

## 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 manufacturer. The name and contact information for the agent is entered in the Remarks section of the application form. The note "Application by an associated manufacturing/marketing business license holder" should also be entered in the form, if the application is filed by an agent manufacturing/marketing authorization holder (of drugs, etc. manufactured by the person applying for accreditation of an overseas manufacturer). An application by an agent should be made by an authorized agent of the manufacturing/marketing business license holder, as a rule; however, there are other permissible cases of application not involving authorized agent (Notification No. 1008-(1) of 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 be 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, PFSB 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 PFSB entitled "Modifications of Handing 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 PFSB 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.

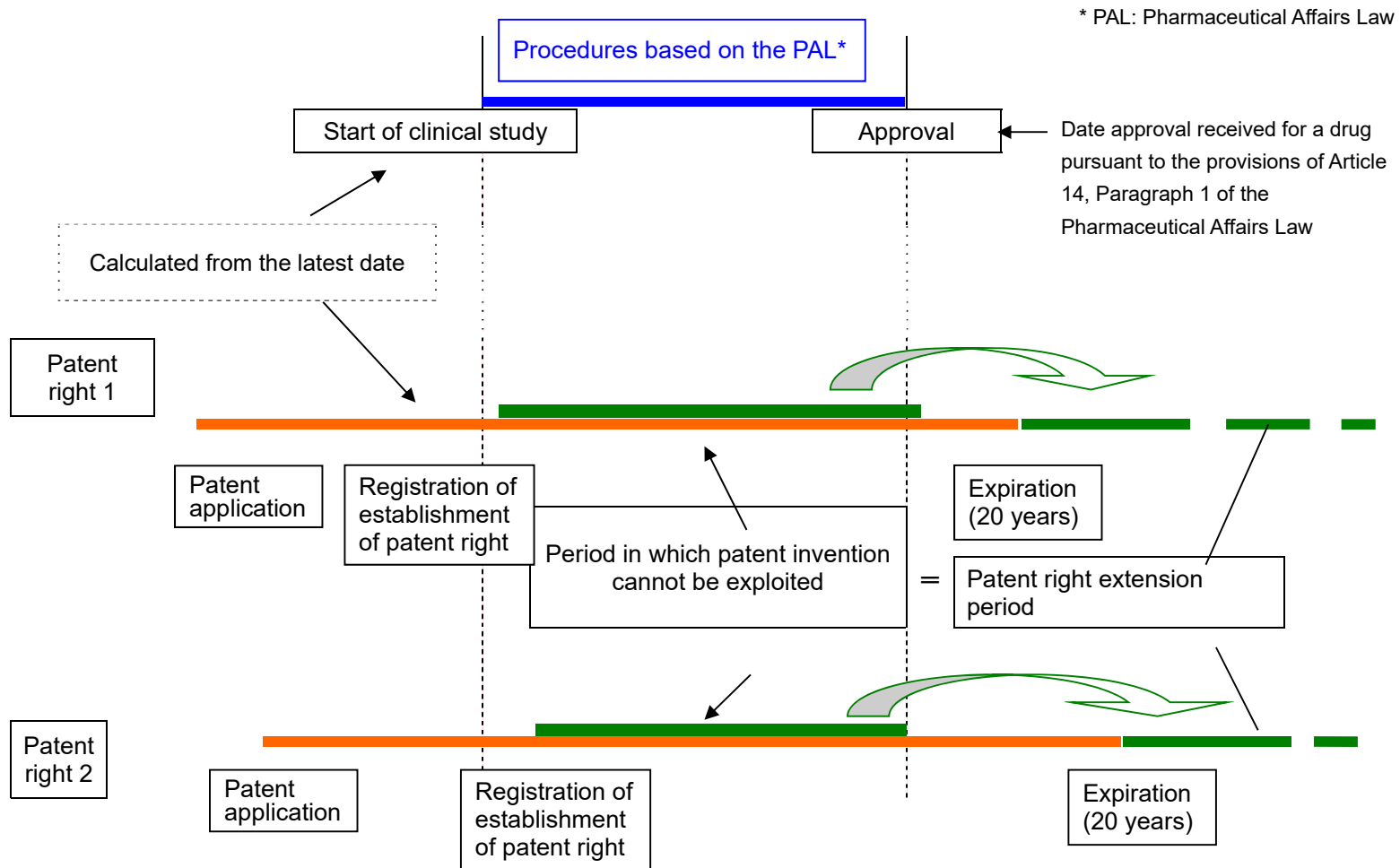
It has been considered necessary to adopt quality and safety assurance measures based on current scientific levels for drugs manufactured using raw materials of human or animal origin. Companies have been requested to undertake voluntary inspections and make adjustments in approval documentation.

