etc.

**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)**

Left Column	Right Column							
	A 1 2 3	B 1 2 3	C 1 2 3	D 1 2 3	E 1 2 3 4 5 6	F 1 2 3 4 5 6 7	G	H
(1) Drugs containing new active ingredients	○ ○ ○	○ ○ ○	○ ○ ○	○ ○ △	○ ○ ○ ○ × △	○ ○ ○ △ ○ △ △	○	○
(2) Drugs with new routes of administration	○ ○ ○	× ○ ○	○ ○ ○	○ △ △	○ ○ ○ ○ × △	○ ○ × △ ○ △ △	○	○
(3-1) Drugs with new indications	○ ○ ○	× × ×	× × ×	○ × ×	△ △ △ △ × △	× × × × × × ×	○	○
(3-2) Prescription drugs with new dosage forms	○ ○ ○	× ○ ○	○ ○ ○	× × ×	○ ○ ○ ○ × △	× × × × × × ×	○	○
(3-3) Drugs with new dosages	○ ○ ○	× × ×	× × ×	× × ×	○ ○ ○ ○ × △	× × × × × × ×	○	○
(4) Non-prescription drugs with new active ingredients for non-prescription drugs	○ ○ ○	× × ○	△ × △ <sup>2)</sup>	× × ×	△ × × × × ×	△ △ × × × △ △	○	○
(5-1) Non-prescription drugs with new administration routes for non-prescription drugs	○ ○ ○	× × ○	△ × △ <sup>2)</sup>	× × ×	△ × × × × ×	△ △ × × × △ △	○	○
(5-2) Non-prescription drugs with new indications for non-prescription drugs	○ ○ ○	× × ×	× × ×	× × ×	△ × × × × ×	× × × × × × ×	○	○
(5-3) Non-prescription drugs with new dosage forms for non-prescription drugs	○ ○ ○	× × ○	△ × △ <sup>2)</sup>	× × ×	△ × × × × ×	× × × × × × ×	○	○
(5-4) Non- prescription drugs with new dosage/administrations for non-prescription drugs	○ ○ ○	× × ×	× × ×	× × ×	△ × × × × ×	× × × × × × ×	○	○
(6) New non-prescription combination drugs	○ ○ ○	× × ○	△ × △ <sup>2)</sup>	× × ×	△ × × × × ×	△ △ × × × △ ×	○	○
(7-1) Non-prescription combination drugs with similar formulations	× × ○	× × ○	△ × △ <sup>2)</sup>	× × ×	△ × × × × ×	△ △ × × × × ×	×	○
(7-2) Non-prescription combination drugs with similar dosage forms	× × ○	× × ○	△ × △ <sup>2)</sup>	× × ×	△ × × × × ×	× × × × × × ×	×	○
(8) Other non-prescription drugs (drugs with approval standards,	× × ○ 1)	× × ○	△ × △ <sup>2)</sup>	× × ×	× × × × × ×	× × × × × × ×	×	×

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. (5-3) "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. (5-4) "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**

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

**Table 6 List of Major Guidelines, etc. on Physicochemical Properties, Specifications, and Tests Methods**

Title	Notification number and date of issuance
Text (Items) on Analytical Validation	Notification No. 755 of the Evaluation and Licensing Division, PAB dated July 20, 1995 (ICH Q2A, currently Q2(R1))
Guidelines on Impurities in Bulk Drugs with New Active Ingredients	Notification No. 877 of the Evaluation and Licensing Division, PAB dated September 25, 1995, partially revised by Notification No. 1204001 of the Evaluation and Licensing Division, PFSB dated December 4, 2006 (ICH Q3A, currently Q3A(R2))
Guidelines on Impurities in Drug Preparations	Notification No. 539 of Evaluation and Licensing Division, PAB, dated June 23, 1997, partially revised by Notification No. 0703004 of the Evaluation and Licensing Division, PFSB dated July 3, 2006 (ICH Q3B, currently Q3B(R2))
Text (analytical procedures) on Analytical Validation	Notification No. 338 of the Evaluation and Licensing Division, PAB dated October 28, 1997 (ICH Q2B, currently Q2(R1))
Guidelines on Residual Solvents in Drug Preparations	Notification No. 307 of the Evaluation and Licensing Division, PMSB dated March 30, 1998, partially revised by Notification No. 0318-(1) of the Pharmaceutical Evaluation Division, PSEHB dated March 18, 2019 (ICH Q3C, currently Q3C(R7))
Guideline for Elemental Impurities	Notification No. 0930-(4) of the Evaluation and Licensing Division, PFSB dated September 30, 2015 (ICH-Q3D)
Setting of Specifications and Test Methods of New Drugs	Notification No. 568 of the Evaluation and Licensing Division, PMSB dated May 1, 2001 (ICH Q6A)
Setting of Specifications and Test Methods of Biological Products (Biotechnological Products/Drug Products Derived from Living Organisms)	Notification No. 571 of the Evaluation and Licensing Division, PMSB dated May 1, 2001 (ICH Q6B)
Guidelines for Handling Internationally Harmonized Specifications of Japanese Pharmacopoeia	Notification No. 574 of the Evaluation and Licensing Division, PMSB dated May 1, 2001
Guidelines Related to Formulation Development	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 (ICH Q8)
Handling of Application of Drugs Containing a Substance with Different Crystalline	Notification No. 0616-(1) of PFSB dated June 16, 2011
Guidelines for development and manufacturing of active pharmaceutical ingredients (chemicals and biotechnological products/biological products)	Notification No. 0710-(9) of the Evaluation and Licensing Division, PFSB dated July 10, 2014 (ICH-Q11)
Questions and answers (Q&As) on guidelines for development and manufacturing of active pharmaceutical ingredients (chemicals and biotechnological products/biological products)	Office Communication dated September 14, 2018

Pharmaceutical Regulations in Japan:

Guidelines for Assessment and Control of DNA Reactive (mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk	Notification No. 1110-(3) of the Evaluation and Licensing Division, PSEHB dated November 10, 2015 (ICH-M7) Partially revised by Notification No. 0627-(1) of the Pharmaceutical Evaluation Division, PSEHB dated June 27, 2018
Matters to be considered in assuring and evaluating quality of nucleic acid drugs	Notification No. 0927-(3) of the Pharmaceutical Evaluation Division, PSEHB dated September 27, 2018

**Table 7 List of Major Guidelines, etc. on Toxicity Tests**

Title	Notification number and date of issuance
Revisions of the Guidelines for Single and Repeated Dose Toxicity Studies	Notification No. 88 of the Evaluation and Licensing Division, PAB dated August 10, 1993 (ICH S4)
Guidance for Toxicokinetics (Evaluation of Systemic Exposure in Toxicity Tests)	Notification No. 443 of the Evaluation and Licensing Division, PAB dated July 2, 1996 (ICH S3A)
Questions and Answers (Q&As) on Use of Microsampling Method in Guidance for Toxicokinetics (Evaluation of Systemic Exposure in Toxicity Tests)	Office Communication dated March 15, 2019
Guidance on Dose Selection for Carcinogenicity Tests of Drugs	Notification No. 544 of the Evaluation and Licensing Division, PAB dated August 6, 1996 (ICH S1C)
Guidance on Dose Selection for Carcinogenicity Tests of Drugs and its supplement	Notification No. 551 of the Evaluation and Licensing Division, PMSB dated July 9, 1998 (ICH S1C(R), currently S1C(R1))
Guidance on Requirements for Carcinogenicity Tests of Drugs	Notification No.315 of the Evaluation and Licensing Division, PAB dated April 14, 1997 (ICH-S1A)
Guidelines for Reproductive and Developmental Toxicity Studies	Notification No. 316 of the Evaluation and Licensing Division, PAB dated April 14, 1997 (ICH S5A/S5B), partially revised by Notification No. 1834 of the Evaluation and Licensing Division, PMSB dated December 27, 2000 (ICH S5B(M), currently S5(R2))
Guidance on the Need for Carcinogenicity Studies of Pharmaceuticals	Notification No. 548 of the Evaluation and Licensing Division, PMSB dated July 9, 1998 (ICH-S1B)
Timing of Preclinical Studies in Relation to Clinical Trials	Notification Nos. 1019 and 1831 of the Evaluation and Licensing Division of PMSB dated November 13, 1998 and December 27, 2000, respectively, partially revised by Notification No. 0219-(4) of the Evaluation and Licensing Division, PMSB dated February 19, 2010 (ICH M3(M), currently M3(R2))
Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals Questions & Answers (Q&A)	Office Communication dated August 16, 2012
Guidance on Genotoxicity Tests of Pharmaceuticals	Notification No. 1604 of the Evaluation and Licensing Division, PMSB dated November 1, 1999 (ICH-S2)
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
Guidance on Immunotoxicity Studies for Human Pharmaceuticals	Notification No. 0418001 of the Evaluation and Licensing Division, PFSB dated April 18, 2006 (ICH S8)
The Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals	Notification No. 1023-(4) of the Evaluation and Licensing Division, PFSB dated October 23, 2009 (ICH S7B)
Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use	Notification No. 0920-(2) dated September 20, 2012 (ICH-S2 (R1))
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
Guideline on Photosafety Evaluation	Notification No. 0521-(1) of the Evaluation and Licensing Division, PFSB dated May 21, 2014 (ICH-S10)

**Table 8 List of Major Guidelines, etc. on Pharmacological Studies**

Title	Notification number and date of issuance
Guidelines for General Pharmacology Studies	Notification No. 4 of the New Drugs Division, PMSB dated January 29, 1991
Safety Pharmacology Study Guidelines	Notification No. 902 of the Evaluation and Licensing Division, PMSB dated June 21, 2001 (ICH-S7A)
Methods of Investigating Drug Interactions	Notification No. 813 of the Evaluation and Licensing Division, PMSB dated June 4, 2001

**Table 9 List of Major Guidelines, etc. on Pharmacokinetic Studies**

Title	Notification number and date of issuance
Guidelines on Pharmacokinetic Studies	
Guidelines on Nonclinical Pharmacokinetic Studies	Notification No. 496 of the Evaluation and Licensing Division, PMSB dated June 26, 1998
Guideline for Repeated Dose Tissue Distribution Studies	Notification No. 442 of the Evaluation and Licensing Division, PAB dated July 2, 1996 (ICH-S3B)
Clinical Pharmacokinetic Studies on Drugs	Notification No. 796 of the Evaluation and Licensing Division, PMSB dated June 1, 2001
Guidelines for Population Pharmacokinetic/Pharmacodynamic Guidelines	Notification No. 0515-(1) of the Pharmaceutical Evaluation Division, PSEHB dated May 15, 2019
Guidelines on validation of bioanalytical methods	
Guidelines on Bioanalytical Methods Validation for Human Studies in New Drug Development	Notification No. 0711-(1) of the Evaluation and Licensing Division, PFSB dated July 11, 2013
Guidelines on Bioanalytical Methods Validation for Human Studies in New Drug Development Questions and Answers (Q&A)	Office Communication dated July 11, 2013
Guidelines on Bioanalytical Methods (Ligand Binding) Validation for Human Studies in New Drug Development	Notification No. 0401-(1) of the Evaluation and Licensing Division, PFSB dated April 1, 2014
Guidelines on Bioanalytical Methods (Ligand Binding) Validation for Human Studies in New Drug Development Questions and Answers (Q&A)	Office Communication dated April 1, 2014
Guidelines on investigation of drug interactions	
Guidelines for Pharmacokinetic Drug Interaction for Drug Development and Proper Information Provision	Notification No. 0723-(4) of the Pharmaceutical Evaluation Division, PSEHB dated July 23, 2018 (partially revised by Office Communication dated February 8, 2019; replacement of a list of errata for partial revision by Office Communication dated February 20, 2019)
Questions and Answers (Q&As) on Guidelines for Pharmacokinetic Drug Interaction for Drug Development and Proper Information Provision	Office Communication dated July 23, 2018

**Table 10 List of Major Guidelines, etc. on Bioequivalence Studies**

Title	Notification number and date of issuance
Guidelines on bioequivalence studies	
Guidelines for Bioequivalence Testing of Generic Drugs	Notification No. 0229-(10) of the Evaluation and Licensing Division, PFSB dated February 29, 2012
Guidelines for Bioequivalence Testing of Oral Solid Dosage Forms with Different Content	Notification No. 0229-(10) of the Evaluation and Licensing Division, PFSB dated February 29, 2012
Guidelines for Bioequivalence Testing of Oral Solid Dosage Forms with Formulation Modifications	Notification No. 0229-(10) of the Evaluation and Licensing Division, PFSB dated February 29, 2012
Guidelines for Bioequivalence Testing of Products with Different Dosage Forms	Notification No. 0229-(10) of the Evaluation and Licensing Division, PFSB dated February 29, 2012
Guidelines for Bioequivalence Studies of Generic Products for Topical Dermatological Use	Notification No. 1124004 of the Evaluation and Licensing Division, PFSB dated November 24, 2006
Guidelines for Bioequivalence Testing of New Additional Topical Dermatological Dosage Forms	Notification No. 1124001 of the Evaluation and Licensing Division, PFSB dated November 24, 2006
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
Concepts regarding evaluation of bioequivalence of various preparations	
Concepts regarding Bioequivalence Studies of Solid Oral Preparations for Handling Changes in Manufacturing Method (Including Q&A)	Office Communication dated April 19, 2013
Basic Concepts regarding Bioequivalence Studies of Generic Powder Inhaler Products	Office Communication dated March 11, 2016
Basic Concepts regarding Bioequivalence Studies of Generic Aqueous Ophthalmic Solution Products	Office Communication dated March 11, 2016
Basic Concepts Regarding Implementation of Bioequivalence Studies of Generic Ophthalmic Solution Products	Office Communication dated November 29, 2018

**Table 11 List of Major Guidelines, etc. on Clinical Evaluation**

Title	Notification number and date of issuance
[1] Guidelines for clinical evaluation of drugs classified by therapeutic category	
Guidelines on Clinical Evaluation of Oral Contraceptives	Notification No. 10 of the First Evaluation and Registration Division, PAB dated April 21, 1987
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
Guidelines on Clinical Evaluation of Antihyperlipidemic Drugs	Notification No. 1 of the First Evaluation and Registration Division, PAB dated January 5, 1988
Guidelines on Clinical Evaluation of Antianxiety Drugs	Notification No. 7 of the First Evaluation and Registration Division, PAB dated March 16, 1988
Guidelines on Clinical Evaluation of Antibacterial Drugs	Notification No. 1023-(3) of the Pharmaceutical Evaluation Division, PSEHB dated October 23, 2017
Reference Information for Guidelines on Clinical Evaluation of Antibacterial Drugs	Office Communication dated October 23, 2017
Guidelines on Clinical Evaluation of Ocular Topical Antimicrobial Drugs	Notification No. 0418-(1) of the Pharmaceutical Evaluation Division, PSEHB dated April 18, 2019
Guidelines on Clinical Evaluation of Drugs to Treat Osteoporosis	Notification No. 742 of the Evaluation and Licensing Division, PMSB dated April 15, 1999, partially revised by Notification of Pharmaceutical Evaluation Division, PSEHB 0707-(1)
Principles for Clinical Evaluation of New Antihypertensive Drugs	Notification No. 0128001 of the Evaluation and Licensing Division, PMSB dated January 28, 2002 (ICH E12A, currently E12)
Guidelines on Clinical Evaluation of Antiarrhythmic Drugs	Notification No. 0325035 of the Evaluation and Licensing Division, PFSB dated March 25, 2004
Guidelines on Clinical Evaluation of Antianginal Drugs	Notification No. 0512001 of the Evaluation and Licensing Division, PFSB dated May 12, 2004
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
Guidelines for Clinical Evaluation of Antirheumatoid Drugs	Notification No. 0217001 of the Evaluation and Licensing Division, PFSB dated February 17, 2006
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
Guidelines for Clinical Evaluation of Prophylactic Vaccines against Infections	Notification No. 0527-(5) of the Evaluation and Licensing Division, PFSB dated May 27, 2010
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
Guidelines for Clinical Evaluation of Antidepressant Drugs	Notification No. 1116-(1) of the Evaluation and Licensing Division, PFSB dated November 16, 2010
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
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
Guidelines on Clinical Evaluation of Hypnotics	Notification No. 1213-(1) of the Evaluation and Licensing Division, PFSB dated December 13, 2011
Guidance for Clinical Evaluation Method of Anticancer Drugs in Pediatric Patients With Malignant Cancer	Notification No. 0930-(1) of the Evaluation and Licensing Division, PFSB dated September 30, 2015
Guidelines for Clinical Evaluation of Drugs, etc. for Treating Acute Spinal Cord Injury	Notification No. 0508-(1) of the Pharmaceutical Evaluation Division, PSEHB and Notification No. 0508-(1) of the Medical Device Evaluation Division, PSEHB dated May 8, 2019
Guidance on Clinical Evaluation of Travelers' Vaccine, etc.	Notification No. 0407-(1) of the Evaluation and Licensing Division, PSEHB dated April 7, 2016

