

CHAPTER 2

Pharmaceutical Laws and Regulations

1. PHARMACEUTICAL LAWS

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

For the enforcement and management of these laws, detailed regulations are prepared by the government in the form of ministerial ordinances and notices, such as the Enforcement Ordinance and the Enforcement Regulations of the Drugs and Medical Devices Law, and notifications issued by the Director General of the Bureaus or the directors of the Divisions in charge in the Ministry of Health, Labour, and Welfare.

2. DRUGS AND MEDICAL DEVICES LAW

The objectives of the Drugs and Medical Devices Law are to improve public health through regulations required to assure quality, efficacy, and safety of drugs, quasi-drugs, cosmetics, medical devices, and regenerative medicine products and to prevent hazard and expansion of hazard in public health caused by use of those products, as well as through measures required to promote R&D of drugs, medical devices and regenerative medicine products that are especially essential for health care.

Modern pharmaceutical legislation originated in Japan with the enactment of the Regulations on Handling and Sales of Medicines in 1889. The Pharmaceutical Affairs Law was enacted in 1943 and has been revised several times since then. The current Pharmaceutical Affairs Law (Law No. 145) is the result of complete revisions in 1948 and 1960. Subsequent revisions have included those related to reevaluation of new drugs after reexamination, notification of clinical study protocols, and items required for sponsoring clinical studies in 1979, those related to direct manufacturing approval applications by overseas pharmaceutical manufacturers, and the transfer of manufacturing or import approvals in 1983, and those related to promotion of R&D of orphan drugs and priority reviews for such drugs in 1993.

In 2002, the Pharmaceutical Affairs Law (Law No. 96 dated July 31, 2002) was revised based on demands for augmentation of safety assurance in keeping with the age of biotechnology and genomics, augmentation of post-marketing surveillance policies, revisions of the approval and licensing system (clarification of the responsibility of companies for safety measures and revisions of the manufacturing approval system in accordance with international coordination) and a radical revision of safety policies for medical devices. According to

the revised Law, the Provisions on the enhancement of safety measures for biological products came into effect on July 30, 2003 and the provisions related to the manufacturing/marketing approval system, manufacturing/marketing businesses, and manufacturing businesses, as well as the provisions related to medical devices came into effect on April 1, 2005.

Thereafter, the Law for Partial Amendment of the Pharmaceutical Affairs Law (Law No. 69 dated June 14, 2006) to revise the OTC drug selling system and strengthen the control of illegal drugs was issued in June 2006 and enforced on June 1, 2009 as planned. The amended Pharmaceutical Affairs Law has classified non-prescription drugs according to potential risks (type 1: especially high risk, type 2: relatively high risk, and type 3: relatively low risk) and the systems of information dissemination and consultation on drugs for each classification were implemented.

In 2013, the Law for Partial Amendment of the Pharmaceutical Affairs Law (Law No. 84 dated November 27, 2013) was issued for strengthening safety measures and for establishing regulations and control on medical devices and regenerative medicine products in view of their properties and characteristics. The Law was enacted on November 25, 2014. In conjunction with this law, the Law for Partial Amendment of the Pharmaceutical Affairs Law and the Pharmacists Law (Law No. 103 dated December 13, 2013) was issued in the same year for clarifying the Internet retailing rules of non-prescription drugs and for tightening regulations on designated drugs/substances. The Law was enacted on June 12, 2014 (provisions strengthening regulation of designated substances were enacted on April 1, 2014).

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

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

- Chapter 1: General Provisions (Articles 1 to 2)
- Chapter 2: Prefectural Pharmaceutical Affairs Councils (Article 3)
- Chapter 3: Pharmacies (Articles 4 to 11)
- Chapter 4: 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 Drugs and Medical Devices Law, cabinet orders, MHLW ordinances, etc. An outline of the main regulations affecting pharmaceuticals is presented here.

3.1 Definition of Drugs

Drugs subject to the regulations in the Drugs and Medical Devices Law are defined as follows in Article 2, Paragraph 1 of the Law.

The term "drugs" refers to the following substances :

- 1) Substances listed in the Japanese Pharmacopoeia.
- 2) Substances (other than quasi-drugs and regenerative medicine products), which are intended for use in the diagnosis, treatment, or prevention of disease in humans or animals, and

which are not equipment or instruments, including dental materials, medical supplies, sanitary materials, and programs.

- 3) Substances (other than quasi-drugs, cosmetics or regenerative medicine products) which are intended to affect the structure or functions of the body of humans or animals, and which are not equipment or instruments.

3.2 Definition of Drugs

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

1) Classification according to use and supply

- (1) Pharmacy drugs (Article 4 in the Law)
Drugs other than guidance- mandatory drugs and non-prescription drugs
Includes prescription drugs
(drugs intended for use by a physician or dentist or under the prescription or instructions of a physician or a dentist)
- (2) Guidance-mandatory drugs (Article 4 in the Law)
Guidance-mandatory drugs are designated by the MLHW as drugs which clinical effects are not as significant as prescription drugs and intended to be selected and used by the consumer based on information provided by the pharmacist, etc. and must be sold via face-to-face consultation with a pharmacist. Deleterious substances and early switch OTC products are applicable. This is a new classification created in amendment of the Pharmaceutical Affairs Law enacted on June 12, 2014 (Law No. 103 dated December 13, 2013).
- (3) Non-prescription drugs (Article 4 in the Law)
Non-prescription drugs are defined as those in which clinical effects are not as significant as in prescription drugs and which a consumer may select and use based on information provided by a pharmacist, etc. Those are neither pharmacy drugs nor guidance-mandatory drugs. Those are classified into three types based on the degree of risks to humans: Type 1 (highly risky), Type 2 (moderately risky) and Type 3 (relatively low risky). In the revised Pharmaceutical Affairs Law enacted on June 12, 2014, non-prescription drugs may be retailed via the Internet in accordance with the proper rule.

2) Classification according to handling regulations related to safety

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

- (1) **Poisonous substances (Article 44 of the Law).**
- (2) **Deleterious substances (Article 44 of the Law).**
- (3) **Drugs requiring a prescription (Article 49 of the Law).**
- (4) **Habit-forming drugs (Article 50 of the Law).**

- (5) **Drugs for specially designated diseases (Article 67 of the Law).**
 - (6) **Narcotics (Narcotics and Psychotropics Control Law).**
 - (7) **Psychotropic drugs (Narcotics and Psychotropics Control Law).**
 - (8) **Opium and powdered opium (Opium Law).**
 - (9) **Cannabis (Cannabis Control Law).**
 - (10) **Stimulants (Stimulant Control Law).**
- 3) **Biological products and specified biological products**

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

(1) Biological products

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

(2) Specified biological products

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

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

Based on the provisions in the Drugs and Medical Devices Law for biological products and specified biological products, the "Manufacturing Supervisors and Import and Marketing Supervisors for Biological Products," "Labeling on the Immediate Container or Packaging," "Entries in the Package Inserts (Notification No. 0515005 of the PMSB dated May 20, 2003)," "Periodic Infection Reporting System (Notification No. 0515008 of the PMSB dated May 15, 2003)," "Records and Their Retention," "Outsourcing of Records and Their Retention," "Dissemination of Information," and "Manufacturing Control and Quality Control" are specified in Notification No. 0515017 of the PMSB dated May 15, 2003 and Notification No. 0520004 of the PMSB dated May 20, 2003, etc.