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.

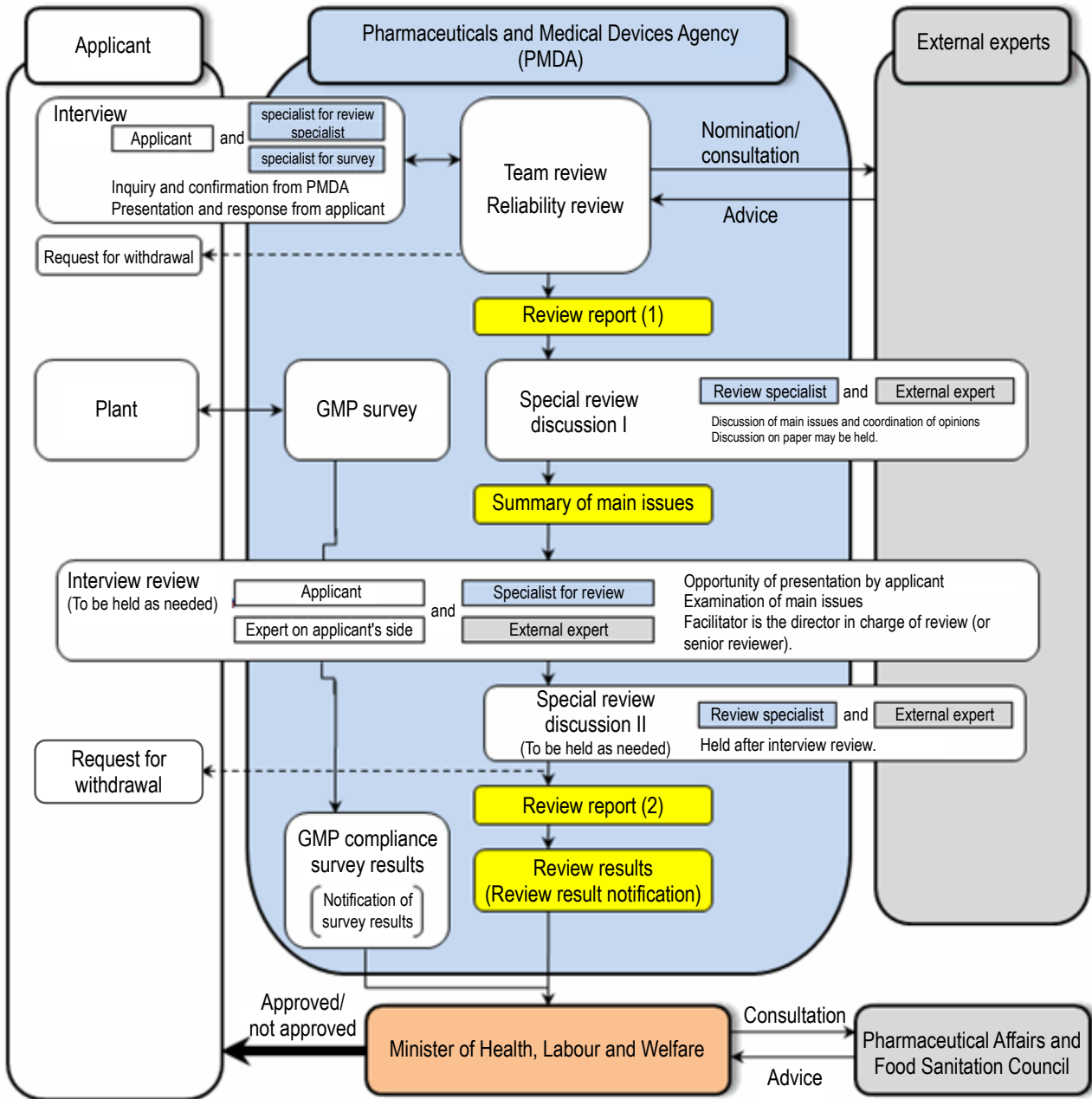
In an office communication of the Compliance and Narcotics Division, PFSB dated September 5, 2006 entitled "Self-checking of Drugs, etc. Using Raw Materials Derived From Cattle Produced in the United States," instructions are given to verify by self-check forms (self-check points) as an additional preventive 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.