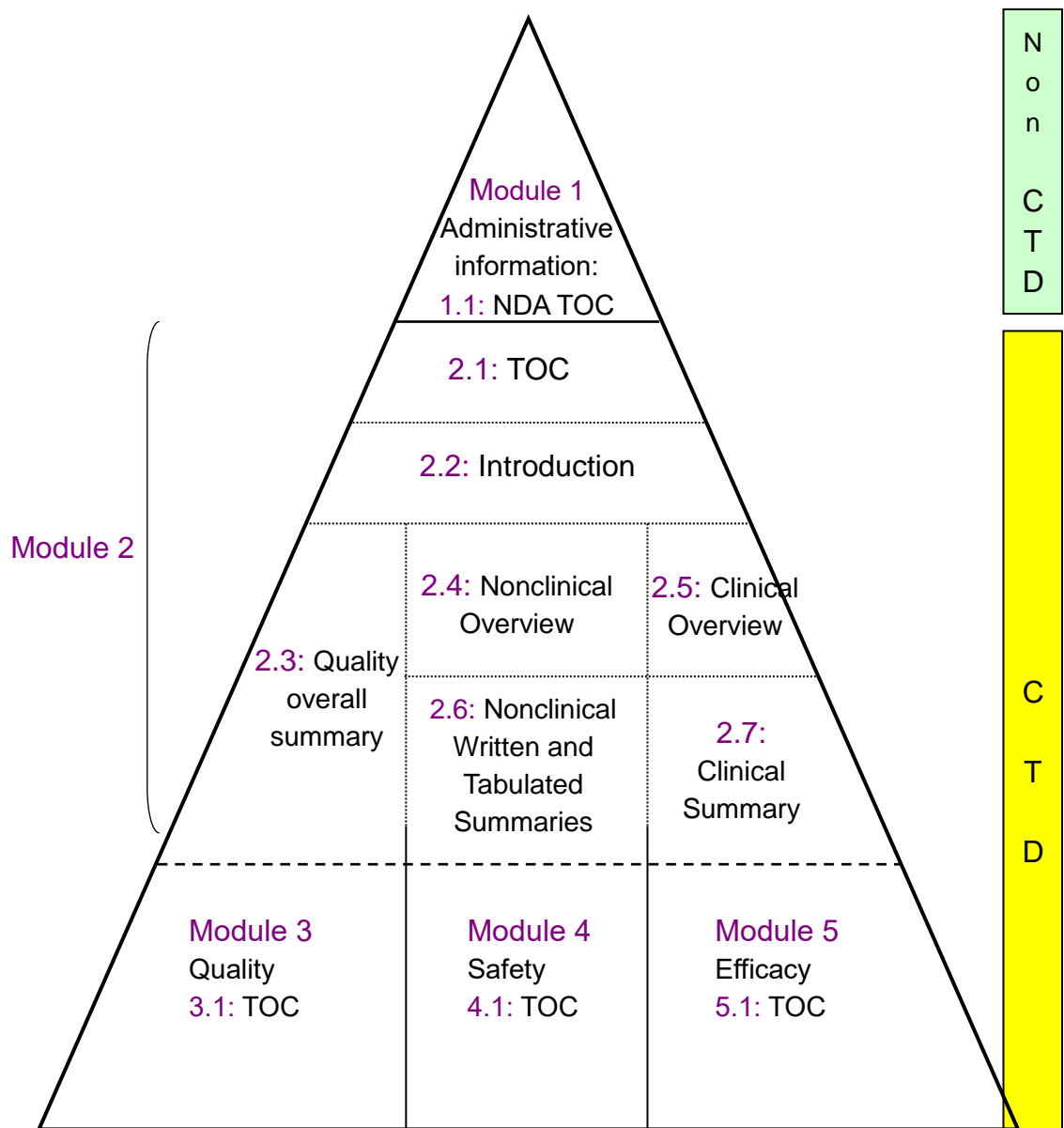
[2] Common guidelines for clinical evaluation	
Studies in Support of Special Populations: Geriatrics	Notification No. 104 of the New Drugs Division, PAB dated December 2, 1993 (ICH-E7) and Q&A dated September 17, 2010
Questions and Answers for "Studies in Support of Special Populations: Geriatrics"	Office Communication dated September 17, 2010
Dose-Response Information to Support Drug Registration	Notification No. 494 of the Evaluation and Licensing Division, PAB dated July 25, 1994 (ICH-E4)
Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions	Notification No. 592 of the Evaluation and Licensing Division, PAB dated May 24, 1995 (ICH-E1)
Structure and Content of Clinical Study Reports	Notification No. 335 of the Evaluation and Licensing Division, PAB dated May 1, 1996 (ICH-E3)
General Considerations for Clinical Trials	Notification No. 380 of the Evaluation and Licensing Division, PMSB dated April 21, 1998 (ICH-E8)
Ethnic Factors to be Considered in the Acceptance of Foreign Clinical Trial Data	Notification No. 672 of the Evaluation and Licensing Division, PMSB dated August 11, 1998 (ICH E5, currently E5(R1)) Q&A by Office Communication dated February 25, 2004, and Q&A-(2) by Office Communication dated October 5, 2006
Statistical Principles for Clinical Trials	Notification No. 1047 of the Evaluation and Licensing Division, PMSB dated November 30, 1998 (ICH-E9)
Clinical Investigation of Medicinal Products in the Pediatric Population	Notification No. 1334 of the Evaluating and Licensing Division, PMSB dated December 15, 2000 (ICH-E11)
Supplement to Clinical Investigation of Medicinal Products in the Pediatric Population	Notification No. 1227-(5) of the Pharmaceutical Evaluation Division, PSEHB dated December 27, 2017 (ICH-E11 (R1))
Choice of Control Group and Related Issues in Conducting Clinical Studies	Notification No. 136 of the Evaluating and Licensing Division, PMSB dated February 27, 2001, partially revised by Office Communication dated April 10, 2001
Guidance for Conducting Microdose Clinical Studies	Notification No. 0603001 of the Evaluating and Licensing Division, PFSB dated June 3, 2008
Clinical Investigation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs	Notification No. 1023-(1) of the Evaluating and Licensing Division, PFSB dated October 23, 2009, Q&A by Office Communication dated October 23, 2009, and Q&A-(2) by Office Communication dated July 3, 2012
Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals	Notification No. 0219-(4) of the Evaluation and Licensing Division, PFSB dated February 19, 2010 (ICH-M3(R2)) and Q&A by Office Communication dated August 16, 2012
General Principles for Planning and Design of Multi-Regional Clinical Trials	Notification No. 0612-(1) of the Pharmaceutical Evaluation Division, PSEHB dated June 12, 2018 (ICH-E17)
[3] Other guidelines for clinical evaluation	
Research on Evaluation of Immunotherapeutic Agents for Malignant Tumors	Iyakuin Kenkyu 11(4), 1980
Research on Evaluation of Blood Preparations, Especially Plasma Fraction Preparations	Iyakuin Kenkyu 15(2), 1984
Research on Overall Evaluation of Interferon Preparations	Iyakuin Kenkyu 15(6), 1984
Guidelines on Clinical Evaluation of Anti-inflammatory Analgesic Drugs	Iyakuin Kenkyu 16(3), 1985
Guidelines on the Design and Evaluation of Sustained-release (Oral) Preparations	Notification No. 5 of the First Evaluation and Registration Division, PAB dated March 11, 1988

Pharmaceutical Regulations in Japan:

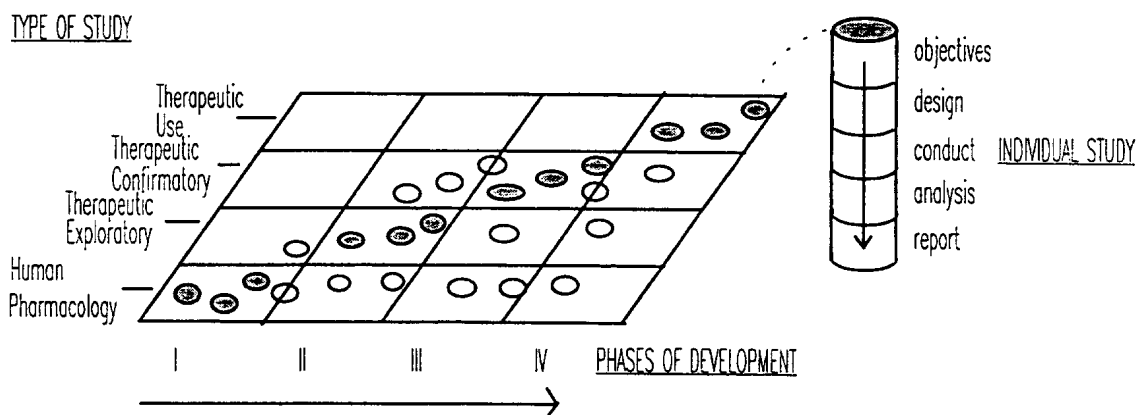
Guidance for Developing Prototype Vaccines in Preparation for Influenza Pandemic	Notification No. 1031-(1) of the Evaluation and Licensing Division, PFSB dated October 31, 2011
Guidance for Clinical Evaluation of Diagnostic Radiopharmaceuticals	Notification No. 0611-(1) of the Evaluation and Licensing Division, PFSB dated June 11, 2012
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
Guideline for PK/PD of Antibacterial Agents	Notification No. 1225-(10) of the Evaluation and Licensing Division, PSEHB dated December 25, 2015
Guideline for Development of Liposomal Preparations	Notification No. 0328-(19) of the Evaluation and Licensing Division, PSEHB dated March 28, 2016 (Office Communication dated March 28, 2016, Q&As)
Reflection Paper on Nucleic Acid (siRNA)-Encapsulated Nanoparticle Formulations	Office Communication dated March 28, 2016
Guidance on Development of Cancer Immunotherapy	Notification No. 0308-(1) of the Pharmaceutical Evaluation Division, PSEHB and Notification No. 0308-(1) of the Medical Device Evaluation Division, PSEHB dated March 8, 2019

**Table 12 List of Major Guidelines, etc. Related to Biotechnology**

Title	Notification number and date of issuance
Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin	Notification No. 329 of the Evaluation and Licensing Division, PMSB dated February 22, 2000 (ICH-Q5A)
Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of R-DNA Derived Protein Products	Notification No. 3 of the Evaluation and Licensing Division, PMSB dated January 6, 1998 (ICH-Q5B)
Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products	Notification No. 6 of the Evaluation and Licensing Division, PMSB dated January 6, 1998 (ICH-Q5C)
Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products	Notification No. 873 of the Evaluation and Licensing Division, PMSB dated July 14, 2000 (ICH-Q5D)
Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process	Notification No. 0426001 of the Evaluation and Licensing Division, PFSB dated April 26, 2005 (ICH-Q5E)
Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products	Notification No. 571 of the Evaluation and Licensing Division, PMSB dated May 1, 2001 (ICH-Q6B)
Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals	Notification No. 0323-(1) of the Evaluation and Licensing Division, PFSB dated March 23, 2012 (ICH-S6(R))
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



**Fig. 11 Organization of ICH Common Technical Documents**



**Fig. 12 Correlation between Development Phases and Types of Study**

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

**Table 13 ICH topics and guidelines - Progress of harmonization**

as of November 20, 2019

<https://www.pmda.go.jp/files/000233035.pdf>

	Quality	
	Code	Topics
<b>Step 5</b>	Q1A(R2) Q1B Q1C Q1D Q1E Q2(R1) Q3A(R2) Q3B(R2) Q3C(R7) Q3D Q4B Q4B(Annex1)(R1) Q4B(Annex2)(R1) Q4B(Annex3)(R1) Q4B(Annex4A, 4B, 4C) (R1) Q4B(Annex5)(R1) Q4B(Annex6)(R1) Q4B(Annex7)(R2) Q4B(Annex8)(R1) Q4B(Annex9)(R1) Q4B(Annex10)(R1) Q4B(Annex11) Q4B(Annex12) Q4B(Annex13) Q4B(Annex14) Q5A(R1) Q5B Q5C Q5D Q5E Q6A Q6B Q7 Q8(R2) Q9 Q10 Q11	Stability testing: New drug substances and products Stability testing: Photostability Stability testing: New & partially revised dosage forms Stability testing: Bracketing and matrixing designs Stability testing: Evaluation of stability data Validation of analytical procedures: Text and methodology Impurities in new drug substances Impurities in new drug products Impurities: Residual solvents Guideline for metal impurities Pharmacopoeias: Harmonized texts for use in ICH regions Test for residue on ignition Test for extractable volume of parenteral preparations Test for particulate contamination of parenteral preparations Microbial limit tests of non-sterile products Disintegration test Uniformity of dosage units Dissolution test Sterility test Tablet friability test Polyacrylamide gel electrophoresis Capillary electrophoresis Analytical sieving Bulk density and tapped density of powders Bacterial endotoxins test Quality of biotechnology products: Viral bioburden Quality of biotechnology products: Genetic stability Quality of biotechnology products: Stability Testing of products Quality of biotechnology products: Cell bank control (cell substrates) Quality of Biotechnology Products: Comparability of products Specifications/test methods: Chemicals/pharmacopoeial harmonization Specifications/test methods: Biological products GMP for active pharmaceutical ingredients Pharmaceutical development Quality risk management Pharmaceutical quality system Manufacturing and development of active pharmaceutical ingredients
<b>Step 4</b>	Q3D(R1) Q12	Guideline for metal impurities (Revision) Pharmaceutical life cycle management

	Quality	
	Code	Topics
<b>Step 3</b>		
<b>Step 2a/2b</b>		
<b>Step 1</b>	Q2(R2)/Q14 Q3C(R8) Q3D(R2) Q5A(R1) Q13	Development of analytical procedures and Q2(R1) (Validation of analytical procedures) (Revision) Impurities: Residual solvents (Revision) Guideline for metal impurities (Revision) Quality of biotechnology products: Viral bioburden (Revision) Continuous manufacturing of drug substances and drug products

	Safety	
	Code	Topics
<b>Step 5</b>	S1A S1B S1C(R2) S2(R1) S3A S3B S4 S5(R2) S6(R1) S7A S7B S8 S9 S10	Need for carcinogenicity studies Testing of carcinogenicity of pharmaceuticals Dose selection for carcinogenicity studies Genotoxicity Toxicokinetics: Assessment of systemic exposure in toxicity studies Pharmacokinetics: Repeated-dose tissue distribution Single- and repeated-dose toxicity studies Reproduction studies of medicinal products Safety evaluation of biological products Safety pharmacology studies The non-clinical evaluation of QT interval prolongation potential Immunotoxicology studies Non-clinical evaluation of anticancer drugs Guidance on photosafety testing
<b>Step 4</b>		
<b>Step 3</b>	S5(R3) S11	Reproduction studies of medicinal products (Revision) Non-clinical safety testing using juvenile animals
<b>Step 2a/2b</b>		
<b>Step 1</b>	S1(R1) S12	Testing of carcinogenicity of pharmaceuticals Nonclinical biodistribution considerations for gene therapy products

	Efficacy	
	Code	Topics
<b>Step 5</b>	E1	The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life threatening condition
	E2A	Clinical safety data management: Definitions and standards for expedited reporting in the clinical phase
	E2B(R2)	Data elements for transmission of individual case safety reports
	E2B(R3)	Implementation guide – data elements and message specification in individual case safety reports (ICSR)
	E2C(R2) E2D	Periodic Benefit-Risk Evaluation Report(PBRER)
	E2E E2F	Post-approval safety data management
	E3	Pharmacovigilance planning (PVP)
	E4	Development of safety update report (DSUR)
	E5(R1)	Structure and content of clinical study reports
	E6(R2)	Dose-response information to support drug registration
	E7	Ethnic factors in the acceptability of foreign clinical data
	E8	Good clinical practice (Supplement)
	E9	Studies in support of special populations: Geriatrics
	E10	General considerations for clinical trials
	E11(R1)	Statistical principles for clinical trials
	E12	Choice of control group and related issues in clinical trials
	E14	Clinical investigation of medicinal products in the pediatric population (Supplement)
	E15	Principles for clinical evaluation of new antihypertensive drugs
<b>Step 4</b>	E16	The clinical evaluation of QT interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs
	E17	Definitions for genomic biomarkers, pharmacogenomics, pharmaco- genetics, genomic data, and sample coding categories
<b>Step 3</b>	E18	Genomic biomarkers related to drug response: Context, structure and format of qualification submissions
	E19	General principle on planning/designing multi-regional clinical trials
<b>Step 2a/2b</b>		Optimisation of safety data collection
<b>Step 1</b>	E2D(R1)	Post-Approval Safety Data Management (Revision)
	E6(R3)	Good clinical practice (Revision)
	E11A	Pediatric extrapolation
	E20	Adaptive clinical trials

	Multidisciplinary	
	Code	Topics
<b>Step 5</b>	M1	Medical dictionary for regulatory activities (MedDRA)
	M2	Electronic standards for transmission of regulatory information
	M3(R2)	Non-clinical safety studies for the conduct of human clinical trials
	M4	Common Technical Document
	M4E(R2)	Guideline on enhancing the format and structure of benefit-risk information in CTD (Revision)
	M7(R1)	Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to reduce potential carcinogenic risk
	M8 M8	e-CTD specification (v. 3.2.2) e-CTD specification (v. 4.0)
<b>Step 4</b>	M9	BCS-based biowaivers
<b>Step 3</b>	M10	Bioanalytical Method Validation
<b>Step 2a/2b</b>		
<b>Step 1</b>	M7(R2)	Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to reduce potential carcinogenic risk (Revision)
	M11	Clinical electronic Structured Harmonized Protocol(CeSHanP)
	M12	Drug interaction studies

- (Note 1) Step 1: Preparation of the draft guideline by the expert working group and agreement  
Step 2a/2b: Approval of the draft of the ICH guidelines by the steering committee and regulatory authority  
Step 3: Hearing of opinions about the draft guideline in each region and revision of the draft guidelines based on the opinions obtained  
Step 4: Final agreement of the ICH guidelines  
Step 5: Incorporation in domestic regulations in each region

- (Note 2) Q&As for the guidelines are not included in the above table. (See the pages of individual topics.)

## 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 GPSP (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 GPSP 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. Since the environment for utilizing the medical information database system (MID-NET) in pharmacovigilance is being established, "Basic Concept of the Use of Medical Information Database in Post-marketing Pharmacovigilance" (Notification No. 0609-(8) of the Pharmaceutical Evaluation Division, PSEHB / Notification No. 0609-(4) of the Safety Division, PSEHB dated June 9, 2017) was issued in June 2017. Thus, the basic concept to be applied when a marketing authorization holder for drugs use the medical information database in post-marketing pharmacovigilance was presented. In April 2018, "Handling of administrative procedures for applications, etc. related to the use of MID-NET" (Notification No. 0401001 from Director of Regulatory Science Center, PMDA, dated April 1, 2018) was issued, and the operation of the MID-NET was started on a full scale. Various information on the notifications related to the use of MID-NET is posted on the website of PMDA.