4) Regenerative medicine products

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

The basic technical requirements to assure the quality

and safety of drugs and medical devices processed from human-derived (autologous) cells and tissues are specified in Notification No. 0208003 of the PFSB dated February 8, 2008. On March 27, 2008, Notification No. 0327027 of the Compliance and Narcotics Division, PFSB on manufacturing control and quality control of drugs and medical devices processed from human-derived (autologous) cells and tissues was issued. The basic technical requirements to assure the quality and safety of drugs and medical devices processed from human-derived (homologous) cells and tissues are specified in Notification No. 0912006 of the PFSB dated September 12, 2008. In addition, separate notifications were issued specifying the basic technical requirements to assure the quality and safety of human-derived (autologous) somatic stem cells, human-derived (homologous) somatic stem cells, human-derived (autologous) iPS (-like) cells, human-derived (homologous) iPS (-like) cells, and human-derived ES cells, (Notification Nos. 0907-(2) to (6) of the PFSB dated September 7, 2012).

3.3 License for Manufacturing/Marketing Businesses

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

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

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

The licensing requirements for drug manufacturing/marketing businesses include the appointment of a general marketing compliance officer of drugs, etc., who is a pharmacist, and compliance with Good

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

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

3.4 License for Manufacturing Business and Accreditation of Overseas Manufacturers

1) Licenses for manufacturing businesses

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

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

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

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

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

2) Accreditation of manufacturing business of overseas manufacturers

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

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

The procedures for obtaining the accreditation are available in the "Q&A on Accreditation of Overseas Manufacturers" in an office communication of the Evaluation and Licensing Division, PFSB dated February 14, 2006. Refer to the PMDA homepage for reference.

Japanese website:

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

English website:

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

- (1) Applicants for accreditation of manufacturing business of overseas manufacturers and their agents
 - **When the applicant is a corporation, the representative (director with representative authority) makes the application.**
 - **The agent applying on behalf of a person intending to obtain a manufacturing/marketing business license should apply with the confirmed type of corporation, name, address and representative of the overseas manufacture. The name and contact information for the agent is entered in the Remarks section of the application form. The note "Application by an associated manufacturing/marketing business license holder" should also be entered in the form, if the application is filed by an agent manufacturing/marketing authorization holder (of drugs, etc. manufactured by the person applying for accreditation of an overseas manufacturers). An application by an agent should be made by an authorized agent of the manufacturing/marketing business license holder, as a rule; however, there are other permissible cases of application not involving authorized agent (Notification No. 1008-(1) of PMDA dated October 8, 2010).**
- (2) Timing of applications for accreditation of overseas manufacturers
 - The application should be submitted by the time of the marketing approval application. When accreditation is not obtained beforehand, "under application" should be entered in the marketing approval application form. (Marketing approval cannot be obtained without accreditation approval.)
- (3) Outline of the structure and facilities of the manufacturing plant required for accreditation of overseas manufacturers and attached documentation
 - **The outline of the structure and facilities of the manufacturing plant should be based on that in the manufacturing business license application in Japan. A list of the structures and facilities must be included.**
 - **When Japanese cannot be used as the language in the attached documentation under special circumstances, a foreign language can be used, but a Japanese translation must be attached in such cases. If the foreign language is not English, certification of the translator must be**

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 or prefectural governor by submitting data and documents for required review on product quality, efficacy, and safety.

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

Marketing approvals require a review to determine whether or not the product in the application is suitable as a drug to be marketed by the marketing authorization holder and confirmation that the product has been manufactured in a plant compliant with GMP. Whenever any approved items are to be revised, the license holder must submit a notification of minor variations or partial changes of approved items and obtain approval of the revision.

3.6 Good Manufacturing Practice (GMP)

GMP specifies that compliance with the Regulations for Buildings and Equipment of Pharmacies, etc. that specify standards for structures and equipment in manufacturing plants for each manufacturing category without relation to the products manufactured is a requirement for a manufacturing business license. Compliance with the GMP ordinance that specifies standards for structures and equipment required for the product concerned as well as standards for manufacturing control and quality control for each manufactured product is a condition for approval of the drug concerned (refer to Chapter 3).

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

MHLW, PMDA, and prefectures had submitted bid for membership to the office of Pharmaceutical Inspection Cooperation Scheme (PIC/S) in March 2012, which guarantees a high level of the implementation of the internationally recognized GMP rules, to further promote international standardization and conformity in GMP

inspection, and then became members since July 1, 2014. The enforcement notification of the GMP was amended accordingly in August 2013 to meet criteria in the PIC/S. (Notification No. 0830-(1) of the Compliance and Narcotics Division dated August 30, 2013.)

3.7 Drug Master File (MF)

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

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 an in-country caretaker to handle the activities of the MF registrant in Japan.

When the registered contents of the MF are changed, an application to change the MF or a minor MF modification notification must be submitted.

When an application to change of the MF is submitted, the manufacturing/marketing authorization holder must submit a partial change application or a slight modification notification for the MF depending on the contents of the change. However, when a change or changes in the MF are slight, the manufacturing/marketing authorization holder is not required to submit a partial change application or a slight modification notification of approved items. In both cases, MF registrants must notify the manufacturing/marketing authorization holder of the change(s) in advance of the implementation of such changes.

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

Japanese website:

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

<http://www.pmda.go.jp/english/review-services/reviews/mf/0001.html>

3.8 Drug Retail Seller Licensing

A license must be obtained from the Prefectural Governor or other specified officials for marketing or otherwise providing of drugs. Licenses for drug retailers

have been classified as follows based on amendment of the Pharmaceutical Affairs Law enacted on June 1, 2009 (Law No. 69 dated from June 14, 2006):

- (1) Store-based drug sellers
- (2) Drug sellers by household distribution
- (3) Drug sellers by wholesale distribution

For store-based drug sellers and drug sellers by household distribution, qualifications (prefectural examination) for newly registered sellers have been established in addition to the those for pharmacists. These sellers can market type 2 and type 3 non-prescription drugs.