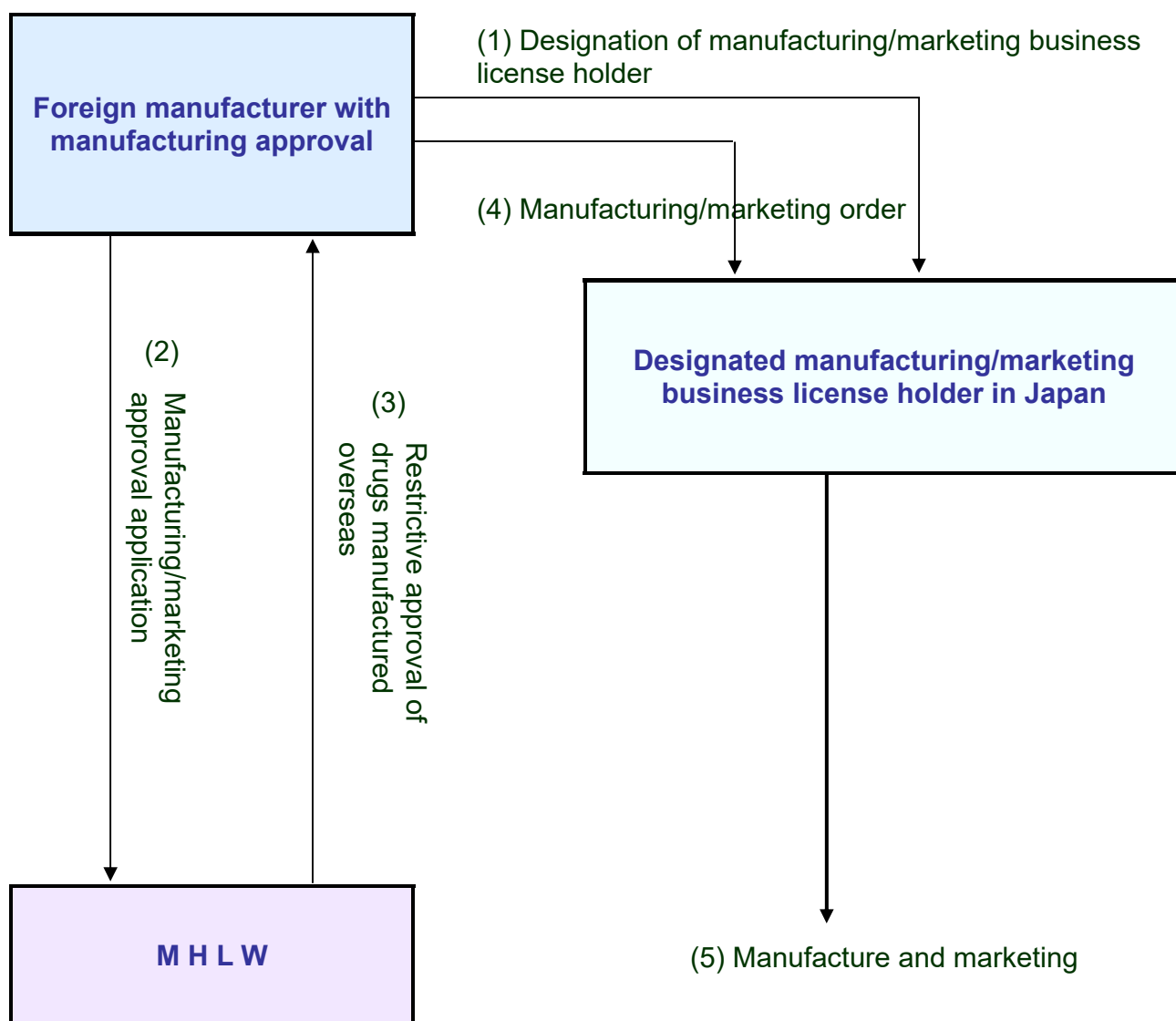
The Standards for Biological Materials were partially revised by Notice No. 375 of the MHLW in September 2014, the countries which were evaluated as having negligible risks according to the BSE risk status of the Office International des Epizooties (OIE) were added to the list of countries of origin 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**