<http://www.pmda.go.jp/safety/mid-net/0002.html>

The GPSP Ministerial Ordinance was revised on October 26, 2017 to add "post-marketing database survey" as a type of post-marketing survey. "Announcement of Ministerial Ordinance Partially Revising Ministerial Ordinance Related to Standards for Conducting Post-Marketing Surveys and Studies on Drugs (Related to MHLW Ordinance Related to Standards for Conducting Post-Marketing Surveys and Studies on Drugs)" (Notification No. 1026-(1) of the Evaluation and Licensing Division, PSEHB dated October 26, 2017) was issued and enforced on April 1, 2018. In association with this revision, "Procedures for Developing Post-marketing Database Survey Plan" was presented by PMDA in January 2018 as a reference for preparation of a post-marketing database survey plan, and "Points to Consider for Ensuring Reliability in Post-marketing Database Surveys of Drugs" (Notification No. 0221-(1) of the Pharmaceutical Evaluation Division, PSEHB dated February 21, 2018) was issued in February 2018. The Q&As for this notification were issued in June 2019 (Office Communication dated June 19, 2019). Moreover, since this revision clarified the positioning of post-marketing surveys using medical information database as a technique of post-marketing surveys, and implementation of efficient and effective surveys with the choice of the scientific technique for the objectives of the survey has come to be required, "How to Proceed with Examination for Development of Plans for Post-marketing Surveys, etc." was proposed by PMDA on January 23, 2018 and the procedure of basic examination for development of a plan for conducting post-marketing surveys, etc. was proposed.

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 GPSP were revised on March 11, 2013 to ensure the development and subsequent implementation of risk management plan (RMP). In March 2016, "Preparation and publication of drug risk management plan" (Notification No. 0331-(13) of the Evaluation and Licensing Division, PSEHB and Notification No. 0331-(13) of the Safety Division, PSEHB both dated March 31, 2016) and "Points to be considered in submission of publication documents of drug risk management plan" (Notification No. 0331001 of the Office of Safety, PMDA dated March 31, 2016) were issued. To promote use of RMPs in clinical practices, these notifications presented points to be considered in preparation and publication of RMP synopsis as well as submission of publication documents to PMDA. "Description on Materials Prepared and Distributed for Additional Risk Minimization Activities in Risk Management Plan (RMP)" (Office Communication dated June 8, 2017) was issued. It was decided to display RMP marks on the materials for health professionals and the materials for patients in order to enable health professionals to be aware that the materials such as the guide to proper use are based on the drug risk minimization activities in RMP. In addition, "Partial Revision of 'Publication of Drug Risk Management Plan'" (Notification No. 1029-(1) of the Pharmaceutical Evaluation Division, PSEHB and Notification No. 1029-(1) of the Safety Division, PSEHB dated October 29, 2018) was issued, and placement of the materials prepared based on RMP for health professionals and for patients on the website of PMDA was decided. In May 2019, "Points to

Consider in Preparation of Materials for Minor Changes of Drug Risk Management Plan (Q&As)" was issued (Office Communication dated May 10, 2019).

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" (Pharmaceutical and Medical Device Act), 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 business of regenerative medicine product and to include the provisions for subcontract of post-marketing safety management tasks specified in Article 18, Paragraph 3, etc. in the Law (Article 98 in the Enforcement Regulations).

Furthermore, the GPSP Ordinance for regenerative medicine products was newly issued in response to the new approval system established in consideration of characteristics of regenerative medicine products (the MHLW Ordinance for standards for conducting post-marketing surveys and studies on regenerative medicine products; 2014 MHLW Ordinance No. 90, dated July 30, 2014). To conduct use-results survey or post-marketing clinical study of a regenerative medicine product, applicable documents have to be prepared under this ordinance. More specific handling procedures were shown in the notification "Description methods of basic plan for evaluation of post-marketing approval conditions and basic plan of post-marketing surveys for regenerative medicine products" (Notification No. 0826-(1) of the Medical Devices Division, PFSB dated August 26, 2015). Since the environment for using medical information

database for collection of post-marketing safety information, etc. for cellular and tissue-based products, etc. is being established, the GPSP Ordinance was partially revised and enforced also for cellular and tissue-based products in the same way as drugs.

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 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

Service 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 Pharmaceutical and Medical Device Act.

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 Pharmaceutical and Medical Device Act.

### (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, and do not have any other factors that may hinder proper and smooth implementation of safety assurance work.

- [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 mutual cooperation with quality assurance supervisors and other supervisors engaged in work related to

marketing of prescription drugs, highly controlled medical devices, or cellular and tissue-based products

- 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.
- [4] When the procedures in [1] or the documents in [2] and [3] are prepared or revised, they must be dated and retained.
- [5] The general marketing compliance officer shall make available the procedures in [1], the documents in [2] and [3] and other documents required for safety assurance work in the office performing the work and also must make available copies of procedures and other related documents in other offices performing safety assurance work.

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

- [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 PMDA
  - Information from foreign governments and overseas organizations
  - Information from other pharmaceutical manufacturing/marketing authorization holders
  - Other safety management information
- [2] The safety management implementation supervisor shall report the records in [1] in writing to the safety management supervisor.
- [3] The safety management supervisor shall preserve the records in [1] and reports in [2].

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

#### **results thereof (Article 8)**

- [1] The safety management supervisor shall perform the following duties:
- Examine the collected safety management information without delay and record the results thereof.
  - Supply all safety information that the quality assurance supervisor, etc. must be familiar with in writing without delay to the quality assurance supervisor, etc.
  - 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 information, medical device information, or information about cellular and tissue-based products, make reports to the Minister of Health, Labour and Welfare, and take other safety assurance measures.
  - Drafts of safety assurance measures shall be reported in writing to the general marketing compliance officer and copies shall be retained.
- [2] When the safety management supervisor has the safety management implementation supervisor examine safety management information, he or she shall issue instructions in writing and retain a copy. Records of the examination performed by the safety management implementation supervisor shall be prepared and reported in writing. The safety management supervisor shall retain these results.

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

- [1] The general marketing compliance

officer must undertake the following duties:

- Appropriately evaluate drafts of safety assurance measures, decide the safety assurance measures to be taken and prepare and retain records thereof.
  - When safety management supervisors undertake safety assurance measures, instructions shall be issued in writing and retained
  - When safety management implementation supervisors undertake safety assurance measures, instructions shall be issued in writing and the safety management 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. In this case, necessary matters regarding the works prescribed in [1] and [2] should be stipulated in the standard operating procedures for post-marketing safety management, etc.

#### **(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 information:
- Objective of early post-marketing phase vigilance
- Method of early post-marketing phase vigilance
- Period of early post-marketing phase vigilance

- Other necessary items
- Revision of the early post-marketing phase vigilance protocol, as situations may require
- When the early post-marketing phase vigilance protocol is prepared or revised, the protocol shall be dated and retained.

[2] The general marketing compliance officer 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.

[3] 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.

[4] 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)**

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

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

[3] When the person appointed beforehand in [1] is a person other than the safety management supervisor, that person

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

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

- [5] The general marketing compliance officer shall examine the necessity of improvements in post-marketing safety management based on the results of in-house inspections and when improvements are necessary, the general 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 management
- [2] Education and training shall be performed as planned by a person appointed beforehand.
- [3] When the person appointed beforehand in [2] is the safety management supervisor, the safety management supervisor shall prepare and retain records of education and training.
- [4] When the person appointed beforehand in [2] is a person other than the safety management supervisor, that person shall prepare records of education and training and report in writing to the safety management supervisor. The safety

management supervisor shall retain these reports.

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

### **(14) Standards for post-marketing safety management of type 2 marketing authorization holders (marketing authorization holders of drugs other than prescription drugs and controlled medical devices, including marketing authorization holders of in vitro diagnostics) (Articles 13 and 14)**

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

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

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

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

- [1] [1] to [3] in Article (14) above.
- [2] Standard operating procedures for post-marketing safety management are not specified.
- [3] Collection of safety information in (7) for quasi-drugs and cosmetics is limited to research reports and other safety

management information.

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

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

- [1] The period of retention of 5 years from the date when the records are no longer utilized. However, the period shall be 10 years for biological products and cellular and tissue-based products, 30 years for specified biological products and specified cellular and tissue-based products, and 15 years for designated controlled medical devices and highly controlled medical devices. Records related to in-house inspections and education and training shall be kept for 5 years from the date of preparation
- [2] Records specified by Ministerial Ordinance can be retained by persons designated by the marketing authorization holder based on the standard operating procedures for post-marketing safety management, etc.

**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. Furthermore, some ordinances were revised on April 1, 2018 because the environment for using medical information database for collection of information of post-marketing safety, etc. of drugs is

being established.

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 reevaluation of prescription drugs. For post-marketing clinical studies forming part of post-marketing surveillance, GCP is also applicable, in addition to GPSP.

**(2) Definitions of terms (Article 2)**

- [1] Post-marketing surveys, etc. refers to drug use-results surveys, post-marketing database 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] Drug use-results survey refers to a survey 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. Such surveys include general use-results surveys, special use results surveys, and surveys for comparing use-results.
- [3] Post-marketing database survey refers to a survey conducted to screen or confirm information related to the incidence of each disease due to adverse drug reactions, together with quality, efficacy and safety using medical information databases offered by the

business handling information database.

- [4] Post-marketing clinical study refers to a study performed to verify assumptions arrived at as a result of studies undertaken with regard to results of clinical studies, drug-use surveys, or post-marketing database survey, or a study 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 by the manufacturing/marketing authorization holder for the proper and smooth conduct of post-marketing surveillance. When standard operating procedure for post-marketing surveillance is prepared or revised, the written procedure should be dated and retained.

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

of post-marketing surveys, etc.

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

- [1] A supervisor of the 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. describing the overview of drug-use results, post-marketing database surveys, and post-marketing clinical studies for each drug individually.
  - To set forth in writing protocols for the implementation of drug use-results surveys, protocol for post-marketing database survey, 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 copies thereof.

- [4] A basic protocol for post-marketing surveys, etc. is not required to be prepared or retained when the RMP is available and retained.
- [5] The manufacturing/marketing authorization holder must respect the opinions provided by the supervisor of post-marketing surveys, etc.
- [6] The manufacturing/marketing authorization holder must not make any statements that would interfere with the supervisor of post-marketing surveys, etc. in the performance of his or her duties.

#### **(5) Post-marketing surveys, etc. (Article 5)**

- [1] Duties to be performed by the supervisor of post-marketing surveys, etc.:
  - To prepare plans, proposals and surveys for implementation of post-marketing surveys, etc.
  - 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)
  - 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)
- [2] The manufacturing/marketing authorization holder must arrange that, for each drug use-results survey, post-marketing database survey, or post-marketing clinical trial, 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.

- [3] 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, post-marketing database survey, and post-marketing clinical studies to the safety management supervisor when the RMP is available for practice.

#### **(6) 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, subjects to be investigated, range of subjects to be investigated, survey method, survey period, items surveyed, analytical items and method and other necessary matters must be established.

The procedures [1] to [3] shall be adopted when a post-marketing database survey is conducted. In this case, "use-results survey" should be read as "post-marketing data base survey," and "medical institution" as "the business handling information database."

**(7) 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

**(8) 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. Records of the results of the in-house inspection are prepared and preserved.
- [2] Post-marketing surveillance supervisors must report in writing the results of the self-inspections to the manufacturing/marketing authorization holder.
- [3] When it is found that improvements must be made in the work based on the results of the self-inspection, the necessary measures must be taken, and records of these measures must be prepared and retained.

**(9) Education and training (Article 9)**

- [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.

**(10) 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.

**(11) Preservation of records in connection with post-marketing surveys, etc. (Article 11)**

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

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

In addition to provisions of the GCP MHLW Ordinance, the provisions of Article 3 through Article 8, Article 10, and Article 11 of this GPSP MHLW apply mutatis mutandis to the collection and preparation of data for reexamination and reevaluation applications in

connection with post-marketing surveys, etc.

### 3. 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). The “Guidelines for Implementation of GPSP On-site Surveys” is partially revised in September 2018 (Notification No. 0913-(9) of the Pharmaceutical Evaluation Division, PSEHB dated September 13, 2018). 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). The notification is partially revised in September 2018 (Notification No. 0913026 of the PMDA dated September 13, 2018). On July 21, 2016, a service of consultation on compliance review for drug reexamination was introduced. This service has allowed an applicant to consult about compliance of the following documents with the reliability standards: applicable documents are planned to be attached in the application for drug reexamination and are related to the previously completed post-

marketing clinical studies and use-results surveys.

### 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. 15** 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 and Medical Device Act (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 228-20 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.

To the Enforcement Regulations of the Pharmaceutical and Medical Device Act, a provision was added on malfunction reports involving a part of device or equipment in drug products approved to be manufactured/marketed with other components including devices or equipment in an integrated form (combination products). It specifies that such reports shall be handled in accordance with provisions for reporting criteria and deadline of malfunction reports of medical devices. In addition, as the Pharmaceutical and Medical Device Act specifies reporting requirements for adverse drug reactions of regenerative medicine products, the Enforcement Regulations included provisions for reporting criteria and deadline of malfunction reports of regenerative medicine products. (Notification No. 1002-(20) of PFSB dated October 2, 2014 "Reporting of adverse drug reactions")

This notification imposes manufacturers and marketing authorization holders on the following reporting obligations: if a reportable malfunction occurs on the device part without reportable adverse drug reactions, they must submit malfunction report only; and if a reportable malfunction occurs with adverse drug reaction, they must submit both malfunction report and adverse drug reaction report.

In June 2017, "Amendment to "Q&As on Reports of Adverse Reactions to Combination Products" (Office Communication dated June 9, 2017) was issued.

### **(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 [R3]) 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. In March 2017, this notification was revised completely (Notification No. 0331-(6) of the Evaluation and Licensing Division, PSEHB / Notification No. 0331-(1) of the Safety Division, PSEHB dated March 31, 2017). Handling of reports of post-marketing adverse reactions before unblinding in post-marketing blinded clinical trials, etc., was stipulated. Handling of electronic transmission of the reports of adverse reactions to quasi drugs and cosmetic products was also stipulated. In addition, this notification was partially revised because of the partial changes in the handling of electronic reports of post-marketing overseas cases of infection and overseas cases of adverse reactions (Notification No. 0710-(1) of the Pharmaceutical Evaluation Division, PSEHB and Notification No. 0710-(1) of the Safety Division, PSEHB). Furthermore, "Q&As on 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))" (Office Communication dated November 28, 2017) was published, and Q&A was revised in association with the partial revision of the previous notification mentioned above (Office Communication dated July 10, 2019).

Furthermore, the procedures including precautions for reception and reporting of the reports of post-marketing adverse reactions and adverse reactions in clinical studies were partially revised, and "Points to Consider in 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. 0331001 of the Office of Review Management of PMDA / Notification No. 0331001 of the Office of Safety I of PMDA / Notification No. 0331002 of the Office of Safety II of PMDA dated March 31, 2017) was issued. As related notifications, "Corrections on Implementation Guide for electronic Transmission of Individual Case Safety Reports" (Notification No. 0315-(6) of the Pharmaceutical Evaluation Division, PSEHB / Notification No. 0315-(1) of the Safety Division, PSEHB dated March 15, 2017) and "Q&A on Electronic Transmission of Individual Case Safety Reports" (Office Communication dated November 8, 2018), and the "User guide regarding the use of EDQM terms for the dosage form and route of administration in safety reports of individual patients in E2B (R3) messages" (Office Communication dated November 8, 2018) were issued, and Q&A was revised in September 2019 (Office Communication dated September 26, 2019).

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.pmda.go.jp/safety/info-services/drugs/adr-info/suspected-adr/0005.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 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 Reporting of Adverse Drug Reactions from Patients

With the aim of collecting reports on the suspected cases of adverse drug reactions directly from patients or their families, thereby utilizing the information in taking safety measures for drugs, the implementation guidelines for "Reporting of adverse drug reactions from patients" were established, and the reception was started at PMDA (Notification No. 0326-(1) of the Safety Division, PSEHB dated March 26, 2019). The contents of the reports from the patients were as shown below.

- (1) Reporter: Patients who experienced symptoms suggestive of adverse drug reactions after the use of the drug or their families

- (2) Drugs to be reported: Prescription drugs, guidance-mandatory drugs, and non-prescription drugs manufactured and marketed in Japan
- (3) Reporting method: PMDA website or postage mail
- (4) Items reported:
  - Information on the reporter
  - Information on patients
  - Information on the drug which is suspected to have caused the symptoms suggestive of adverse drug reactions
  - Information on other drugs used
  - Information on symptoms
  - Information on medical institutions that can provide detailed information

When information is reported, the PMDA will confirm the contents reported, and enter the information on the database, except for personal information including the name, etc. PMDA will organize the information reported, and report them to the Ministry of Health, Labour and Welfare periodically. The Ministry of Health, Labour and Welfare will report the status of reporting to the Committee on Safety of Drugs of the Council on Drugs and Food Sanitation, and will take any necessary safety measures.

Information on the reported cases will be publicized on the website of PMDA after being processed in a way that individual patients cannot be identified.

#### 4.4 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.

In April 2017, "Notification on the System of Periodic Infection Reports for Regenerative Medicine Products and Biological Products" (Notification No. 00428-(1) of the PSEHB dated April 28, 2017) was issued to change the format of reports, and to require submission of the reports by electronic media. Moreover, "Q&A on the System of Periodic Infection Reports for Regenerative Medicine Products and Biological Products" (Office Communication dated July 29, 2017) was issued in July 2017.