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

3.9 Quality Standards and Government Certification

The Japanese Pharmacopoeia, Japanese Pharmaceutical Codex, Japanese Pharmaceutical Excipients, and other similar standards have been specified as quality standards.

Certain specified drugs such as biological products must not be marketed or supplied without government certification based on batch tests.

3.10 Labeling and Package Inserts

Specified items must be entered on the immediate container of drugs. The package inserts must contain indications, dosage/administration, precautions, and precautions for handling. In addition, all ingredients used as excipients must be included. Entries in the package inserts of biological products are specified in Notification No. 0515005 of the PMSB dated May 15, 2003 and labeling on the immediate container or packaging of biological products is specified in Notification No. 0515017 of the PMSB dated May 15, 2003. These specifications came into effect from July 30, 2003. According to the Pharmaceutical Affairs Law amended on April 1, 2005, a new regulatory category for prescription drug labeling "Caution: Use only with a prescription from a physician" and a labeling item for manufacturer/marketing business instead of manufacturer or importer were added.

The Law for Partial Amendment of the Pharmaceutical Affairs Law enacted on June 1, 2009 (Law No. 69, June 14, 2006) requires the manufacturer of non-prescription drugs to prescribe in labeling matters specified in the Law in accordance of the level of potential risks.

To prevent medical accidents due to misunderstandings, assure traceability, and improve the efficiency in prescription drug distribution, the implementation of barcode labeling for prescription drugs (excluding in vitro diagnostics) (Notification No. 1 of the Economic Affairs Division, HPB and No. 1 of the Safety Division, PFSB both dated June 29, 2012) and preparation of medication guides for patients are being promoted so that the patient understands the prescription drug correctly and serious adverse drug reactions can be discovered at an early stage (Notification No. 0228001 of the Safety Division, PFSB and No. 0228002 of the Compliance and Narcotics Division, PFSB both dated February 28, 2006).

In the revised Pharmaceutical Affairs Law enacted on November 25, 2014 (Law No. 84, November 27, 2013), the new package insert notification system was introduced to enhance safety assurance measures.

Manufacturing/marketing authorization holders must prepare package inserts based on scientific knowledge and information obtained from latest literatures, etc. to provide related information. Furthermore, the PMDA must be notified of the name and necessary information in precautions for usage and handling in the package insert prior to initiation of manufacturing/marketing or amendment. The package insert must be published on the PMDA website immediately after submission of the notification.

3.11 Proper Advertisement

The "Standards for Proper Advertisement of Drugs, etc." have been established for the purpose that advertisement of drugs, etc. should 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. A person intending to advertise drugs, etc. should make efforts to disseminate accurate information so that users may use the drug, etc. properly. The standards include interpretation of the Law about description of names, indications or dosage/administrations, etc. of the drug, etc. as well as matters to be adhered to otherwise misuse or abuse may be encouraged or confidence may be lost among general users (Notification No. 1339 of the PAB dated October 9, 1980).

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

3.12 Good Laboratory Practice (GLP)

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

The GLP ordinance was partially revised by MHLW Ordinance No. 114 entitled "MHLW Ordinance to Partially Amend the MHLW Ordinance on Standards for Implementation of Nonclinical Studies on Safety of Drugs" and the amendment was enacted on August 15, 2008. Notification No. 0620059 of the PMDA entitled "Establishment of Guidelines for Drug GLP and Medical Device GLP On-site Inspections" was issued on June 20, 2008 and partially amended on November 21, 2014 (Notification No. 1121005 of the PMDA).

3.13 Good Clinical Practice (GCP)

"Clinical trials" refer to studies with the objective of collecting data on clinical trial results from among the data attached to drug approval application forms. In Japan, clinical trials are conducted in accordance with the GCP which was implemented to assure scientific quality and

reliability of clinical study data. This GCP was replaced by the Standards for the Conduct of Clinical Studies (so-called "New GCP"; 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 notifications of the Pharmaceutical Affairs Bureau (March 1997) and the Evaluation and Licensing Division, PFSB (May 1997).

The new GCP was enacted in April 1998. Between 1999 and 2002, GCP regulations were revised and updated for the activation of clinical trials, including the utilization of site management organizations (SMOs), training of clinical research coordinators (CRCs), and the requirement of a site monitoring system. In 2003, a system of investigator-initiated clinical trials was officially introduced in accordance with the Partial Amendment of the Pharmaceutical Affairs Law (Ministerial Ordinance No. 106, 2003). Since then, the GCP has been often revised to ensure the validity of clinical trials, secure the safety of study subjects, and promote efficient and smooth conduct of the trials based on recommendations from the Study Group on the Efficient Conduct of Clinical Trials, and certain ministerial ordinances and notifications for implementation have been issued.

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

- 2005

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

- 2006

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

- 2007

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

- 2008

The GCP ordinance (MHLW Ordinance No. 24, 2008) made public disclosure of IRB review results in summary format compulsory. Then, "the Registration of IRB Information (Request)" (Notification No. 1001013 of the Evaluation and Licensing Division, PFSB dated October 1, 2008) was issued to provide an environment for trial-related people to easily access IRB information and to inform the public of such information.

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

2008).

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

- 2011

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

- 2012

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

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

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

- 2013

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

3.14 Good Post-marketing Study Practice (GPSP)

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

3.15 Reexamination and Reevaluation

Manufacturing/marketing authorization holders must perform post-marketing surveys on new drugs so that

efficacy and safety can be reconfirmed by reexamination by the MHLW for a specified period after marketing approval. All drugs, including those that have completed reexamination must undergo reevaluation to recheck their efficacy, safety, and quality in accordance with progress in medical and pharmaceutical sciences.

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

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

The reexamination period for drugs with new active ingredients is eight years as a rule (Notification No. 0401001 of the PFSB dated April 1, 2007).

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

3.16 Adverse Drug Reaction (ADR) and Infection Reporting

When manufacturing/marketing authorization holders of drugs are informed of any adverse reactions, infections, etc. as specified by MHLW ordinance for trial products or their marketed products, they must report them to the Minister within the specified period (Notification No. 0317006 of the PFSB dated March 17, 2005). Handling of safety reporting is described in CHAPTER 4.

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

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

The final report of the "Special Committee on Identification and Prevention of Recurrences of Drug-Induced Hepatitis" published in March 2010 discusses problems and future prospects related to the drug adverse event reporting system, pharmacovigilance programs, and the problems of off-label drug use and use of unapproved drugs.