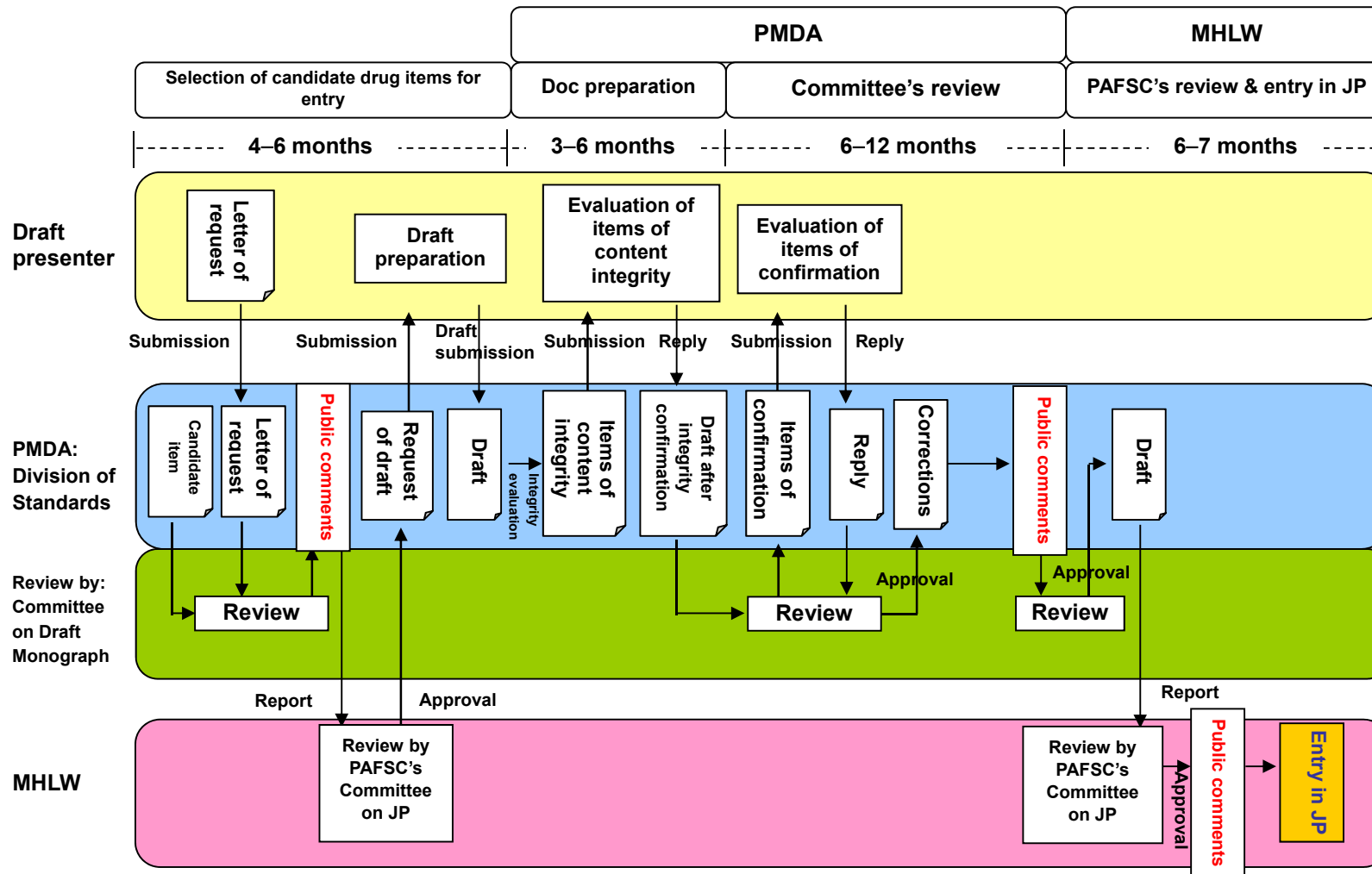


Fig. 7 Flowchart of Drug Listing in Japanese Pharmacopoeia



**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), phenylmethyaminopropanes (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>