## **6. REEXAMINATION 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 GPMS, 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 GPMS 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:
  - Drugs with new routes of administration
- (4) Reexamination from 4 to within 6 years after the date of approval:
  - New prescription combination drugs
  - 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).

When an additional indication is obtained during the reexamination period, the reexamination period for the additional indication will be as described

below.

- When the existing indication is a usual indication  
When the additional indication is a usual indication: 4 years or the residual period of the reexamination period for the existing indication  
When the additional indication is an indication of an orphan drug: 10 years
- When the existing indication is an indication of an orphan drug  
When the additional indication is a usual indication: 5 years and 10 months  
When the additional indication is an indication of an orphan drug: 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, post-marketing database 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 post-marketing surveys, etc. 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; post-marketing database surveys, and 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. 16** 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)

In November 2017, "Documents to be Attached to Application for Reexamination of New Prescription Drugs" (Notification No. 1128-(2) of the Pharmaceutical Evaluation Division, PSEHB dated November 28, 2017) was issued, and handling of reexamination

documents was reconsidered to incorporate the concept of RMP in reexamination, to evaluate the benefit-risk balance of drugs more appropriately and to seek its maintenance and improvement, and to cope with revision of GPSP Ordinance. This notification will be applied to the application for reexamination to be filed on October 1, 2019 or after that. In association with issuance of this notification, "Partial Revision of 'Format of Appendix to Periodic Safety Update Report and Other Procedure of Description'" (Notification No. 1128-(5) of the Pharmaceutical Evaluation Division, PSEHB and Notification No. 1128-(4) of the Safety Division, PSEHB dated November 28, 2017, and "Partial Revision of 'Procedures of Paper Compliance Review and On-site GPSP Surveys of Data for Reexamination and Reevaluation of Drugs '" (Notification No. 1128005 of the Evaluation and Licensing Division, PFSB dated November 28, 2017) were also issued. In June 2018, "Questions and Answers (Q&As) for 'Documents to be Attached to Application for Reexamination of New Prescription Drugs'" (Office Communication dated June 1, 2018) was issued.

## 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. 17** Reevaluation System).

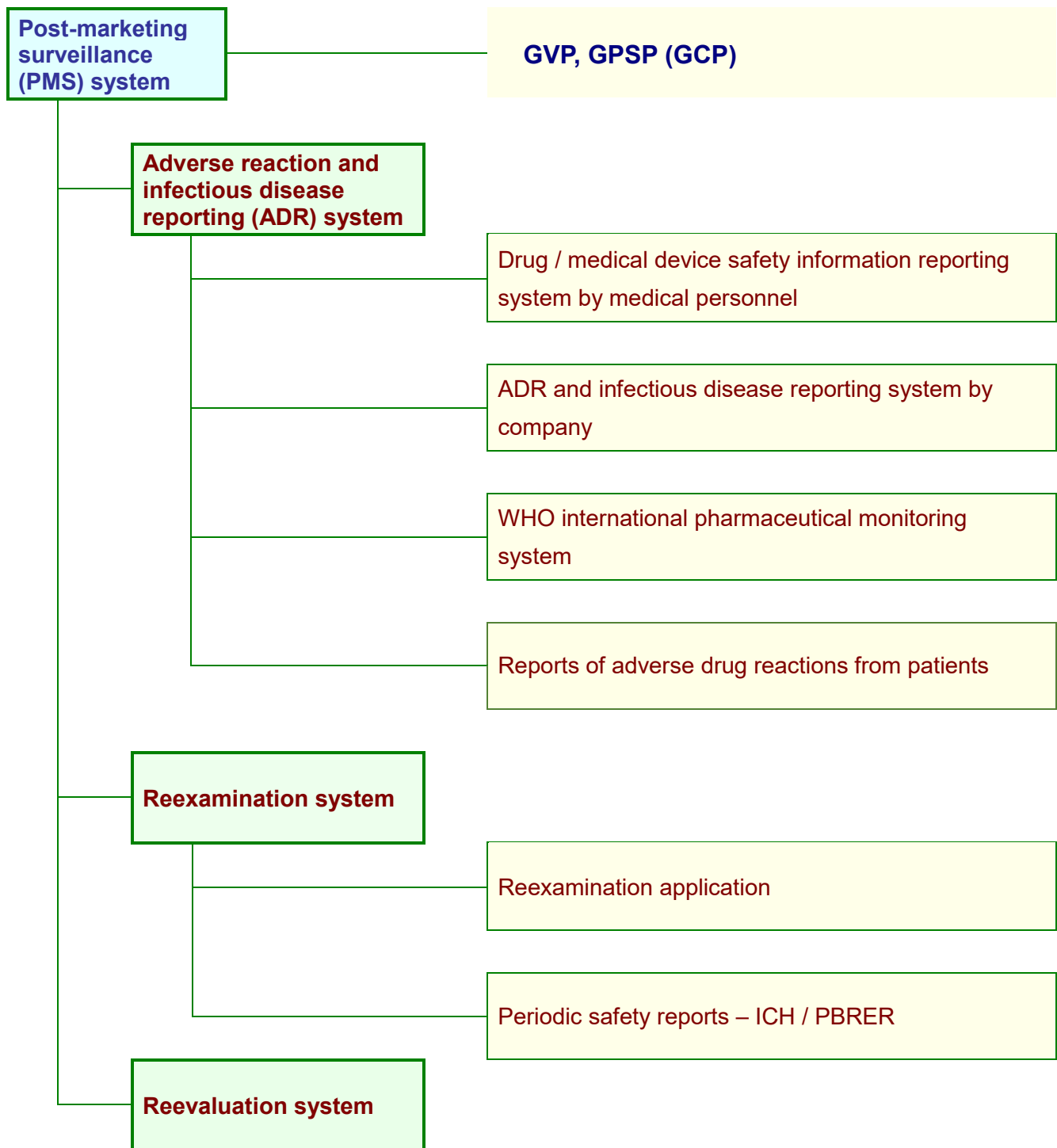
The new reevaluations were designated from February 1990.

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.

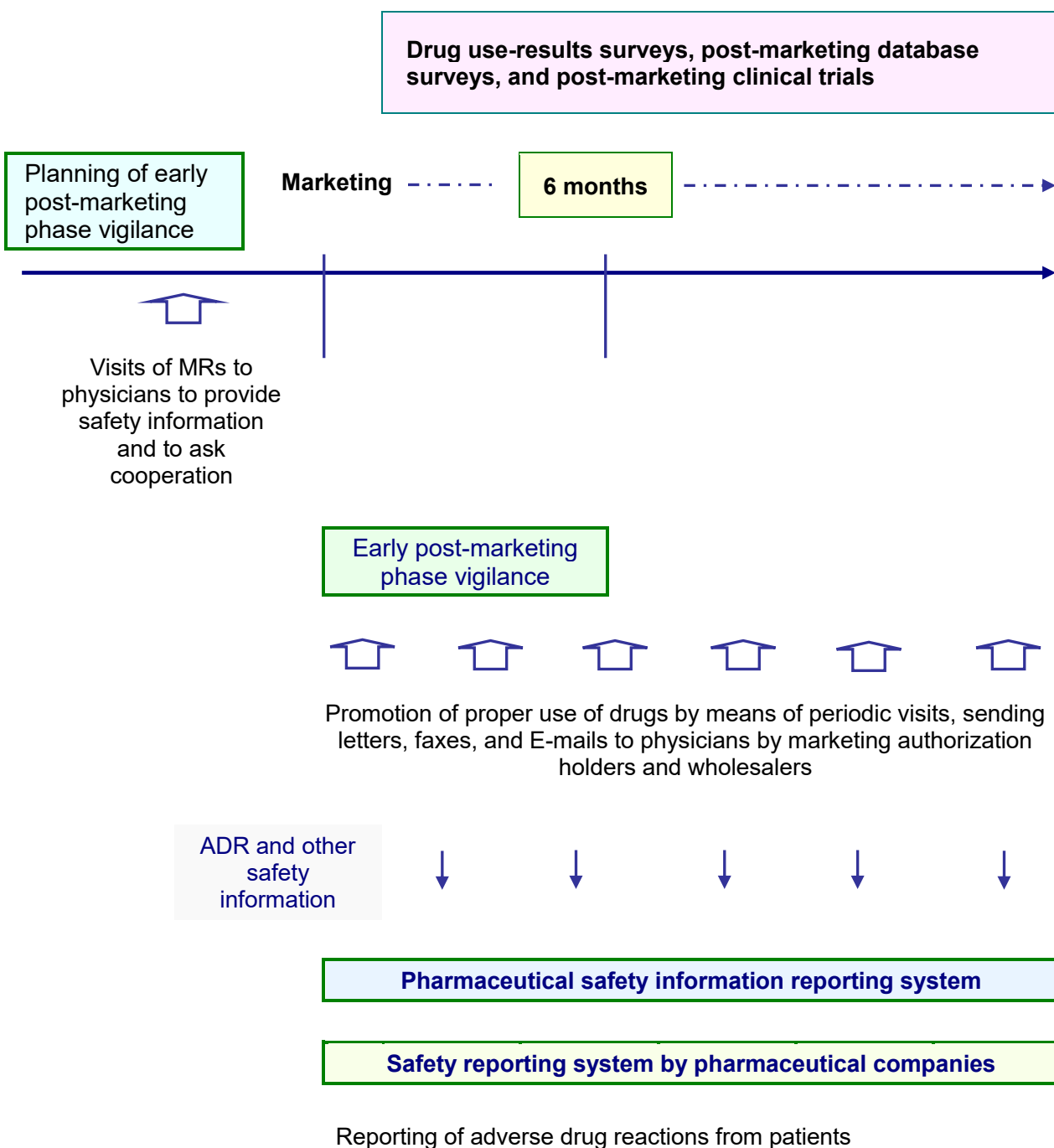
Thereafter, a notification entitled the "Guidelines for Bioequivalence Studies on Generic Drugs" was issued in December 22, 1997 and partially revised on May 31, 2001 (Notification No. 786 of the Evaluation and Licensing Division, PMSB) and on November 24, 2006 (Notification No. 1124004 of the Evaluation 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

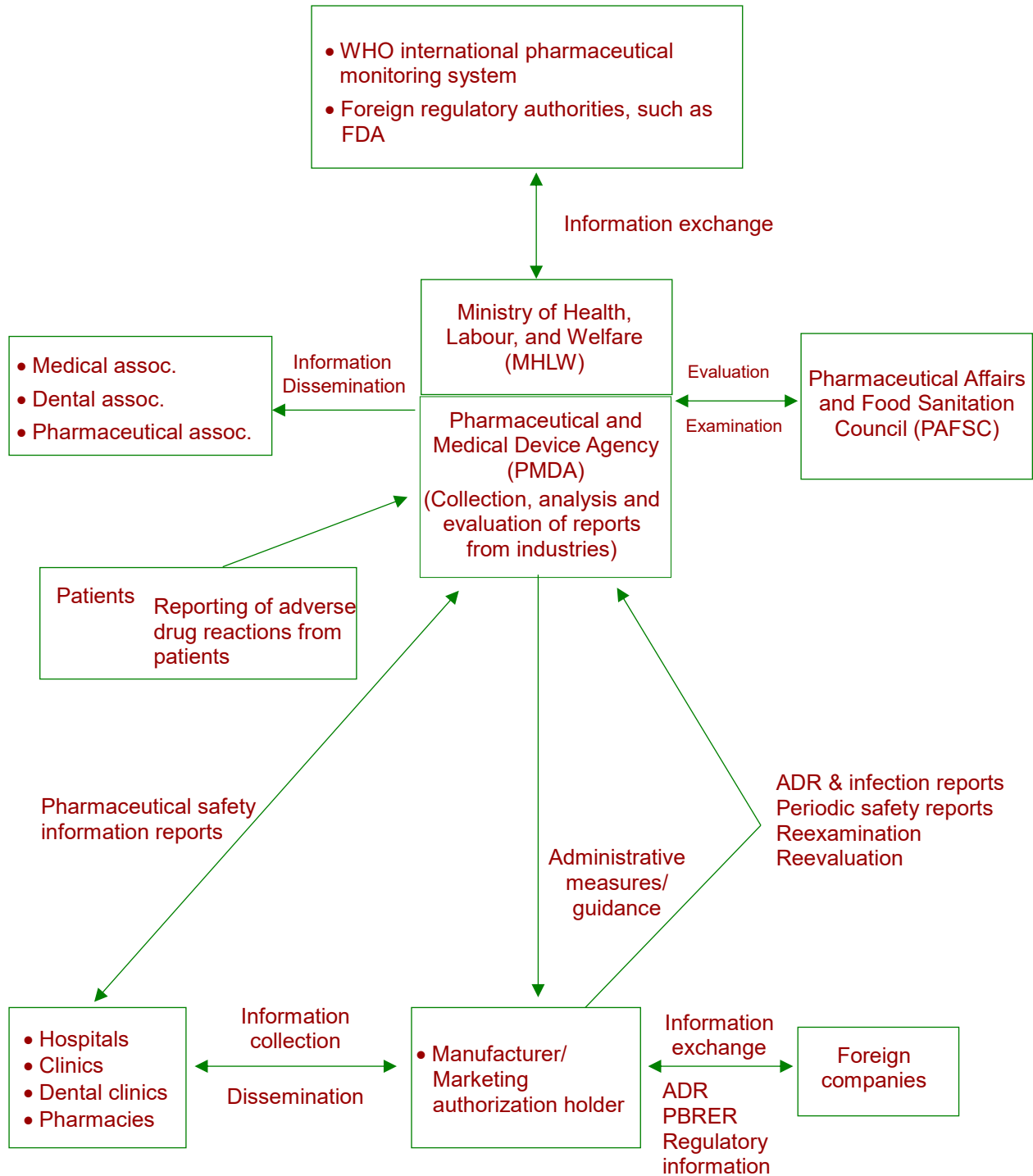
published on March 23, 1999.



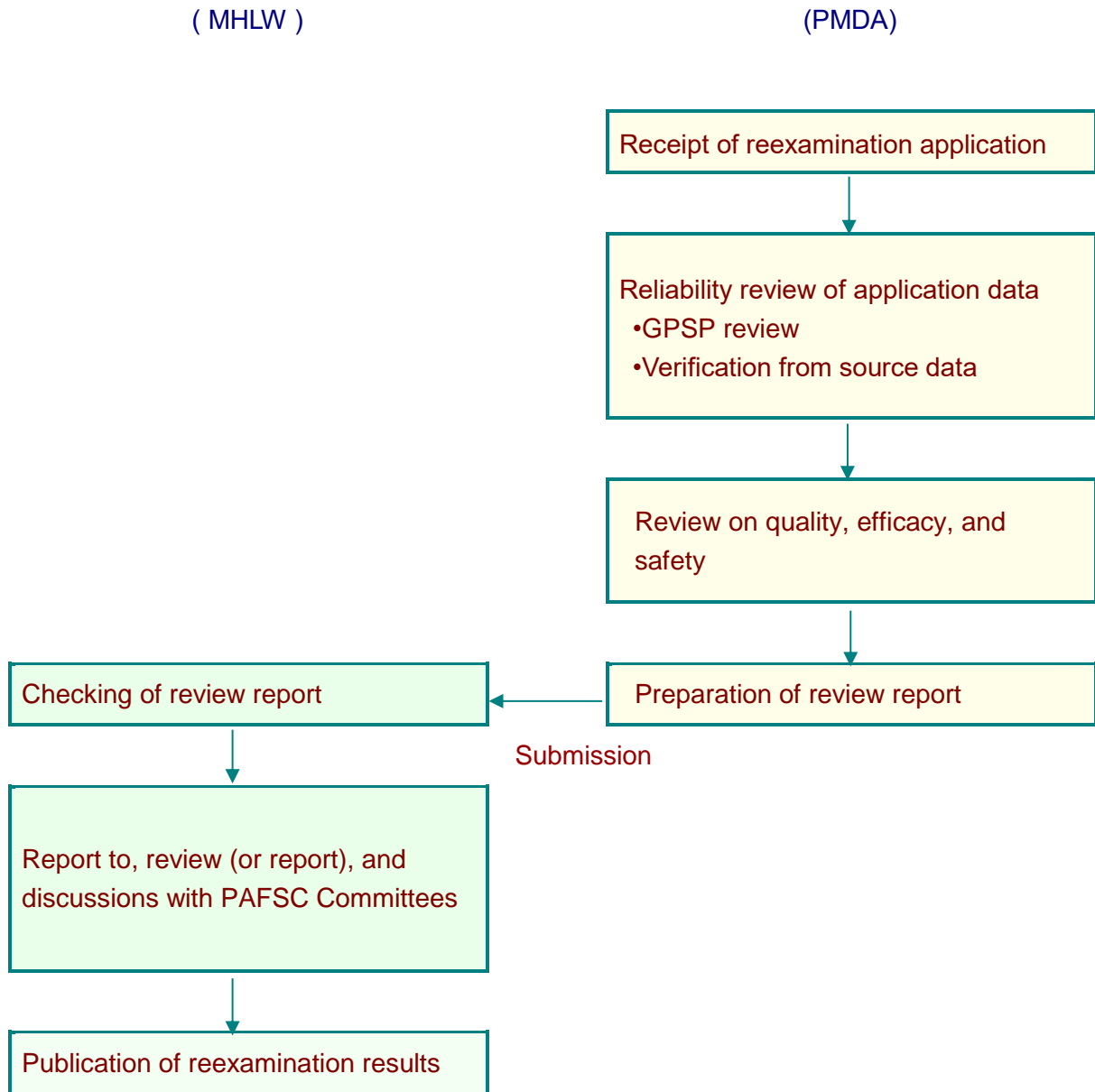
**Fig. 13 Pharmaceutical Post-marketing Surveillance System**