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

3.17 Risk Management Plan

The basic requirement to ensure the safety of drugs in clinical practice is to develop and implement appropriate measures to manage potential risks of drug-related events based on information collected during the development to post-marketing phases of a new drug's life cycle. The Ministry issued the Risk Management (RMP) Guidance (Notification No. 0411-(1) of the Safety Division of PFSB and No. 0411-(2) of the Evaluation and Licensing Division of PFSB both dated April 11, 2012) to support the

manufacturing/marketing authorization holder in developing risk minimization plans for the reduction of treatment-related risks in addition to conventional pharmacovigilance plans following drug approval.

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

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

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

3.18 Dissemination of Information

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

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

With the enactment of the Law Concerning Access to Information Held by Administrative Organizations on April 1, 2001, anyone has the right to request disclosure of documents retained by national government organizations. This law covers disclosure of documents retained by government organizations except those concerning non-disclosable information such as information on individuals, information on corporations, etc. This was partially amended by Cabinet Order No. 371, on December 21, 2005.

Based on this Law, the MHLW must disclose the contents of its reviews (records of meetings of the PAFSC, new drug approval information dossiers, etc.), as a rule, and new procedures for processing work related to public disclosure of information retained by the PFSB were specified (Notification No. 0330022 of the PFSB dated March 30, 2007).

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

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

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

Later, the criteria for disclosure of Adverse Drug Reaction Report Forms were revised by Notification No. 4 of the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ) dated January 6, 2004. Notification No. 0330011 of the PMDA dated March 30, 2011 specifies points to consider in the disclosure of information related to new drug approval reviews and subsequently issued Notification No. 0325-(1) of the Evaluation and Licensing Division, PFSB dated March 25, 2013 partially modified the procedures for public disclosure.

3.20 Patent System

The patent term is 20 years from the time of application as a rule. However, if the patent cannot be implemented because of laws and regulations to ensure safety of drugs and regenerative medicine products, etc. the patent term can be extended for a maximum of 5 years. The extension is for the period that the patented invention cannot be used, such as the period from the date of the start of clinical trials or date of patent registration, whichever is later, until one day prior to the date on which the patentee receives approval for the drug. (For regenerative medicine products, the term may be extended until acquisition of conditional approval and the extension does not cover the subsequent period to acquisition of approval.)

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

Generic drugs will not be approved until the substance (application) patent has expired. Branded products are protected from generics during this period. However, in

the past if some of the indications or dosage and administration of branded products were patented, partial approvals were not granted because of patent protection, but with Notification No. 065001 of the Economic Affairs Division, HPB and No. 0605014 of the Evaluation and Licensing Division, PFSB dated June 5, 2009, partial approvals of indications or dosage and administration not covered by the patent are permitted.

Japanese website of the Patent Office:

<http://www.jpo.go.jp/indexj.htm>

English website:

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

3.21 Drug Abuse Control

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

June 26, the final day of the International Narcotics Conference held in 1987, was designated as “International Drug Abuse Eradication Day.” At a special United Nations meeting on narcotics in 1998, the “Declaration on Guidance to Prevent Drug Abuse” was adopted.

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

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

Measures for the regulation of designated drugs (drugs with a high probability of such actions as excitation of the central nervous system that present a risk to public health and hygiene) have been added to the Drugs and Medical Devices Law as countermeasures against “dangerous illegal drugs”. In particular, importing, manufacturing, marketing, giving and storing for selling, etc. of such designated drugs with intended use other than healthcare have been prohibited. On February 28, 2007, the Guidelines on Monitoring of Import of Designated Drugs were issued (Notification No. 0228009 of the PFSB). On February 20, 2013, MHLW Ordinance No. 19 was revised and issued to implement comprehensive control of

controlled drugs/substances.

In the Law for Partial Amendment of the Pharmaceutical Affairs Law enacted on April 1, 2014 (Law No. 103, 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, 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 soled in a wide area, and advertisement should be restricted more strictly.

4. MARKETING APPROVALS

4.1 Drug Marketing Approvals

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

4.2 Marketing Approval Reviews

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

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

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

It is necessary to submit a "list of persons involved in compilation of attached data" and a "list of competitive products and companies" in relation to persons who participated in clinical studies submitted as application data immediately after application submission, prior to the expert

meeting, and prior to meeting of the Committee on Drugs.

The evaluation process followed by the PMDA is as follows (see the PMDA website). The applicant can confirm the status of review progress for each product applied for with the manager of the PMDA review team (Notification No. 1227001 of the PMDA dated December 27, 2010).

- <http://www.pmda.go.jp/review-services/drug-reviews/0001.html> (1) Interview (presentation, inquiries, and replies)
- (2) Team review
 - (3) Inquiries and replies
 - (4) Application for GMP inspection (about 6 months before the meeting of the Committee on Drugs)
 - (5) Review report (1)
 - (6) Expert meeting (includes at least three clinical specialists as experts)
 - (7) General review conference (main agenda items and names of participating experts made available 2 weeks prior to meeting; presentation) (very uncommon)
 - (8) Follow-up expert meeting
 - (9) Review report (2)
 - (10) Report to the Evaluation and Licensing Division, PFSB

The PAFSC is then consulted for discussions by the related committees and the Pharmaceutical Affairs Committee as required on the basis of the review report. After the report of the PAFSC report is obtained and it is confirmed that the standards are met in a separate GMP compliance review, the Minister grants the new drug manufacturing/marketing approval (**Fig. 5. Flowchart of Approval Review**). "Information Concerning New Drug Approval" prepared from the review data is placed on the website of the PMDA so that accurate information concerning the quality, efficacy, and safety obtained during the approval review process is supplied to medical institutions, etc.

In reviews of new drugs prepared from vaccine or blood, the specifications and test methods are examined on site by the National Institute of Infectious Diseases prior to approval, as necessary.

When active ingredients, dosage, administration route, and indications are the same as those of approved drugs (so-called "generic drugs"), a review by the PMDA is undertaken after reviews on drug equivalence and compliance, and approval is granted.

A basic notification concerning drug approval reviews was issued on April 8, 1999 and came into force for approval reviews of drugs from April 1, 2000. Later, following repeated revisions and with the enactment of the Drugs and Medical Devices Law, "**On Drug Approval Applications**" (PFSB Notification No. 1121-(2) dated November 21, 2014) was issued. The current categories are as follows:

- (1) Drugs containing new active ingredients
- (2) New prescription combination drugs
- (3) Drugs with new routes of administration
- (4) Drugs with new indications
- (5) Prescription drugs with new dosage forms
- (6) Drugs with new dosages
- (7) Biosimilar Products
- (8) Prescription drugs with additional dosage forms

(9) Prescription combination drugs with similar formulations

(10) Other prescription drugs

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

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

Regarding the total review time for new drugs, it was decided to raise the percentile of the standard total review time in stages starting from FY2014, aiming to reach a review time of 9 months for priority review products and 12 months for ordinary review products at 80th percentile by 2018. In view of this, **“On the Handling of Approval Applications for Improvement of the Predictability, etc. of New Drug Approvals and Approach to Total Review Time” Notification No. 1006-(1) of PFSB and Notification No. 1006-(1) of Compliance and Narcotics Division dated October 6, 2014**” was issued, setting out the policy of conducting preliminary interviews for planned reviews and indicating procedures, etc. for contacting applicants in case of difficult approval reviews, with a view to improving the predictability of reviews and the transparency of the review process. A timeline for the standard process of new drug approval reviews was also indicated (Administrative Notice of the Evaluation and Licensing Division, PFSB dated January 30, 2015). On April 17, 2008, **“Points to Consider for Reviewers Related to New Drug Approval Review Work”** was issued. This showed the basic conditions related to new drug review activities in the PMDA and was intended to clarify the main points to consider in reviews and to assure uniform awareness of PMDA reviewers concerning review work.

Japanese website :

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

English website :

<http://www.pmda.go.jp/english/review-services/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 Nos. 0527004, 0825001, and 0707-(3) [partial amendment] of the Evaluation and Licensing Division, PFSB dated May 27, 2004, August 25, 2008, and July 7, 2009, respectively).

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

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

4.4 Regulatory Strategy Consultations for Regenerative Medicine Products

It is specified in the notifications that safety- and quality-related issues on drugs, etc. processed from cells and tissues as well as drugs for gene therapy are to be discussed with PMDA through regulatory strategy consulting from the early stage of research and development (Notification of No. 0630-(2) of PFSB entitled **“Modifications of Handling of Medicinal Products and Medical Devices Utilizing Cells and Tissues to Comply with Implementation of Regulatory Strategy 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 strategy consultation are available in Notification No. 1121001 of PMDA entitled **“Guidelines for Regulatory Strategy Consultations”** dated November 21, 2014. For regenerative medicine products, clinical trials should be initiated after a regulatory strategy consultation for quality and safety with PMDA.

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

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

4.6 Priority Review System and Designation of Drug Products for Priority Reviews

1) Priority review system

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

(1) Priority review criteria

(A) Seriousness of indicated diseases

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

(B) Overall assessment of therapeutic usefulness

- (i) There is no existing method of treatment, prophylaxis, or diagnosis.**
- (ii) Therapeutic usefulness with respect to existing treatment**
 - a) Standpoint of efficacy
 - b) Standpoint of safety
 - c) Reduction of physical and mental burden on the patient

(2) Designation of drug products for priority reviews

When drugs are designated for priority reviews, opinions of experts on such designations are compiled by the PMDA immediately after the application and reported to the MHLW. Based on this report, the Evaluation and Licensing Division decides whether or not to apply the priority review. The Evaluation and Licensing Division notifies this decision to the applicant and the PMDA. The Evaluation and Licensing Division reports this application to the next meeting of the review committee concerned of the PAFSC and obtains their approval. Products for priority review are given priority at each stage of the review process as much as possible. When products subject to priority review are approved as new drugs, this fact is made public.

2) Review of products designated for priority interview advice

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

4.7 Restrictive Approval System

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

4.8 Orphan Drugs

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

Drugs designated as orphan drugs are entitled to certain priority measures such as financial aid, tax relief on research expenses, guidance and advice, priority review, and extension of the reexamination period from the conventional 8 years to a maximum of 10 years for drugs and from 4 years to a maximum of 7 years for medical devices.

4.9 Drugs for Pediatric Use

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

At present, laws and regulations aimed at drug development and direct promotion of information dissemination in the pediatric field such as those in the EU and United States do not exist in Japan. When clinical trials are planned for dose setting, etc. in children during approval applications or after approval of drugs intended for use in children to collect information on experience of use in pediatric populations, the reexamination period can be now extended for a set period not exceeding 10 years in consideration of special surveys and clinical studies during the reexamination period (Notification No. 1324 of the PMSB dated December 27, 2000).

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

Requests for the addition of indications by related academic societies can be handled by an application for partial changes in approved items such as indications or dosage/administration on the basis of clinical studies or clinical results in accordance with notifications (No. 4 of the Research and Development Division, Health Policy Bureau and No. 104 of the Evaluation and Licensing Division, PMSB dated February 1, 1999), when the necessity of additional indications in healthcare are confirmed and requests to study are made by the Research and Development Division

of the Health Policy Bureau. This can also be applied to drugs intended for use in the pediatric field. In these notifications, it states that whole or part of the clinical studies do not have to be performed again and when the indications related to off-label use are public knowledge in medicine or pharmacology, this can be applied to judgments on whether or not to approve indications.

The Special Committee on Unapproved Drugs was founded in December 2004 to study drugs not approved in Japan for which efficacy was established and approvals granted in the West and perform periodic surveys and scientific evaluations of requests of academic societies and patients. Separately, in March 2006, the Special Committee on Pediatric Drug Treatment was established to collect and evaluate evidence on the efficacy and safety of unapproved pediatric drugs. Thereafter, both special committees were developmentally reorganized into a new "Special Committee to Investigate Unapproved Drugs and Off-Label Use of Drugs Urgently Required for Healthcare" in February 2010. The committee started wide-ranging discussions on off-label drugs including unapproved drugs and pediatric drugs.

4.10 Unapproved Drugs and Drugs of Off-label Use

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

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

(the development requests, etc., at the first recruitment)

http://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_jryou/iyakuhin/kaihatsuyousei/list120423.html

(the development requests, etc. at the second recruitment)

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

4.11 Packaging Strategy for World-first Products

In June 2014, the "Strategy of Sakigake" for leading the world in the practical application of innovative medical

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

1) Review system for designated world-first products

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

2) Scheme for prompt practical use of unapproved drugs

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

4.12 Biosimilar Products

For biological products, it is difficult to prove the equivalence of active ingredients with those of existing drugs unlike with chemically synthesized drugs, but with the advances made in technology, biosimilars (or follow-on biologics) have been developed in recent years as products with equivalence to and the same quality as existing biological products. WHO and major countries have established new legal systems and specified technological policies. In March 2009, policies for the assurance of the quality, safety and efficacy of biosimilar products (Notification No. 0304007 of PFSB dated March 4, 2009) were formulated in Japan. "Biosimilar products" were established as a new application category for prescription drugs (Notification No. 0304004 of the Evaluation and Licensing Division, PFSB dated March 4, 2009). Documents on points to consider in approval applications (Notification No. 0304015 of the Evaluation and Licensing Division, PFSB dated March 4, 2009) and handling of non-proprietary and brand names (Notification Nos. 0304011 and 0214-(1) of the Evaluation and Licensing Division, PFSB dated March 4, 2009 and February 14, 2013, respectively) were also issued. In March 2010, "Questions and answers on policies to verify the quality, efficacy, and safety of biosimilar products" was issued (Office Communication of the Evaluation and Licensing Division,

PFSB dated March 31, 2010).