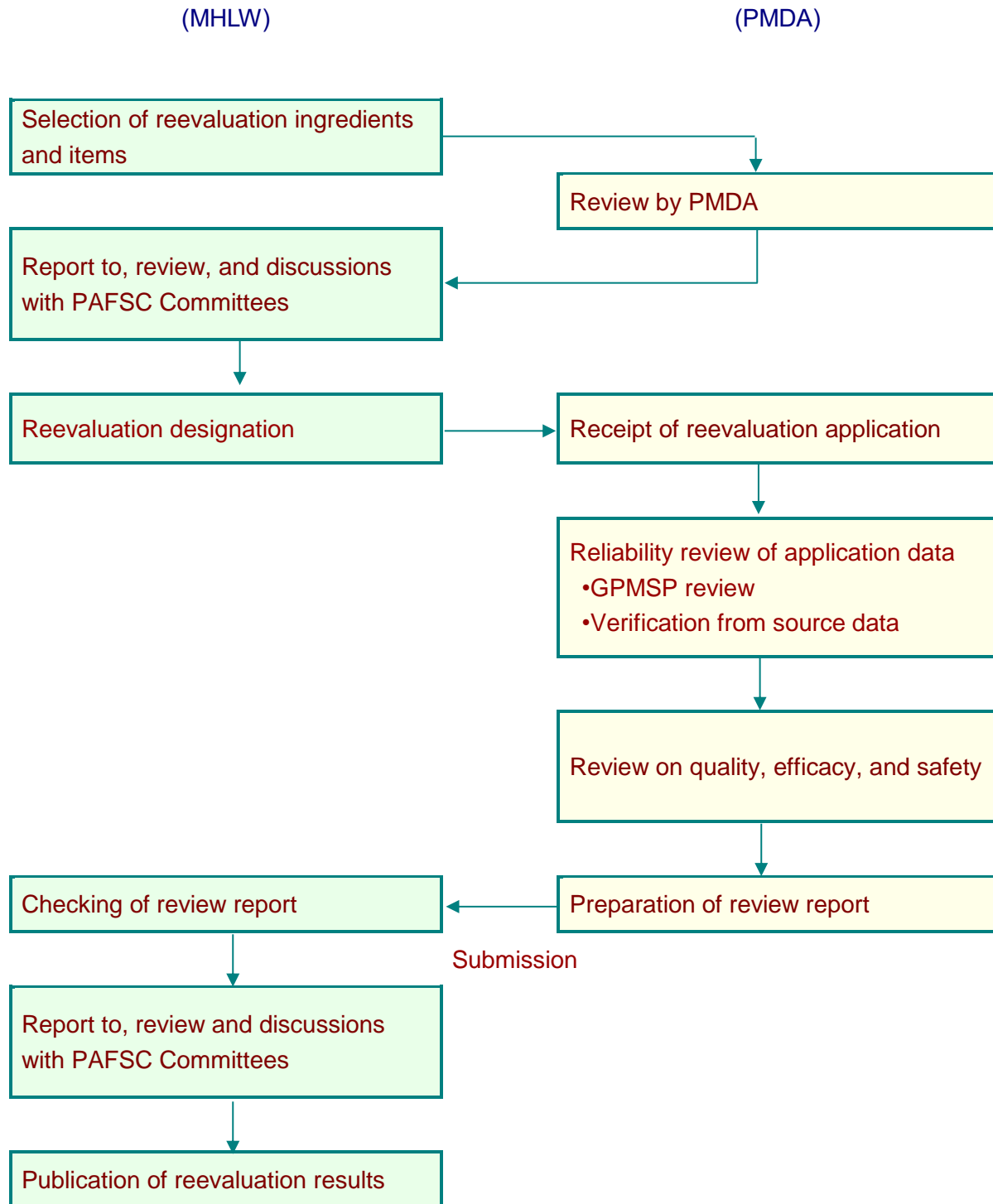
**Fig. 14 Post-marketing Collection and Reporting of Pharmaceutical Safety Information**



**Fig. 15 Collection and Reporting of Pharmaceutical Safety Information**



**Fig. 16 Reexamination System**



**Fig. 17 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 health professionals including 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 actual items to be included, order of their inclusion, and preparation of package inserts, as well as guidelines on the preparation of Precautions for package inserts. Important information on adverse reactions, etc. obtained and evaluated in post-marketing surveillance on product safety must be reflected in package inserts. Because of the limitations on space and the amount of information that can be presented in package inserts, manufacturers and marketing authorization holders may prepare various types of information to supplement the package inserts.

Concerning the format and the contents of the package inserts and precautions for use, 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 dated November 24, 1993 and Notice No. 1445 of the Japan Pharmaceutical Manufacturers Association dated November 21, 1994).

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 (Notification No. 606 of PAB dated April 25, 1997, Notification No. 59 of the Safety Division, PAB dated April 25, 1997, and Notification No. 607 of PAB dated April 25, 1997).

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.

After that, the guidelines on preparation of package inserts were revised and the following notifications were issued to make the package inserts easier to understand and easier to use reflecting the dramatic changes in the situation surrounding medicine, including advancement of medical care, aging of the society, and advancement of IT technology, and proposal of "Review of the Drug Administration for Preventing Recurrence of Drug-induced Sufferings (Final Proposal)" in 2010, and proposals made in Health and Labour Sciences Research from 2008 to 2013 and subsequent examination.

- (1) Guidelines on Preparation of Package Inserts for Prescription Drugs (Notification No. 0608-(1) of the PSEHB dated June 8, 2017)
- (2) Points to Consider Regarding Guidelines on Preparation of Package Inserts for Prescription Drugs (Notification No. 0608-(1) of the Safety Division, PSEHB dated June 8, 2017)

The major points of improvement are reconsideration of the items and structure, including abolishment of the sections of "Relative

contraindications" and "Careful administration," and addition of a section of "Use in patients with special backgrounds," and overall improvement of the information to be entered. The guidelines were applied from April 2019 (the transitional measure period for approved products will be 5 years). Subsequently, Questions and Answers for the Guidelines on Preparation of Package Inserts for Prescription Drugs (Office Communication of the Pharmaceutical Safety Division of MHLW dated January 17, 2019, and Office Communication of Office of Pharmacovigilance I and Office of Pharmacovigilance II of PMDA dated January 17, 2019) were issued.

For generic drugs, "Improvement of Provision of Information in Package Inserts, etc. of Generic Products" (Notification No. 0413-(2) of the Pharmaceutical Evaluation Division, PSEHB and Notification No. 0413-(1) of the Safety Division, PSEHB dated April 13, 2018) was issued to improve provision of information, and the notification requires that the same information as that provided in the package inserts, etc. of the branded products should be provided in the sections of "Pharmacokinetics," "Clinical Studies" and "Pharmacology."

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 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 the package insert includes all of the information before amendment (that is, old package insert printed at the time of amendment), and all of the following requirements are 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 homepage, 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 homepage 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 homepage 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 New Guidance on the Style and Format of Package Inserts

### 1) Basic Rules for Compilation of Package Inserts

- (1) Package inserts and other relevant documents for prescription drugs shall be prepared by the marketing authorization holders of the drugs in accordance with the provisions set forth in each item of Article 52, Paragraph 1 of the Pharmaceutical and Medical Device Act so that the necessary information is provided to healthcare professionals such as physicians, dentists, and pharmacists to ensure the safety of patients taking the drugs and to promote their proper use of drugs.
- (2) Information to be included in package inserts shall be that required for use of the drugs within the scope of approval, as a rule. However, other information that is considered to be important and particularly necessary shall be provided.
- (3) Information shall be described in the order specified in “Sections and their Order” with its section number concerned. When there is no information to be provided in a section, the section

may be omitted, but the section number shall not be moved up.

- (4) The "PRECAUTIONS" shall include the sections from "1.WARNINGS" to "15. OTHER PRECAUTIONS" excluding "3. COMPOSITION AND PRODUCT DESCRIPTION," "4. INDICATIONS" and "6. DOSAGE AND ADMINISTRATION" among those listed "Sections and their Order."
- (5) Even if drugs contain the same ingredient, if their routes of administration vary, the package inserts shall be separately prepared to avoid misunderstanding by users.
- (6) When precautions and adverse reactions markedly differ according to indications or dosage and administration, they shall be separately described.
- (7) Information to be described in the Sections "PRECAUTIONS" and "PRECAUTIONS FOR HANDLING" of generic drugs and bio-similar products shall be, in principle, the same as that of their original drugs and original biological drugs. However, this is not applicable to the case where different information needs to be described according to the differences of each product.
- (8) Deletion or changing of information currently included shall only be done on the basis of sufficient rationale.
- (9) Information shall not be repeated in two or more different sections.
- (10) Related sections should be mutually referred to.
- (11) Description in the sections belonging to "PRECAUTIONS," can be not quantitative but comprehensive (e.g., carefully, periodically, frequently, or as

appropriate) if data is lacking or insufficient.

## 1.2 Headings and Their Sequence in Package Inserts

The layout of a package insert (image) after revision of the guidelines for preparation are shown below. Refer to **Fig. 18** Layout of Package Insert Based on Revised Guidelines for Preparation (Image) for the layout. Information for all sections from "Warning" shall be described with its section number concerned. When there is no information to be provided in a section, the section may be omitted, but the section number shall not be moved up.

### \* Headings and Their Sequence in Package Inserts

- A. Date of preparation and/or revision(s) of the package insert
- B. Standard Commodity Classification No. of Japan, etc.
- C. Approval Number, Date of Initial Marketing in Japan
- D. Storage, Shelf Life
- E. Therapeutic Category
- F. Regulatory Classification (specified biological product, biological product, poisonous substance, deleterious substance, habit-forming drug, prescription drug, etc.)
- G. Name of Product [brand name, non-proprietary name, Japanese Accepted Name (JAN), etc.]
  1. WARNINGS
  2. CONTRAINDICATIONS (This drug should not be administered to the following patients.)
  3. COMPOSITION AND PRODUCT DESCRIPTION
    - 3.1 Composition
    - 3.2 Product Description
  4. INDICATIONS
  5. PRECAUTIONS CONCERNING INDICATIONS
  6. DOSAGE AND ADMINISTRATION
  7. PRECAUTIONS CONCERNING DOSAGE

- AND ADMINISTRATION
8. IMPORTANT PRECAUTIONS
  9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS
    - 9.1 Patients with Complication or History of Diseases, etc.
    - 9.2 Patients with Renal Impairment
    - 9.3 Patients with Hepatic Impairment
    - 9.4 Persons with Reproductive Potential
    - 9.5 Pregnant Women
    - 9.6 Breast-feeding Women
    - 9.7 Pediatric Use
    - 9.8 Geriatric Use
  10. INTERACTIONS
    - 10.1 Contraindications for Co-administration  
(This drug should not be co-administered with the following drugs.)
    - 10.2 Precautions for Co-administration (This drug should be co-administered with caution.)
  11. ADVERSE REACTIONS
    - 11.1 Clinically Significant Adverse Reactions
    - 11.2 Other Adverse Reactions
  12. INFLUENCE ON LABORATORY TESTS
  13. OVERDOSAGE
  14. PRECAUTIONS CONCERNING USE
  15. OTHER PRECAUTIONS
    - 15.1 Information Based on Clinical Uses
    - 15.2 Information Based on Nonclinical Studies
  16. PHARMACOKINETICS
    - 16.1 Blood Level
    - 16.2 Absorption
    - 16.3 Distribution
    - 16.4 Metabolism
    - 16.5 Excretion
    - 16.6 Patients with Specific Backgrounds
    - 16.7 Drug Interactions
    - 16.8 Others
  17. CLINICAL STUDIES
    - 17.1 Clinical Studies for Efficacy and Safety
    - 17.2 Post-marketing Surveillance, etc.
    - 17.3 Others

18. PHARMACOLOGY
  - 18.1 Mechanism of Action
19. PHYSICOCHEMICAL PROPERTIES
20. PRECAUTIONS FOR HANDLING
21. APPROVAL CONDITIONS
22. PACKAGING
23. REFERENCES
24. REFERENCE REQUEST AND CONTACT INFORMATION
25. PRECAUTION CONCERNING HEALTH INSURANCE BENEFITS
26. MARKETING AUTHORIZATION HOLDER, etc.

### 1.3 Precautions

The Precautions are prepared voluntarily by the manufacturer of the drug concerned or under the guidance of the MHLW based on the guidelines in the MHLW notifications listed previously. Information obtained from post-marketing drug use results (clinical experience) surveys, and foreign and domestic case reports and research reports is collected and evaluated, and the Precautions are revised to incorporate the latest data as required. Revisions based on the results of reexaminations and/or reevaluations are undertaken as required.

The headings\* used in the Precautions are as follows. Refer to No. 606 of PAB, Notification No. 0608-(1) of the PSEHB, Notification No. 0608-(1) of the Safety Division, PSEHB, 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 (This drug should not be administered to the following patients.) (in black letters and encased in red.)
- 3) Precautions related to indications (In the event of such precautions, they are entered

under the heading "Precautions" following "Indications" in the package insert.)

- 4) Precautions related to dosage and administration (In the event of such precautions, they are entered under the heading "Precautions" following "Dosage and Administration" in the package insert.)
- 5) Important precautions
- 6) Precautions concerning patients with specific backgrounds
- 7) Drug interactions (Use the formats which are easy to understand, such as tables. Enter non-proprietary name or drug indication classification as drug name.)
  - See MHLW Notification (Notification No. 0723-(4) of the Pharmaceutical Evaluation Division, PSEHB dated July 23, 2018) and the Q&As (Office Communication dated July 23, 2018) for basic way of thinking about provision of information and precautions related to 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
- 8) Adverse reactions (Describe adverse reactions which occur in association with the use of the drug. Describe the incidence based on the results of clinical trials, etc. conducted accurately and objectively.)
  - (1) Clinically significant adverse reactions
  - (2) Other adverse reactions
- 9) Effects on laboratory tests
- 10) Overdosage
- 11) Precautions concerning use
- 12) Other precautions (toxicity obtained in animal studies requiring particular caution, etc.)

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)

## 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.

All ingredients as a rule, except for the ingredients stipulated in the MHLW Notification (Notification No. 0608-(1) of the Safety Division, PSEHB dated June 8, 2017) shall be included in the package insert because of the social responsibility to disclose as much information as possible related to drugs as life-related products. A voluntary agreement of the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ) (FPMAJ Notification No. 170 dated March 13, 2002) should be referred to.

## 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

For prevention of medication accidents related to prescription drugs, Notification No. 935 of the PMSB was issued on September 19, 2000 to specify that brand name should include information of the dosage form and specification or content in addition to brand name (example, XXXX Capsules 25 mg) in principle. By Notification No. 0602009 of the PFSB dated June 2, 2004, relevant companies were requested to take active measures. 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 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 Japanese Society of Generic and Biosimilar 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 Consultation Works Related to Revision of Package Insert**

Package inserts are updated whenever necessary based on collection and evaluation of the information obtained from post-marketing use-results surveys of drugs, case reports in Japan and abroad, and literature reports.

In the meantime, PMDA newly established three consultations regarding package inserts of drugs on December 25, 2017 to improve consultation works for those who desire revision based on the results of post-marketing clinical studies, etc.: "Consultation for preliminary confirmation of revision of drug package insert" and "Consultation for drug package insert revision" in which appropriateness of the revision of the package insert is evaluated based on evaluation

including efficacy, and "Consultation for investigating conformance to evidence data for drug package insert revision" in which reliability of the data on clinical studies which serve as the rationale for the package insert revision is verified.

### **1.8 Information about English Package Insert**

For the purpose of further promotion of harmonization of international regulations and international cooperation in the area of pharmaceutical products and medical devices, it is required to proactively send information regarding pharmaceutical regulations in Japan to the international society. Concerning package inserts, "Guidance on English Translating of Package Inserts for Prescription Drugs" targeting the package inserts prepared based on the new instructions was compiled to facilitate English translation and provision of information (Notification No. 0329-(8) of the Safety Division, PSEHB dated March 29, 2019). This Guidance lists "drugs approved in Japan for the first time in the world," "drugs with a new mechanism of action," "drugs approved based on multi-regional joint study data," "drugs for which English translation of the review report is disclosed on the website of PMDA," "drugs for which English translation of review reports is publicized," and "other drugs for which provision of information to foreign countries is useful" as the drugs for which English translation of package inserts is recommended.

## **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.

- Outline of Prescription Pharmaceutical Product Information

- Pharmaceutical Interview Forms
- Commentaries on "Precautions" in package inserts of new drugs

New drugs that are approved after October 2001 are marked with a logo commonly adopted by the pharmaceutical industry indicating that the drug is subject to early post-marketing phase vigilance for such a period of time as specified in labeling (6 months after the start of marketing).

## 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 promote proper use of their drugs. The material is available in two types: the general outline version showing 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.

The Outline of Prescription Pharmaceutical Product Information is prepared on the basis of the "Guidelines for Preparation of Outlines of Prescription Pharmaceutical Product Information" (prepared by the Japan Pharmaceutical Manufacturers Association [JPMA], developed in September 2015). To ensure consistency of the content with that of the package insert, attention should be paid to the JPMA Code of Practice.

In addition, the Outline of Prescription Pharmaceutical Product Information is internally reviewed by the pharmaceutical company and voluntarily reviewed by JPMA. Because administrative disciplinary actions were taken in 2014 and 2015 against the advertisement violating the law (Article 66) that prohibits false or exaggerated advertisements, the system to strengthen the internal

review system of pharmaceutical companies was introduced in 2016, such as placement of the responsible organization of the internal review outside of the sales division and involvement of a third party in the internal review in principle. For the voluntarily review of JPMA, expansion of the scope and introduction of the electronic review system were conducted in 2017.

## 2.2 Pharmaceutical Interview Forms (IF)

In medical settings, physicians and pharmacists, etc. collect detailed information about drugs through interviews with medical representatives (MR) of pharmaceutical companies and utilize such information in daily works. Pharmaceutical Interview Forms (IFs) used to specify questions to be asked for such purposes, but in order to reduce the burden on pharmacists and MRs, the replies (detailed information) to the questions are already entered, and the IF are supplied to health professionals from pharmaceutical company as academic material to be used in explanations and discussions concerning the product.

The Japanese Association of Hospital Pharmacists published new preparation guidelines in November 2018, and IFs are being prepared in the new format for new drugs approved from April 2019.

"Guidelines for preparation of interview forms for generic products" was issued by the Japan Generic medicines Association for generic products. The guidelines mainly introduce the examples of the sections describing the data which are deemed to be unique to generic products, such as the results of bioequivalence studies, elution studies, and stability studies, as well as the procedures for describing these issues. The guidelines are used as the standards for preparation of IF together with the guidelines of the Japanese Association of Hospital Pharmacists.

Basically, IFs are provided in electronic media of PDF files. However, they can be searched on the

website of PMDA together with the package inserts.

### 2.3 Commentaries on "Precautions" in Package Inserts of New Drugs

Commentaries are prepared by marketing authorization holders of drugs for detailed explanation of "Precaution" when a new drug is launched.

Reflecting the notification of revision of the instructions for package inserts and precautions in April 1997, a guide to preparation of the commentaries was published (Notification No. 88 of the Safety Division, PAB dated June 27, 1997) and commentaries have been prepared for the new drugs launched after that.

## 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 instructions for 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)
- Instructions for 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, revision of precautions for use, etc., 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 PMDA homepage "Consultation regarding examination/implementation of safety measures (for companies)."

<http://www.pmda.go.jp/safety/consultation-for-mah/0007.html>

<http://www.pmda.go.jp/files/000144200.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. 19** and **Fig. 20**).

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 homepage for consultations on revision, etc. of package inserts applied for by companies and procedures for applications for other consultations.

<http://www.pmda.go.jp/safety/consultation-for-mah/0001.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, PFSSB 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, etc. 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 homepages. If the marketing authorization holder knows patient groups that use the products concerned, the safety information should be distributed to such groups.

The information will also be placed in the homepage of the PMDA together with the safety flash report (blue letters) in the following section.

Japanese:

<https://www.pmda.go.jp/safety/info-services/drugs/calling-attention/esc-rsc/0001.html>

English:

<https://www.pmda.go.jp/english/safety/info-services/drugs/esc-rsc/0001.html>

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 homepage 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 Pharmaceutical Safety Division of Pharmaceutical Safety and Environmental Health Bureau 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, PFBSB 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 homepages. 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 homepage 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 Pharmaceutical Safety Division of Pharmaceutical

Safety and Environmental Health Bureau when distribution has been completed as specified by the office.

**3.3 Commentaries on "Precautions" in Package Inserts of New Drugs**

As a rule, MRs distribute the commentaries to medical institutions before new drugs are used in medical practice in order to assure proper use of new drugs.

**3.4 Distribution of Information by 'Notices of Revision of Precautions'**

The marketing authorization holder must prepare Notices of Revision of Precautions specifying the contents of revision after any revision of the precautions for use, and distribute it to medical institutions (Notification No. 1031-(1) of the Safety Division, PFSB dated October 31, 2014, and Notification No. 129 of the JPMA dated February 26, 2015).

**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 PMDA beforehand).

**2) Format and content**

The paper must be not 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 Director of the Safety Division of PFSB or the decision to make a voluntary revision.

### 3.5 Dissemination of Information for Drugs That Have Completed Reexamination or Reevaluation

Once the reevaluation results and reexamination results are available, the marketing authorization holder of the drug concerned disseminated information by preparing a "Notice of Reevaluation Results" and "Notice of Reexamination Results" as required, which they distribute to medical institutions. The FPMAJ compiles all of the reevaluation results and publishes a "Notice of Prescription Drug Reevaluation Results" in the journals of the Japan Medical Association, Japan Dental Association, and Japan Pharmaceutical Association.

### 3.6 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 homepage for information on drugs, 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 has been published since June 1973 and is available and regularly updated at the following PMDA homepage.

Japanese:

<http://www.pmda.go.jp/safety/info-services/drugs/calling-attention/safety-info/0043.html>

English:

<https://www.pmda.go.jp/english/safety/info-services/drugs/medical-safety-information/0002.html>

### 3.7 Dissemination of Information by Drug Safety Update

Drug Safety Update (DSU) is published for prescription drugs and the DSU of the OTC version (Information of revisions of precautions for use for OTC drugs) is published for non-prescription drugs under the supervision of the Ministry of Health, Labour and Welfare as the information journals which summarize and comprehensively and promptly convey information on revisions of the Precautions evaluated by the Ministry of Health, Labour and Welfare.

The Society of Japanese Pharmacopoeia and the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ) have been jointly editing and publishing the DSU, since September 1992 (10 times per year) (published by the FPMAJ since Issue No. 128 dated April 2004). The journal is distributed by mail to medical institutions nationwide including approximately 10,000 hospitals, 90,000 clinics and 60,000 dental clinics, as well as about and 50,000 pharmacies and dispensing facilities within one month after printing.

The DSU of the OTC version has been edited and published by the Japan Federation of Self-Medication Industries since November 2015.

These journals are available immediately after publication at the following the PMDA homepage.

<http://www.pmda.go.jp/safety/info-services/drugs/calling-attention/dsu/0001.html>  
<http://www.pmda.go.jp/safety/info-services/drugs/calling-attention/otc-dsu/0001.html>

### 3.8 Medical Guides for Patients

Marketing authorization holders for drugs will prepare medical guides for patients for obtaining marketing approvals, etc. of drugs if considered necessary by the Ministry of Health, Labour and Welfare. To promote the accurate understanding of patients, etc. regarding prescription drugs to help early detection of serious adverse reactions, the documents explain the matters that are particularly important to know when using drugs based on the package insert with simple expressions (Notification No. 0630001 of PFSB dated June 30, 2005, Notification No. 0331-(1) of the Safety Division, PFSB dated March 31, 2014, and Notification No. 0331-(8) of the Compliance and Narcotics Division, PFSB).

### 3.9 Manual for Handling Disorders due to Adverse Drug Reactions

The Ministry of Health, Labour and Welfare started the “Project to Take Comprehensive Measures for Serious Adverse Reactions” in 2005 with the aim of making the transition from the reactive safety measures to predictive and preventive safety measures. A manual for handling disorders due to adverse drug reactions, which comprehensively cover the methods of treatment and discrimination to be utilized by patients as well as physicians, pharmacists, nurses, etc. in clinical settings for adverse reactions that need to be given high priority judging from the seriousness has been created in cooperation with experts, etc. in related academic associations. The revisions and updates reflecting the latest findings will be made by the end of FY2020.

[https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou\\_iryuu/iyakuhin/topics/tp061122-1.html](https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryuu/iyakuhin/topics/tp061122-1.html).

## 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.

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 risk management plan (RMP), 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.

Standard Generalized Markup Language (SGML) was adopted as the basic format for information about package inserts of prescription drugs, but was changed to Extensible Markup Language (XML) from April 2019 to cope with the revised instructions for package inserts and to improve the convenience of the package insert search system of PMDA's HP.

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 for information on drugs, to medical personnel who have registered their e-mail address with the Agency. <http://www.pmda.go.jp/safety/info-services/medi-navi/0006.html>

## 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 excipients for prescription drugs, refer to Section 1.4 on 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 homepage (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. 18 Layout of Package Insert Based on Revised Guidelines for Preparation (Image)**

\*\* Revised: Month, 20XX (Version XX, ○ ○)

Name of therapeutic category

Storage:  
Expiration  
date:Nonproprietary name, standard name,  
or name designated on Japanese Pharmacopoeia

Regulatory classification

Prescription drug <sup>Note)</sup>**Brand Name**

Name of Product

Note) Caution : Use under prescription from a physician, etc.

Standard Commodity  
Classification No. of Japan

	●mg	▲mg
Approval No.		
Date of initial marketing in Japan	XX, 20XX	XX, 20XX

**1. Warning****2. Contraindications** (This product is contraindicated in the following patients.)**3. Composition and description****3.1 Composition**

&lt;Table format &gt;

**3.2 Description of drug product**

&lt;Table format &gt;

**4. Indications****5. Precautions related to indications****6. Dosage and administration****7. Precautions related to dosage and administration****8. Important precautions****9. Precautions related to patients with special backgrounds****9.1 Patients with complications or disease history****9.2 Patients with renal dysfunction****9.3 Patients with hepatic dysfunction****9.4 Persons with reproductive ability****9.5 Pregnant women****9.6 Lactating women****9.7 Pediatric use****9.8 Elderly use****10. Drug interactions****10.1 Contraindications for coadministration** (This product should not be coadministered with the following drugs.)

Drug name	Signs, symptoms and treatment	Mechanism and risk factors

**10.2 Precautions for coadministration** (XX should be administered with care when coadministered with the following drugs.)

Drug name	Signs, symptoms and treatment	Mechanism and risk factors

**11. Adverse reactions****11.1 Clinically significant adverse reactions**

11.1.1○○

**11.2 Other adverse reactions**

	≥○%	0.1 to ≤○%	≤ 0.1%	Unknown frequency

**12. Effects on laboratory tests****13. Overdosage****14. Precautions concerning use****15. Other precautions****15.1 Information based on clinical use****15.2 Information based on nonclinical studies****16. Pharmacokinetics****16.1 Blood concentration****16.2 Absorption****16.3 Distribution****16.4 Metabolism****16.5 Excretion**

16.6 Patients with special backgrounds

16.7 Drug interactions

16.8 Others

17. Clinical studies

17.1 Studies on efficacy and safety

17.2 Post-marketing surveillance, etc.

17.3 Others

18. Pharmacology

18.1 Mechanism of action

18.2 ○○ action

19. Physicochemistry

20. Precautions in handling

21. Approval conditions

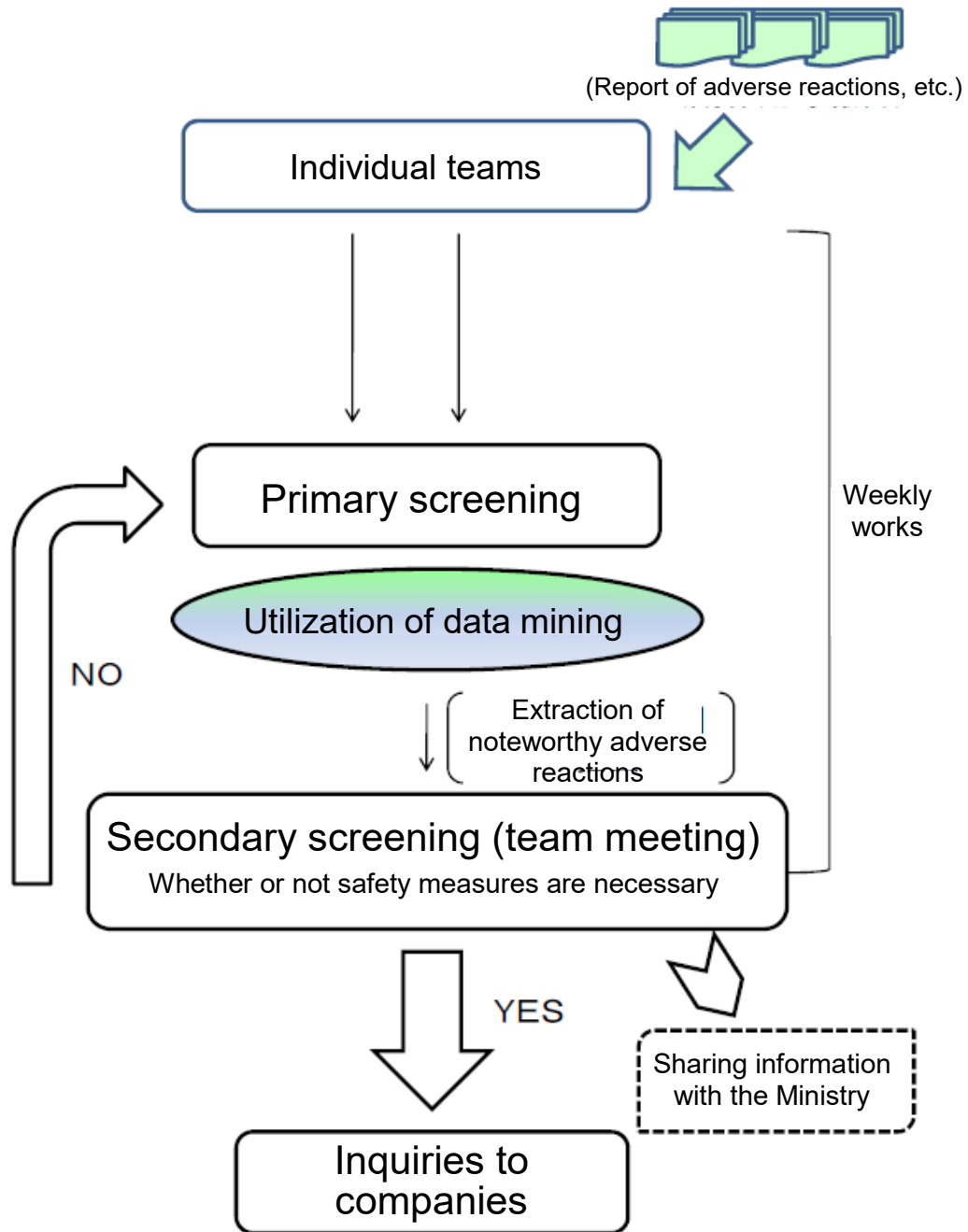
22. Packaging

23. References

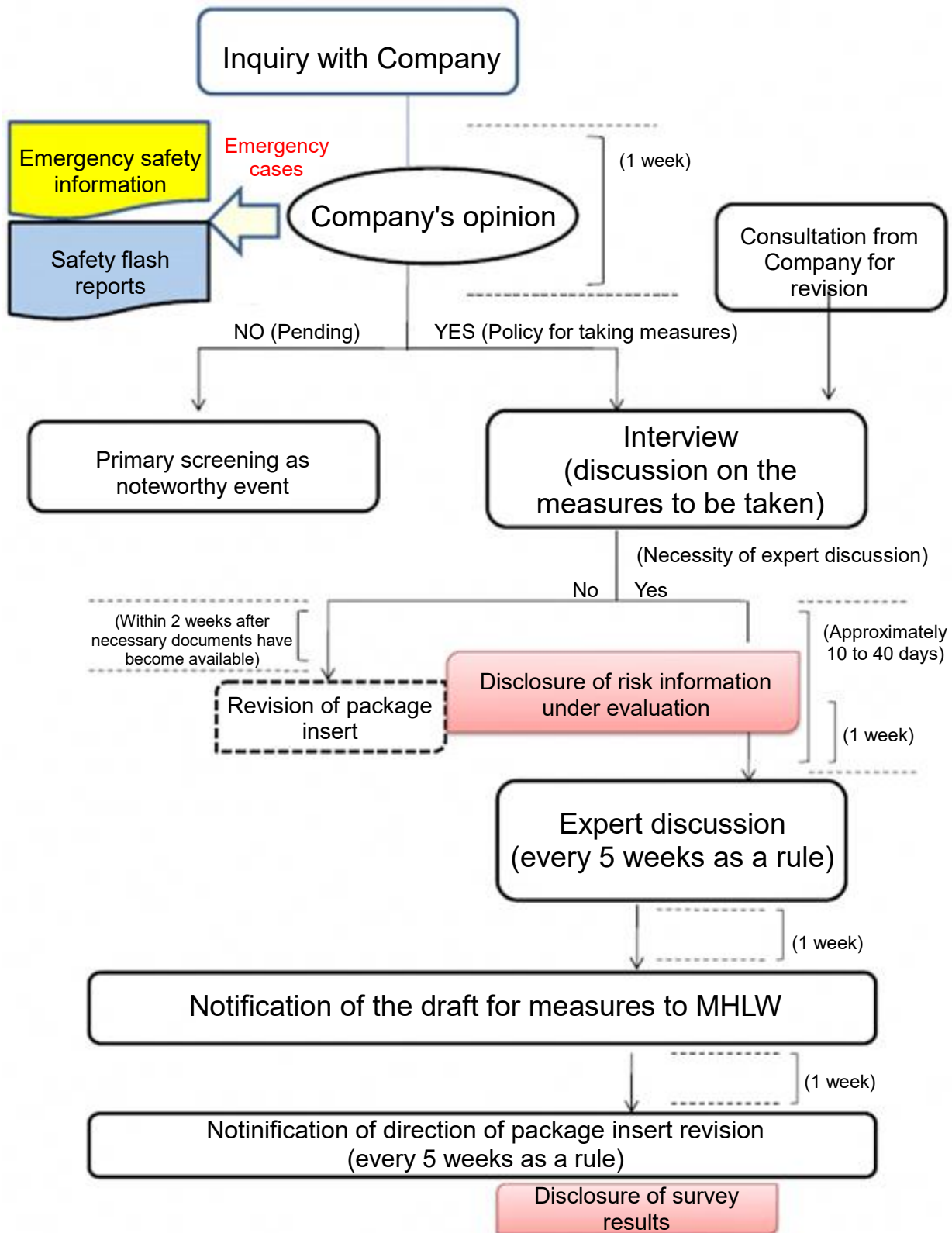
24. Request for literature should be made to:

25. Precautions related to insurance benefits

26. Manufactured and distributed by:



**Fig. 19 Standard Procedures for Revision of Package Insert at PMDA (1)**



**Fig. 20 Standard Procedures for Revision of Package Insert at PMDA (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.