4.13 Combination Products

A “combination product” is defined as a drug that was approved to be manufactured/marketed with other components including devices or 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).

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

4.14 Codevelopment

The objective of codevelopment is to reduce the risk of development of new drugs and to promote more efficient development. Codevelopment regulations, including requirements for composition of the codevelopment group and requirements for those preparing the data, had been specified in the past, but codevelopment was deregulated by the basic guidelines for drug approval applications issued on April 8, 1999.

The main points of this deregulation included cancellation of the requirement that the group had to include members with previous experience in receiving a new drug approval. Among the requirements for those preparing the data, it was previously required that when the codevelopment group performed a clinical trial, group members had to be joint sponsors of the trial, but currently other members in the group can use data in applications from clinical trials performed by any member of the group.

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

4.15 Transfer of Marketing Approvals

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

4.16 Approval Applications for Drugs Manufactured Overseas

Pharmaceutical manufacturers outside Japan can apply

directly under their own name for marketing approval if they perform the studies regarding quality, efficacy, and safety required for the drugs they intend to export to Japan and undertake the necessary procedures (Fig. 6. Procedure for manufacturing and marketing approval of drugs for overseas manufacturers in Japan). In such cases, the overseas manufacturer appoints a marketing authorization holder in Japan among those that have received a marketing business license of the type corresponding to approved product. The appointed marketing authorization holder takes measures required to prevent the onset of health and hygiene-related hazards caused by the approved drug in Japan and can also undertake manufacturing and marketing in Japan.

4.17 Issuing of Certificates for Exported Drugs by MHLW

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

Currently, the MHLW issues the following certificates upon request: business licenses for marketing and manufacturing of drugs, etc., marketing approvals for drugs, etc., attached documentation for new drug marketing applications, GLP compliance for drugs, notifications of clinical trial for investigational products, certifications of pharmaceutical formulations based on the WHO certification system, statements of approval and licensing status of pharmaceutical products, and GMP compliance for drugs, and GMP compliance for investigational drugs. (Table 2. Divisions of the Pharmaceutical and Food Safety Bureau in Charge of Certification Work). Export certificates on drugs, quasi-drugs, etc, are issued using the specified format via the PMDA. The notification of export certifications requires the applicant of certification to inquire the Ministry of 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. 0128-(1) of the PFSB dated January 28, 2011).

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

In October 2013, the issue of GMP certificate based on the mutual recognition system for drug GMP (MRA) with the EU countries was terminated and replaced with product registration in the EudraGMDP database that was provided by the European Medicines Agency (EMA). The countries to which the certification system is applied are required to be those with which the mutual agreements for GMP were exchanged with Japan. The product items that are subject to this certification system do not include biological products, bulk drugs, or sterile products. The contents to be certified are prepared and registered by the PMDA in the EudraGMDP database based on information submitted by the manufacturer. Registered information is publicly accessible in the database, as a rule (Notification No. 0628-(4) of the Compliance and Narcotics Division, PFSB dated June 28, 2013).

5. JAPANESE PHARMACOPOEIA AND OTHER STANDARDS

5.1 Japanese Pharmacopoeia (JP)

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

Since it was first published in June 1886, the JP has been revised several times. The Drugs and Medical Devices Law specifies that the JP must be subjected to a complete revision at least once every 10 years, and such revisions have actually appeared every 5 years since the 9th revision in April 1976. In addition, the JP has been partially revised before the complete revision even 5 years since the 11th Edition.

Japanese website:

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

English website:

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

The PAFSC held a meeting of its Subcommittee on the Japanese Pharmacopoeia to cope with recent progress in the medical and pharmaceutical sciences and the requests from ICH in November 2001. The basic compilation policies that include the characteristics and role of the JP, the actual measures taken for the 15th edition to achieve the basic policies, date of enforcement, and items related to the organization of the Committee on the Japanese Pharmacopoeia were formulated. Content regulations including clarification of significance and specifications of contents were examined and the JP basic content regulations were published in a report of the PAFSC entitled "Future Approaches to the Japanese Pharmacopoeia" in December 2002. The 16th edition of the JP was finalized in March 2011, and then the basic compilation policies of the 17th edition were announced in September 2011.

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

(1) Basic policies

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

(2) Role and characteristics of the JP

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

demand at the time.

The JP is compiled by utilizing the knowledge and experience of many pharmaceutical professionals. It is a book of standards that can be utilized widely by people in the field.

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

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

(3) Date of enforcement

The 16th edition of the JP was issued in Notice No. 65 of the MHLW dated March 24, 2011 and was enforced from April 1, 2011. The edition was updated by Notice No. 519 (Supplement 1) dated September 27, 2012 and was enforced from October 1, 2012. Supplement II was issued on February 28, 2014 and enacted on the same date.

(4) Selection of products for entry in the JP

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

(5) The compilation review organization for the JP

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

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

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

5.2 Standards Based on Article 42 of the Pharmaceutical Affairs Law

For drugs that require special precautions with respect to public health and sanitation, several necessary standards

have been established concerning the methods of manufacture, properties, quality, storage methods, etc. based on Article 42 of the Law. The following standards exist at present:

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

5.3 Standards for Biological Materials

The Standards for Biological Materials were specified in Notice No. 210 issued by the MHLW in 2003 for quality and safety assurance of raw materials and packaging materials manufactured from biological materials and used in the manufacturing process for drugs, quasi-drugs, cosmetics, and medical devices based on the provisions of Article 42, Paragraph 1 (Standards of Drugs, etc.) of the Law. These standards including interim measures came into effect from July 30, 2003. They consist of General Notices, General Rules for Blood Products, General Rules for Human-derived Biological Products, and General Rules for Animal-Derived Biological Products. The Standards for Cell and Tissue-Derived Drugs and Medical Devices were abolished on July 29, 2003. With the specification of the Standards for Biological Materials, the Minimum Requirements for Biological Products were partially revised by MHLW Notice No. 211 in 2003 and the General Rules for Blood Products were abolished by the Minimum Requirements for Biological Products.

Notice No. 262 issued by the MHLW on July 5, 2004 states that the standards for raw materials of biological origin have been partially revised as indicated below. These revisions, including interim measures, came into effect on the day of notification.

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

Based on Notice No. 310 of the MHLW dated September 28, 2007, Chile was removed from the list of countries of origin of raw materials originating from cows and other ruminants. Based on Notice No. 343 of the MHLW dated July 1, 2009, the use of raw materials of ruminant origin with Canada as the country of origin was approved to be used within the same range as that of materials from the

United States as the country of origin.