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 on the basis of Article 76, Item 2 of the Health Insurance Act (Act No. 70, 1918) and Article 71, Item 1 of the Act on Assurance of Medical Care for Elderly People (Act No. 80, 1982), and according to the Calculation Method of Medical Fees (Public Notice No. 59 of the Ministry of Health, Labour and Welfare in 2008) (partially revised on August 19, 2019 by Public Notice No. 85 of the Ministry of Health, Labour and Welfare).

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 changed

to 4,955 (number of payment classification: 2,462) in April 2018 and forecast of the application of this billing system has been extended to 1,730 hospitals (approximately 490,000 beds) in April 2018.

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).

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.

At the same time, 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. Later in 2014, a new rule for an additional indication of an orphan drug was added to ensure that repricing shall be considered when the sales of the orphan drug increases at least 10 times than

originally expected and exceeds 10 billion yen. In 2016, while conflicting topics of evaluation of innovative drugs and maintenance of nationwide comprehensive health insurance system were being discussed, repricing for market growth was applied in an exceptional manner as a measure of reconciliation when the annual sales exceeded 100 billion yen but not 150 billion yen and reached at least 1.5 times of the originally expected sales, and when the annual sales exceeded 150 billion yen and reached at least 1.3 times of the originally expected sales. Thus, special repricing of drugs was implemented.

Reflecting the issues of unapproved drugs and the time-lag in new drug approval, a new “premium system for the promotion of innovative drug discovery and resolution of off-label use” was applied to the new drugs without generic drugs as of 15 years after listing (discrepancy shown in the drug price survey is smaller than the mean discrepancy for all products) after discussion at the Central Chuikyo, and the pilot operation was continued until 2016. In April 2018, a rule was established to strictly select the target products in view of innovativeness and usefulness, and to gradually set the premium according to the status of research and development by companies. On the other hand, the evaluation of cost-effectiveness of drugs and medical devices was introduced on a trial basis in April 2016 and was implemented on a full scale in April 2019.

In addition, the rule of special lowering (Z2) adopted from 2014 was reconsidered for long-listed products (branded products with generic products), and a new rule was introduced to classify the products with the generic product replacement rate of 80% or more (G1 product) and those with the rate of less than 80% (G2 product) as of 10 years after the first listing of a generic product and to gradually lower each drug price to the level of the drug price of generic products.

Furthermore, to ensure stable supply of drugs with high medical needs covered by health insurance, the drug price maintenance system for basic drugs was

to be implemented as a pilot operation. This system may be applied to drugs meeting all of the following requirements (except for sufficiently profitable drugs):

- [1] The drug has an established position in clinical settings and is clearly known to be widely used in clinical practices.
- [2] Of the concerned already listed drug as well as all similar drugs with the same composition and dosage form category as those of the former, at least one drug has been on a NHI Price List for 25 years or longer.
- [3] If there are similar drugs with the same composition and dosage form category as those of the concerned already listed drug, the mean discrepancy of the similar drugs including the concerned already listed drug between the NHI price and current market price does not exceed that of all the listed drugs.
- [4] The discrepancy of the concerned already listed drug between the NHI price and current market price does not exceed the mean discrepancy of all the already listed drugs.

The products previously subjected to repricing due to unprofitable sales and the drugs against pathogens serving the medical platform for years and medical narcotics were added to the target products in the revision of the NHI price list in 2016, and the drug efficacy classifications, etc. which showed discrepancy of 2% or less 3 times in the past were added in the revision in 2018. The pilot operation is still continued.

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. 0819-2 of the Health Insurance Bureau dated August 19, 2019, "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 covers 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 >

New drug price = weighted average value of market price in survey x (1 + consumption tax rate) + current reimbursement price x R/100 (however, the new price shall not exceed the current reimbursement price).

This pricing formula is applied to products that are sold in large quantities, and the prices for drugs sold in lower quantities are adjusted using the revision rate for drugs of the same class and same indication.

From 1992, prices were revised as described above 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 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 was institutionalized in 2018.

Drug prices listed in the NHI Price List were revised to include consumption tax because the consumption tax rate was raised to 8% in April 2014 and 10% in October 2019.

The results of reimbursement price revisions from 1967 through 2019 and the annual changes in the drug expenses in 1993 and afterwards and the estimated divergence rate are shown in [Table 14](#) (History of Reimbursement Price Revisions) and [Table 15](#) (Annual Changes in Drug Expenses and Estimated Divergence Rate).

## 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 10-20% 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 16](#) (Requirements for Applying Premiums).

Furthermore, it has been decided to apply premium to the drug price itself from the point of view of evaluation of innovation in drug pricing by cost calculation although some adjustment is made depending on the level of disclosure.

A special calculation formula was introduced for new combination drugs (oral preparations): as a rule, the price is set at 80% of the total of prices of individual drugs.

To assure transparency of the pricing system, drug pricing formulas were made public in March 2000 (the most recent revision is given in Notification No. 0819-2 of the Health Insurance Bureau dated August 19, 2019, “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. 0329-5 of the Health Policy Bureau dated March 29, 2019, “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. 0207-(2) of the Economic Affairs Division, Health Policy Bureau dated February 7, 2018.

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. 21** (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. 0819-2 of the Health Insurance Bureau dated August 19, 2019, “Drug Pricing Standards.”) Procedures for calculation of reimbursement prices were specified in detail in September 2000 (most recent revisions: Notification No. 0329-5 of the Health

Policy Bureau dated March 29, 2019, “Handling of Entries of Prescription Drugs in the NHI Price List” and Notification No. 0207-(2) of the Economic Affairs Division, Health Policy Bureau dated February 7, 2018 “Method for Submission of Requests for Entry in the NHI Price List for Prescription Drugs”).

- 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 0.5. The factor is 0.4 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.

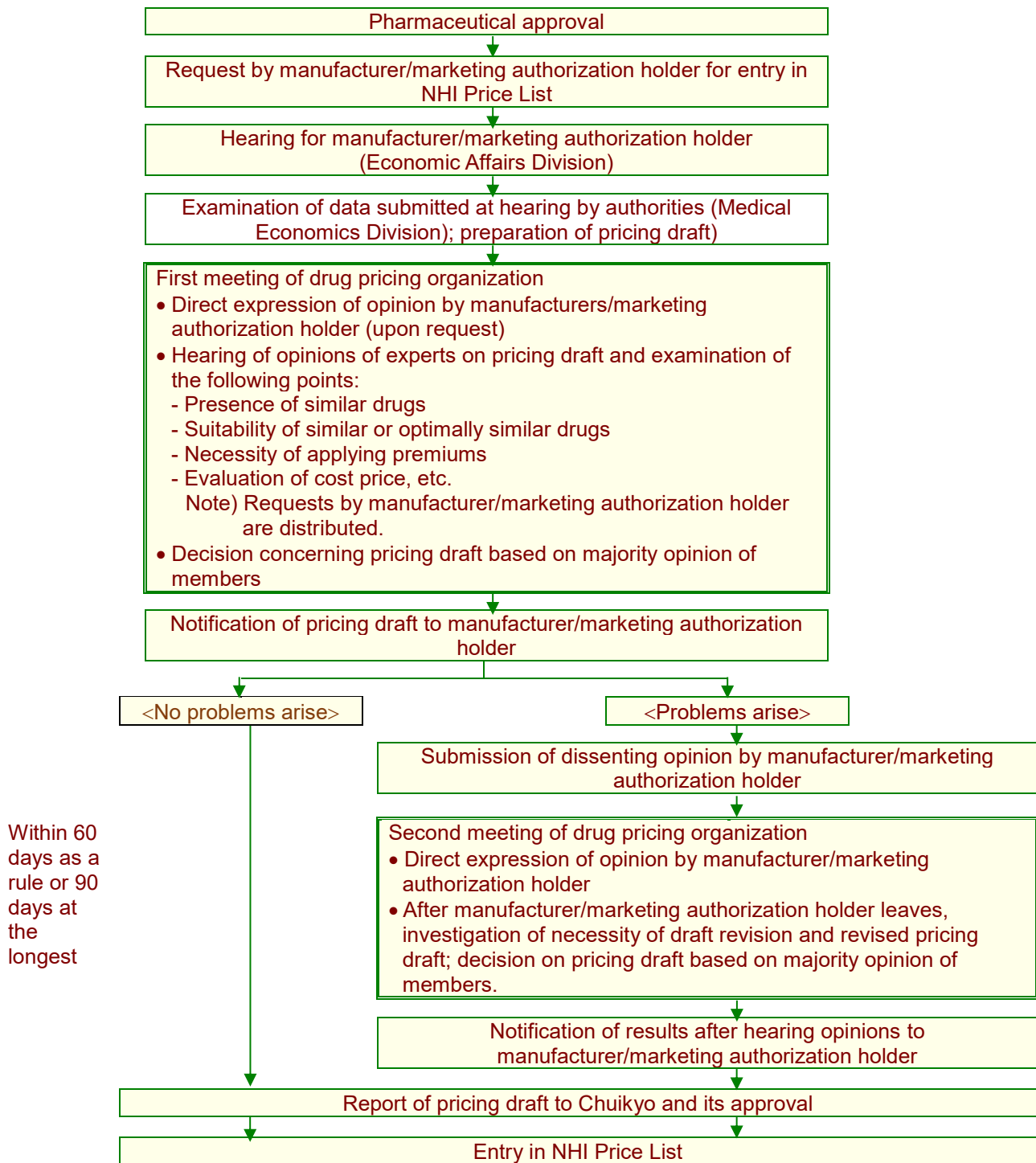
A special formula was introduced for biosimilar products. A premium (maximally 10/100 of the standard) is added to the standard price (the factors are 0.7 and 0.6, respectively) depending on qualitative and quantitative data obtained from clinical trials.

## 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 “Special Committee 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 “Pharmaceutical Development Support Center” in May 2009 to improve regulatory systems and structures to support the development of such

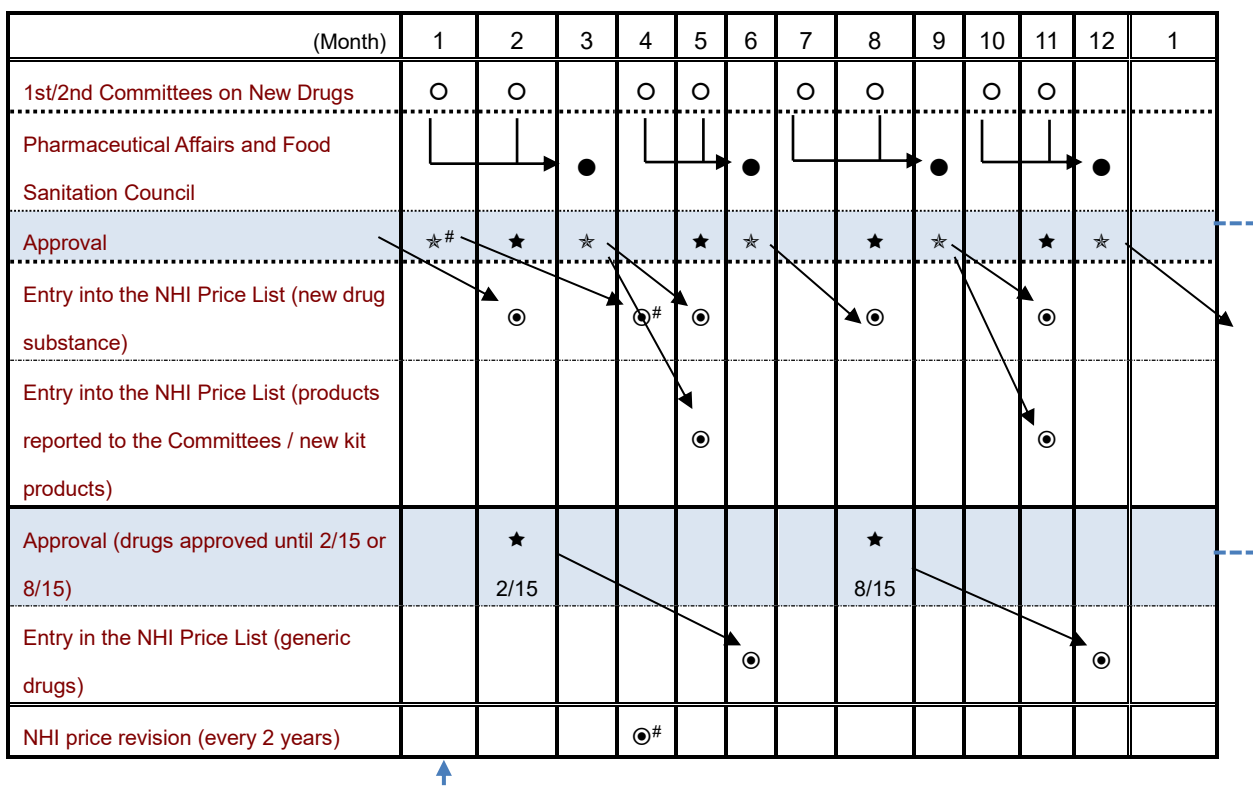
drugs and new indications by pharmaceutical companies. The Chuikyo also joined the support and they discussed potential approaches and introduced the new “Premium System for the Promotion of Innovative Drug Discovery and Resolution of Off-Label Use” in April 2010 on a trial basis.

In addition, the Ministry established “Special Committee to investigate Unapproved Drugs and Off-Label Use of Drugs Urgently Required for Healthcare” 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, that committee has been evaluating individual drugs and indications to determine if they are worthy to be reimbursed by the National Health Insurance System before 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.



**Fig. 21 Reimbursement Pricing Flow-sheet for New Drugs**

- (Note 1) The parts in the double box    show parts involving the drug pricing organization
- (Note 2) Time clock (agreed on at MOSS conferences)  
Entry in price list 4 times per year. Listing within 60 days as a rule or 90 days at the longest provided that there are no further problems with the pricing draft.



- 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. 22 Correlation between the Time of Marketing Approval Based on Pharmaceutical Affairs Law and the Time of Entry in the NHI Price List**

**Table 14 History of Reimbursement Price Revisions**

Revision date	Revision category	Number of products listed	Revision rate		Remarks
			Based on drug cost	Based on medical expenses	
1967.10.1	Complete	6,831	▲10.2%	–	
1969.1.1	Complete	6,874	▲5.6%	▲2.4%	
1970.8.1	Complete	7,176	▲3.0%	▲1.3%	
1972.2.1	Complete	7,236	▲3.9%	▲1.7%	
1974.2.1	Complete	7,119	▲3.4%	▲1.5%	
1975.1.1	Complete	6,891	▲1.55%	▲0.4%	
1978.2.1	Complete	13,654	▲5.8%	▲2.0%	Listing by brand
1981.6.1	Complete	12,881	▲18.6%	▲6.1%	
1983.1.1	Partial	16,100 ( 3,076)	▲4.9%	▲1.5%	81% bulk line system
1984.3.1	Complete	13,471	▲16.6%	▲5.1%	
1985.3.1	Partial	14,946 ( 5,385)	▲6.0%	▲1.9%	
1986.4.1	Partial	15,166 ( 6,587)	▲5.1%	▲1.5%	
1988.4.1	Complete	13,636	▲10.2%	▲2.9%	Revised bulk line system
1989.4.1	Complete	13,713	+2.4%	+0.65%	Increase by the amount equivalent to consumption tax
1990.4.1	Complete	13,352	▲9.2%	▲2.7%	
1992.4.1	Complete	13,573	▲8.1%	▲2.4%	Weighted average fixed price range system R15
1994.4.1	Complete	13,375	▲6.6%	▲2.0%	R13
1996.4.1	Complete	12,869	▲6.8%	▲2.6% (Including partial change of the drug price calculation system and material costs, etc.)	R11
1997.4.1	Complete	11,974	▲4.4% In addition, the amount equivalent to consumption tax +1.4%	▲1.27% In addition, the amount equivalent to consumption tax +0.4%	R10 (Long-listed product R8)
1998.4.1	Complete	11,692	▲9.7%	▲2.7%	R5 (Long-listed product R2)
2000.4.1	Complete	11,287	▲7.0%	▲1.6%	Adjustable range 2%
2002.4.1	Complete	11,191	▲6.3%	▲1.3%	Adjustable range 2% (lowering for branded product by a fixed rate)
2004.4.1	Complete	11,993	▲4.2%	▲0.9%	Adjustable range 2% (lowering for branded product by a fixed rate)

Revision date	Revision category	Number of products listed	Revision rate		Remarks
			Based on drug cost	Based on medical expenses	
2006.4.1	Complete	13,311	▲6.7%	▲1.6%	Adjustable range 2% (lowering for branded product by a fixed rate)
2008.4.1	Complete	14,359	▲5.2%	▲1.1%	Adjustable range 2% (lowering for branded product by a fixed rate)
2010.4.1	Complete	15,455	▲5.75%	▲1.23%	Adjustable range 2% (lowering for branded product by a fixed rate)
2012.4.1	Complete	14,902	▲6.00%	▲1.26%	Adjustable range 2% (lowering for branded product by a fixed rate)
2014.4.1	Complete	15,303	▲5.64% In addition, the amount equivalent to consumption tax +2.99%	▲1.22% In addition, the amount equivalent to consumption tax +0.64%	Adjustable range 2% (lowering by a fixed rate for branded products for which replacement by generic products is slow)
2016.4.1	Complete	15,925	▲5.57%	▲1.22%	Adjustable range 2% (lowering by a fixed rate for branded products for which replacement by generic products is slow) In addition, ▲0.19% for repricing for market growth, and ▲0.28% for special repricing for market growth (based on medical expenses)
2018.4.1	Complete	16,434	▲7.48%	▲1.65%	Adjustable range 2% (lowering by a fixed rate for branded products for which replacement by generic products is slow) Out of the revision rate, ▲1.36% is for revision of actual price, etc. and ▲0.29% is for drastic reformation of the drug price system (based on medical expenses)
2019.10.1	Complete	16,510	▲4.35% In addition, the amount equivalent to consumption tax +1.95%	▲0.93% In addition, the amount equivalent to consumption tax +0.42%	

(Note) The number in parentheses in the space for the "number of products listed" in partial revision indicates the number of products to be revised.