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

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

5.4 Quality Standards Based on Notifications

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

- Japan Pharmaceutical Codex
- Japan Crude Drug Codex
- Insecticide Standards
- Standards for Raw Materials for in vitro Diagnostics
- Japan Pharmaceutical Excipient Standards
- Japan Standards of Quasi-drug Ingredients

5.5 Government Batch Test

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

At present, a part of biological products is subject to such testing. The designated testing institution is the National Institute of Infectious Diseases.

6. PHARMACEUTICAL SUPERVISION

6.1 Pharmaceutical Supervision

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

- Revocation of approval or change orders in approved items
- Revocation of licenses or business suspension orders
- Temporary suspension of sales and disposal of drugs,

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, manufactured or approved products should report to the effect that it initiated recall, recall status, and to the effect that it has completed recall to the prefectural governor. (Article 68-11 of the Law and Article 228-22 of the Regulation.)

Such products should be recalled as having a concern in safety or efficacy due to a failure or as violating the Drugs and Medical Devices Law or approved condition, and all recall information is published on the PMDA website.

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 the EU. Class I: Serious health damage or death may be caused by use of the product.

Class II: Transient or medically-curable health damage may be caused by use of the product, or serious health damage may not be caused by use of the product.

Class III: Health damage may not be caused by use of the product.

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

6.3 Prevention of Medical Accidents Caused by Drugs, etc.

A notification was issued to eliminate mistakes in the use of drugs, etc., in connection with the name, container, specifications, etc. in order to prevent medication accidents (Notification No. 935 of the PMSB dated September 19, 2000). More active participation of related companies was requested in Notifications No. 1127003 of the PFSB dated November 27, 2003 and No. 0602009 of the PFSB dated June 2, 2004. For the brand names of new drugs, guidance on the use of a flowchart to avoid use of similar names for newly approved drugs applied in the Japan Pharmaceutical Information Center (JAPIC) is given in an Office Communication dated October 17, 2005. General principles for brand names of generic drugs are given in Notification No. 0922001 of the Evaluation and Licensing Division, PFSB dated September 22, 2005.

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

6.4 Safety Measures against Bovine Spongiform Encephalitis (BSE)

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

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

As a preventive measure in keeping with international trends to enhance safety measures for drugs and medical devices using bovine-derived raw materials, Notification No. 0414004 of the PMSB dated April 14, 2003 concerning bovine-derived raw materials was issued to require precautions related to the site of use and other factors, handling of blood products, handling of products derived from human urine and handling of approvals. Based on Notification No. 0522002 of the PMSB of 2003, "Canada" was added to countries in which BSE occurred in Attached Table 1 and "Canada" was removed from countries of low risk for BSE in Attached Table 2 of the Notification No. 1069 of the PMSB of 2001.

Following the confirmation of a cow infected with BSE in the United States in December 2003, the PFSB issued Notification No. 0218004 dated February 18, 2004 entitled "Quality and Safety Assurance Related to Drugs, medical devices, etc., manufactured using bovine and other ruminant-derived products and bovine and other ruminant-derived spinal products from the United States" and Notification No. 0218001 of the Evaluation and Licensing Division, PFSB and Notification No. 0218003 jointly issued by the Evaluation and Licensing Division and the Safety Division, PFSB dated February 18, 2004 entitled "Handling of Approvals with Respect to Quality and Safety Assurance Related to Drugs, Medical Devices, etc., Manufactured Using Bovine and Other Ruminant-Derived Products and Bovine and Other Ruminant-Derived Spinal Products from the United States". Notification No. 0705001 of the PFSB dated July 5, 2004 entitled "Handling of Approval Applications Concerning Quality and Safety Assurance of Drugs and Medical Devices Manufactured Using Bovine and Other Ruminant-Derived Products and Bovine and Other Ruminant-Derived Spinal Products from the United States Associated with the Partial Revision of the Standards for Biological Materials" was issued.

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

It has been considered necessary to adopt quality and safety assurance measures based on current scientific levels

for drugs manufactured using raw materials of human or animal origin. Companies have been requested to undertake voluntary inspections and make adjustments in approval documentation.

Notice 262 issued by the MHLW in July 2004 partially revised the Standards for Biological Materials and Notification No. 0705001 of the PFSB dated July 5, 2004 entitled "Partial Revision of the Standards for Biological Materials" was issued. Notification No. 0325003 of the Evaluation and Licensing Division, PFSB dated March 25, 2005 entitled "Handling of TSE Data Associated with Enforcement of the Partially Amended Pharmaceutical Affairs Law" was also issued.

In an office communication of the Compliance and Narcotics Division, PFSB dated September 5, 2006 entitled "Self-checking of Drugs, etc. Using Raw Materials Derived 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. The Evaluation and Licensing Division of PFSB issued Notification No. 0928001 dated September 28, 2007 entitled "Handling of Pharmaceutical Products Using Bovine-Derived Materials to Comply with Partial Revision of the Standards for Biological Materials," notifying the removal of Chile from the list of countries free from where biological materials can be imported for medical use and again requested the industry to self-inspect the compliance with the Standards for Biological Materials. Incidents of BSE were reported in Brazil in December 2012 and in Norway in January 2015 and, in both cases, the Ministry issued a notification to local departments and the industry to implement voluntary inspection and preventive measures (Notification No. 1211-(8) of the PFSB dated December 11, 2012 and Notification No. 0130-(12) of the PFSB dated January 30, 2015).