**Table 15 Annual Changes in Drug Expenses and Estimated Divergence Rate**

<b>Year</b>	<b>National medical expenditures (A) (trillion yen)</b>	<b>Drug expenses (B) (trillion yen)</b>	<b>Drug expense ratio (B/A) (%)</b>	<b>Estimated divergence rate (C) (%)</b>
<b>FY1993</b>	<b>24.363</b>	<b>6.94</b>	<b>28.5</b>	<b>19.6</b>
<b>FY1994</b>	<b>25.791</b>	<b>6.73</b>	<b>26.1</b>	<b>–</b>
<b>FY1995</b>	<b>26.958</b>	<b>7.28</b>	<b>27.0</b>	<b>17.8</b>
<b>FY1996</b>	<b>28.454</b>	<b>6.97</b>	<b>24.5</b>	<b>14.5</b>
<b>FY1997</b>	<b>28.915</b>	<b>6.74</b>	<b>23.3</b>	<b>13.1</b>
<b>FY1998</b>	<b>29.582</b>	<b>5.95</b>	<b>20.1</b>	<b>–</b>
<b>FY1999</b>	<b>30.702</b>	<b>6.02</b>	<b>19.6</b>	<b>9.5</b>
<b>FY2000</b>	<b>30.142</b>	<b>6.08</b>	<b>20.2</b>	<b>–</b>
<b>FY2001</b>	<b>31.100</b>	<b>6.40</b>	<b>20.6</b>	<b>7.1</b>
<b>FY2002</b>	<b>30.951</b>	<b>6.39</b>	<b>20.7</b>	<b>–</b>
<b>FY2003</b>	<b>31.538</b>	<b>6.92</b>	<b>21.9</b>	<b>6.3</b>
<b>FY2004</b>	<b>32.111</b>	<b>6.90</b>	<b>21.5</b>	<b>–</b>
<b>FY2005</b>	<b>33.129</b>	<b>7.31</b>	<b>22.1</b>	<b>8.0</b>
<b>FY2006</b>	<b>33.128</b>	<b>7.10</b>	<b>21.4</b>	<b>–</b>
<b>FY2007</b>	<b>34.136</b>	<b>7.40</b>	<b>21.7</b>	<b>6.9</b>
<b>FY2008</b>	<b>34.808</b>	<b>7.38</b>	<b>21.2</b>	<b>–</b>
<b>FY2009</b>	<b>36.007</b>	<b>8.01</b>	<b>22.3</b>	<b>8.4</b>
<b>FY2010</b>	<b>37.420</b>	<b>7.88</b>	<b>21.1</b>	<b>–</b>
<b>FY2011</b>	<b>38.585</b>	<b>8.44</b>	<b>21.9</b>	<b>8.4</b>
<b>FY2012</b>	<b>39.212</b>	<b>8.49</b>	<b>21.7</b>	<b>–</b>
<b>FY2013</b>	<b>40.061</b>	<b>8.85</b>	<b>22.1</b>	<b>8.2</b>
<b>FY2014</b>	<b>40.807</b>	<b>8.95</b>	<b>21.9</b>	<b>–</b>
<b>FY2015</b>	<b>42.364</b>	<b>9.56</b>	<b>22.6</b>	<b>8.8</b>
<b>FY2016</b>	<b>42.138</b>	<b>9.22</b>	<b>21.9</b>	<b>–</b>
<b>FY2017</b>	<b>43.071</b>	<b>9.46</b>	<b>22.0</b>	<b>9.1</b>

\* The estimated divergence rate for FY2018 is 7.2%.

(Note)

- National medical expenditures (surveyed by Health Statistics Office for Counselor for Director-General for Statistics and Information Policy, Ministry of Health, Labour and Welfare) are the estimated expenditures required for treatment of injuries and diseases at medical institutions, etc. in the fiscal year concerned. It is obtained by adding the expenditures for industrial accidents, polluter pays principle (for pollution-related health damage, etc.), self pay for all expenses, acupuncture and moxibustion, etc. to the total medical expenditures covered by medical insurance.

- Drug expenses are estimated by assuming that drugs are used for industrial accidents, etc. in the same percentage as in the cases covered by health insurances, and multiplying the national medical expenditures with the drug expense ratio for medical insurance. Drug expenses for the cases in which the drug expenses such as DPC are calculated together with the hospitalization fee are not included.
- The hyphen (-) in the space for the estimated divergence rate indicates that the data is not available because the drug price survey was not conducted.
- After introduction of the long-term care insurance in FY2000, a part of the national medical expenditures was shifted to long-term care insurance.

The drug price revision implemented in 2018 is outlined below:

The revision rate is -7.48% on the drug price basis and -1.65% on the medical care expenditure basis.

Among them, the portion for revision of actual price, etc. accounted for 6.17% on the drug price basis and 1.36% on the medical care expenditure basis. The proportion attributable to the drug price system reform accounted for 1.31% on the drug price basis and 0.29% on the medical care expenditure basis.

The numbers of products listed on the price list as of April 2018 are shown in the following table.

	Oral	Injection	Topical	Dental	Total
Announced number	10,253	3,827	2,324	28	16,432

#### 1. Drug price revision for long-listed drugs

- (1) Drug price lowering for original drugs with slow replacement with generic drugs
  - 1) For original drugs (except for orphan drugs, etc.) between 5 years and 10 years after listing of the first generic drug for which the rate of replacement with generic drugs is <80%, the drug price is lowered by the following percentage from the value calculated based on the actual market price.
    - i. Replacement rate <40%, 2.00%
    - ii. Replacement rate  $\geq$ 40% and < 60%, 1.75%
    - iii. Listed drugs with replacement rate  $\geq$ 60% and < 80%, 1.50%
- (2) Lowering of drug price to the price of generic drugs for long-listed drugs 10 years or more after listing of generic drugs
  - 1) Among the original drugs (except for orphan drugs, etc.) 10 years or more after listing of the first generic drug, the price of the drugs for which the rate of replacement with generic drugs reached 80% or more (except for the cases in which the indications of the original drug and the generic drug are not identical; hereinafter referred to as G1 product) is lowered to the following amount.
    - i. Drugs subjected to drug price revision for the first time after falling under G1 product  
2.5 times of the weighted mean of the price of generic drugs
    - ii. Drugs subjected to drug price revision for the first time after passage of 2 years after falling under G1 product  
2 times of the weighted mean of the price of generic drugs
    - iii. Drugs subjected to drug price revision for the first time after passage of 4 years after falling under G1 product  
1.5 times of the weighted mean of the price of generic drugs
    - iv. Drugs subjected to drug price revision for the first time after passage of 6 years after falling under G1 product  
Weighted mean of the price of generic drugs

- 2) Among the original drugs (except for orphan drugs, etc.) 10 years or more after listing of the first generic drug, the price of the drugs other than G1 products (hereinafter referred to as G2 product) will be lowered to the following price. The rules in 3) will be applied to biological products.
- Drugs subjected to drug price revision for the first time after falling under G2 product  
2.5 times of the weighted mean of the price of generic drugs
  - Drugs subjected to drug price revision for the first time after passage of 2 years after falling under G2 product  
2.3 times of the weighted mean of the price of generic drugs
  - Drugs subjected to drug price revision for the first time after passage of 4 years after falling under G2 product  
2.1 times of the weighted mean of the price of generic drugs
  - Drugs subjected to drug price revision for the first time after passage of 6 years after falling under G2 product  
1.9 times of the weighted mean of the price of generic drugs
  - Drugs subjected to drug price revision for the first time after passage of 8 years after falling under G2 product  
1.7 times of the weighted mean of the price of generic drugs
  - Drugs subjected to drug price revision for the first time after passage of 10 years after falling under G2 product  
1.5 times of the weighted mean of the price of generic drugs
- 3) For the products the amount calculated by the rules in 2) is higher than the amount lowered according to the following classification, the price will be revised to the amount lowered according to the following classification, regardless of the rules in 2) (C).
- Replacement rate is <40%, 2.00%
  - Replacement rate is  $\geq 40\%$  and < 60%, 1.75%
  - Listed drugs with replacement rate  $\geq 60\%$  and < 80%, 1.50%
- 4) Number of ingredients and number of products of target drugs
- Drug price lowering for original drugs with slow replacement with generic drugs (Z2)

	Replacement rate of generic drugs			Total
	<40%	$\geq 40\%$ <60%	$\geq 60\%$ <80%	
Number of ingredients	30	34	21	85
Number of products	60	79	68	207

- Lowering of drug price to the price of generic drugs for long-listed drugs 10 years or more after listing of generic drugs

Classification			Number of ingredients	Number of products
G1			38	85
G2			137	293
C	Replacement rate of generic drugs	<40%	111	275
		≥40% and <60%	98	189
		≥60% and <80%	59	108
	Total for C		268	572
Total			443	950

## 2. Premium for addition, etc. of indication of pediatric indication or rare disease and verification of true clinical usefulness

Number of ingredients/ products subject to premium for addition, etc. of pediatric indication

	Pediatric indication	Rare disease	Verification of true clinical usefulness	Total
Number of ingredients	7	11	1	19
Number of products	27	19	3	49

## 3. Repricing for market growth and repricing for change of dosage and administration

Number of ingredients/ of products of target drugs

	Repricing for market growth	Special repricing for growth	Repricing for change of dosage and administration
Number of ingredients	9	2	3
Number of products	19	4	5

## 4. Price zone of generic drugs

Number of price zones	Number of ingredient specifications	Number of ingredient specifications at each price as compared with maximum price		
		<30%	30%-50%	≥50%
1	1,440	23	332	1,085
2	364	95	348	285
3	83	83	83	83

## 5. Basic drugs

- (1) For the drugs satisfying the following requirements, integrate the price to the brand with the largest sales volume, and maintain the price.
- It should be clear that the medical positioning has been established, and the drug is widely used in clinical settings.
  - Among all similar drugs for which the listed product, component, and dosage form are same, identical, the time after the date of drug price listing is more than 25 years for some of the products.
  - If there is any similar drug for which the listed product, component, and dosage form are same, the mean discrepancy rate for the similar drugs including the listed product is not larger than the mean discrepancy rate for all listed drugs.

- iv. The discrepancy rate of the listed drug from the actual market price is not larger than the mean discrepancy rate for all listed drugs.

Classification	Number of ingredients	Number of products
Unprofitable	119	370
Pathogenic organisms	81	205
Narcotics	9	24
Crude drugs	48	55
Ointment base	3	3
Dental topical analgesics	1	3
Total	261	660

\* Any drugs falling under multiple classifications should be included in the classification listed higher.

#### 6. Repricing for unprofitable products

The drug price was increased from the current drug price because of being unprofitable.

Target ingredient: 87

Number of products: 184

#### 7. Premium for promotion of innovative drug discovery and resolution of off-label use

##### (1) Target of premium

##### 1) Target products

New drugs meeting all of the following requirements

I) 15 years or less after drug price listing without entry of generic drugs

II) Falling under any of the following requirements

i. Drugs approved for indications designated for orphan drugs

ii. Drugs for which development is requested publicly based on the results of examination by the Unapproved Drug, etc. Review Committee

iii. Drugs for which plus correction for premium for innovativeness, premium for usefulness (I), premium for usefulness (II) or operating margin was applied at the time of drug price listing, or drugs for which special repricing associated with drug price revision for a listed drug for which true clinical usefulness was verified after marketing at the time of drug price revision (hereinafter referred to as the product subject to premium)

iv. Drugs with new mechanism of action falling under the criteria for innovativeness and usefulness

v. Drugs for which only one or two drug(s) with similar pharmacological action existed at the time of drug price listing, listed within 3 years after listing of the first drug with similar pharmacological action, and for which the drug with similar pharmacological action listed first is a product subject to premium or satisfies the criteria for innovativeness and usefulness

III) For any combination product for which drug price is calculated as an exceptional measure for new medical combination products, an active ingredient of any listed product more than 15 years after the date of drug price listing, or an active ingredient of any listed product for which generic drugs have been listed on the drug price list must not be contained

IV) The drug is not subject to repricing

## 2) Target company

The target company for premium for new drug discovery must not be a company which showed inappropriate behaviors, such as refusal of development and unreasonable delay in development, for the products for which development is requested by the Ministry of Health, Labour and Welfare, based on the results of examination in the Unapproved Drug, etc. Review Committee.

## 3) Procedure of drug price revision

For the products falling under 1), the amount obtained by multiplying the amount with the premium coefficient for the value calculated based on the actual market price, etc., with the drug price before revision set as the upper limit, will be added, only if the products are produced by the companies listed in 2).

## 4) Number of ingredients/products satisfying the conditions for premium

	Number of ingredients	Number of products
i. Orphan drugs	147	229
ii. Products for which development is publicly requested	8	17
iii. Products subject to premium	91	184
iv. Drugs with new mechanism of action satisfying the criteria	51	92
v. Drug 3 years or less after the drug with new mechanism of action, which is ranked third or less, and for which the first product is a product subject to premium or a product meeting the criteria	17	38
Total	314	560

\* Any drugs falling under multiple classifications should be included in the classification listed higher.

\* In addition, one ingredient, 2 products were additionally listed on 3/14 as a product subject to premium.

## 5) Number of companies in each company category

	Category I	Category II	Category III	Total
Number of companies	23	54	6	83

## 6) Total amount for innovative drug discovery premium: 81 billion yen

## (2) Products for which the amount equivalent to premium was returned

1) For new drugs who no longer satisfy the requirements in 1) i) or iii) or 2) in the previous section, the total amount equivalent to the premium in the past drug price revision will be deducted from the value calculated from the actual market price.

## 2) Number of ingredients/products returning the premium amount

Number of ingredients: 57

Number of products: 143

3) Total amount of innovative drug discovery premium, etc. deducted: 65 billion yen

## 8. Others

## Drug price investigation result for 2017

## (1) Mean discrepancy rate: 9.1%

\* Mean discrepancy rate is calculated as {Total of (current drug price×sales volume) — total of (actual sales unit price×sales volume)} / Total of (current drug price×sales volume).

## (2) Percentage of generic drugs in volume: 65.8%

\* Percentage of generic drugs in volume is calculated as (Volume of generic drug) / {(volume of original drug with generic drugs) + (volume of generic drugs)}.

## (3) Settlement rate (on the drug price basis) = 97.7%

\* Settlement rate (on the drug price basis) is based on the results of the survey on the status of price settlement (for September 2017).

## (4) Percentage for each classification

Classification		Number of products	Percentage against total on the drug price basis	Percentage of volume against total
Original drugs	Without generic drugs	2,276	55.8%	16.9%
	With generic drugs	1,667	22.5%	21.5%
Generic drugs		9,254	15.0%	40.2%
Other products		3,241	6.7%	21.4%

\*1 "Other products" include products of Japanese Pharmacopoeia, herbal extracts, crude drugs, biological products (vaccines and blood products, etc.) and drugs approved in 1967 or before.

\*2 Number of products is the figure as of April 2018, and discrepancy rate, percentage against total on the drug price basis, percentage of volume against total, and percentage of volume of generic drugs are based on the volume and drug price as of investigation in September 2017.

\*3 Since figures are rounded to the first decimal place, the total of the percentages may not be equal to 100.0%.

**Table 16 Requirements for Applying Premiums**

&lt;Types, requirements and rates of premiums&gt;

(1)	<b>Premium for innovativeness (rate: 70-120%)</b> 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)	<b>Premium for usefulness I (35-60%)</b> Applied to new drug products in the NHI Price List that meet two of the three requirements listed above
(3)	<b>Premium for usefulness II (5-30%)</b> Applied to new drug products in the NHI Price List that meet one of the following requirements (excluding products to which the innovativeness premium or usefulness premium (I) is applied):
	1) The newly entered drug has a clinically useful new mechanism of action.
	2) The newly entered drug has been shown objectively to be more effective and safe than existing (comparator) drugs in the same class.
	3) The newly entered drug has been shown objectively to offer, as a result of formulation improvement, greater therapeutic usefulness than other drugs in the same class.
	4) The newly entered drug has been shown objectively to improve treatment of the indicated disease or trauma.
(4)	<b>Premium for pediatric use (5-20%)</b> Applied to new drug products in the NHI Price List meeting all of the following requirements:
	1) The newly entered drug is explicitly shown in the Indications section or Dosage and Administration section to be indicated for children (including infants, suckling infants, newborns, and low-birthweight infants).
	2) The premiums for pediatric use must not have been given to comparator drugs available in the NHI Price List.
(5)	<b>Premium for marketability (I) (10-20%)</b> Applied to new drug products in the NHI Price List meeting all of the following requirements:
	1) Orphan drugs pursuant to the provisions of Article 77-2 of the Pharmaceutical Affairs Law in the NHI Price List for which the orphan indications for the disease or trauma are the main indications of the drugs concerned.
	2) The premium for marketability (I) must not have been given to comparator drugs available in the NHI Price List.
(6)	<b>Premium for marketability (II) (5%)</b> 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):
	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.
	2) The premium for marketability (I) or (II) must not have been given to comparator drugs available in the NHI Price List.
(7)	<b>Premium for the world's first registration in Japan (10%-20%)</b> 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):
	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
	2) A new drug first approved in Japan
	3) A new drug ascertained not to be marketed solely in Japan based on foreign clinical development status (including R&D plan), clinical trial notification, etc.
	4) A new drug for which premium for innovativeness or usefulness I is applicable

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