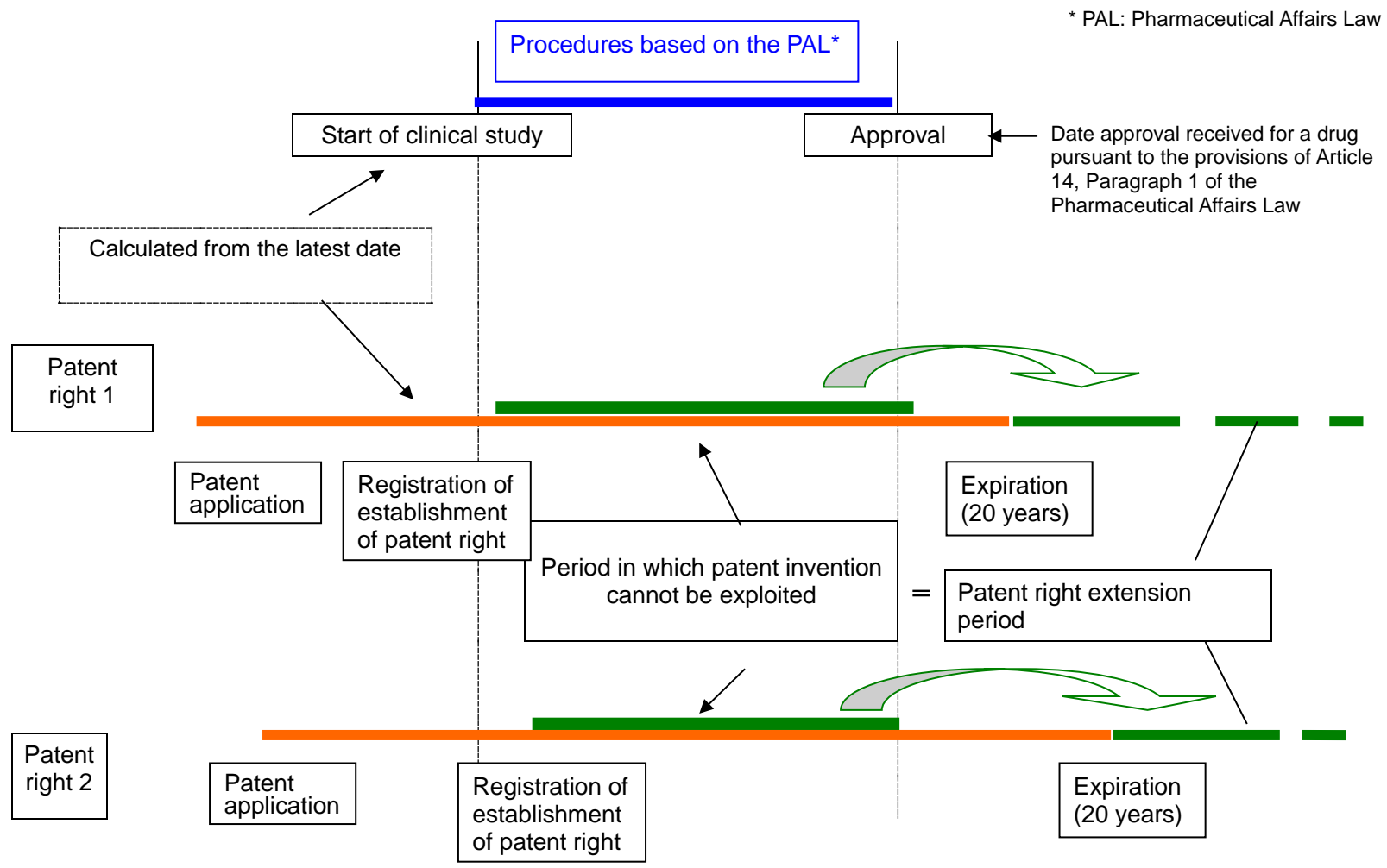


Fig. 4 Flowchart of Patent-Life Extension

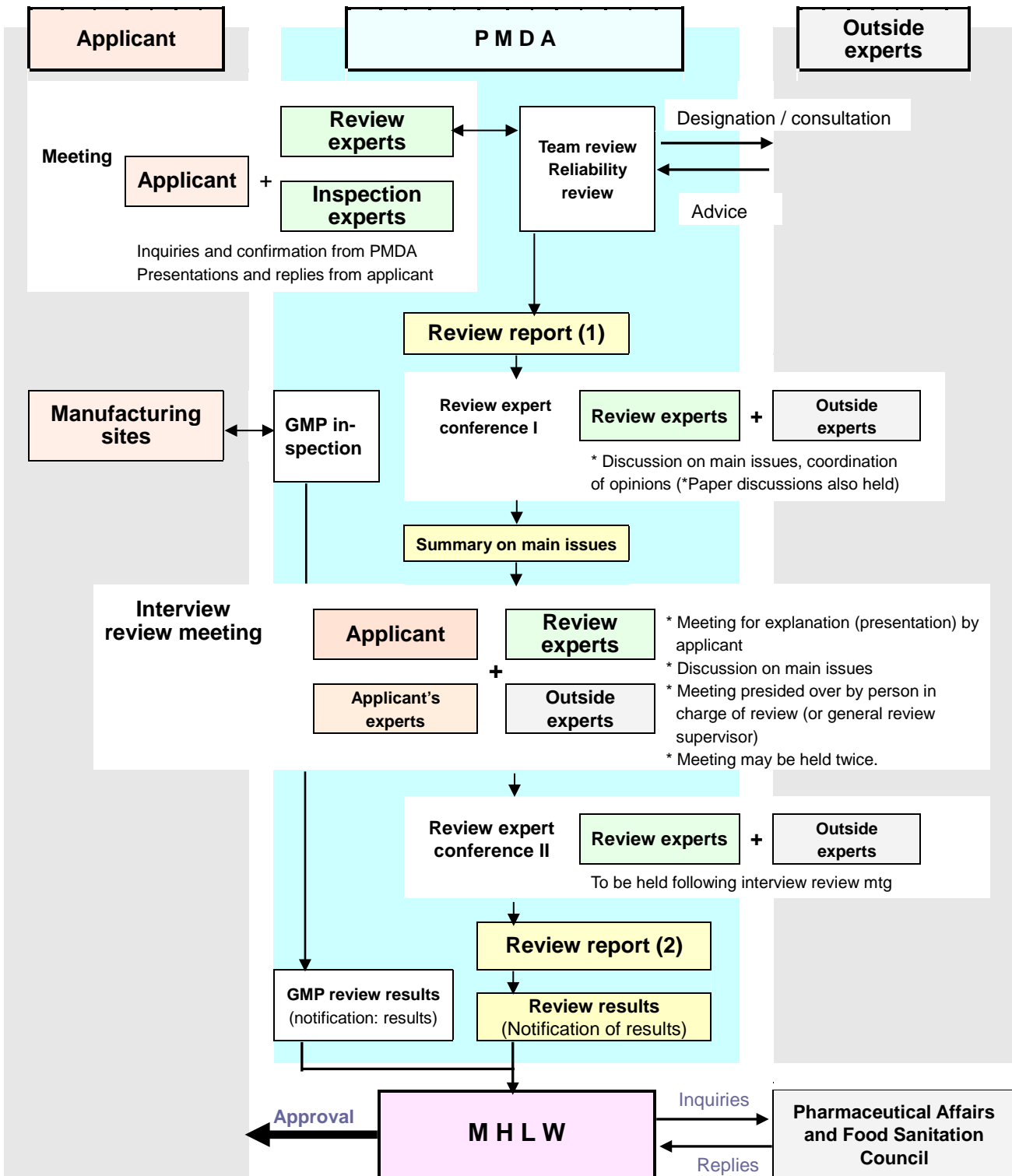


Fig. 5 Flowchart of Approval Review

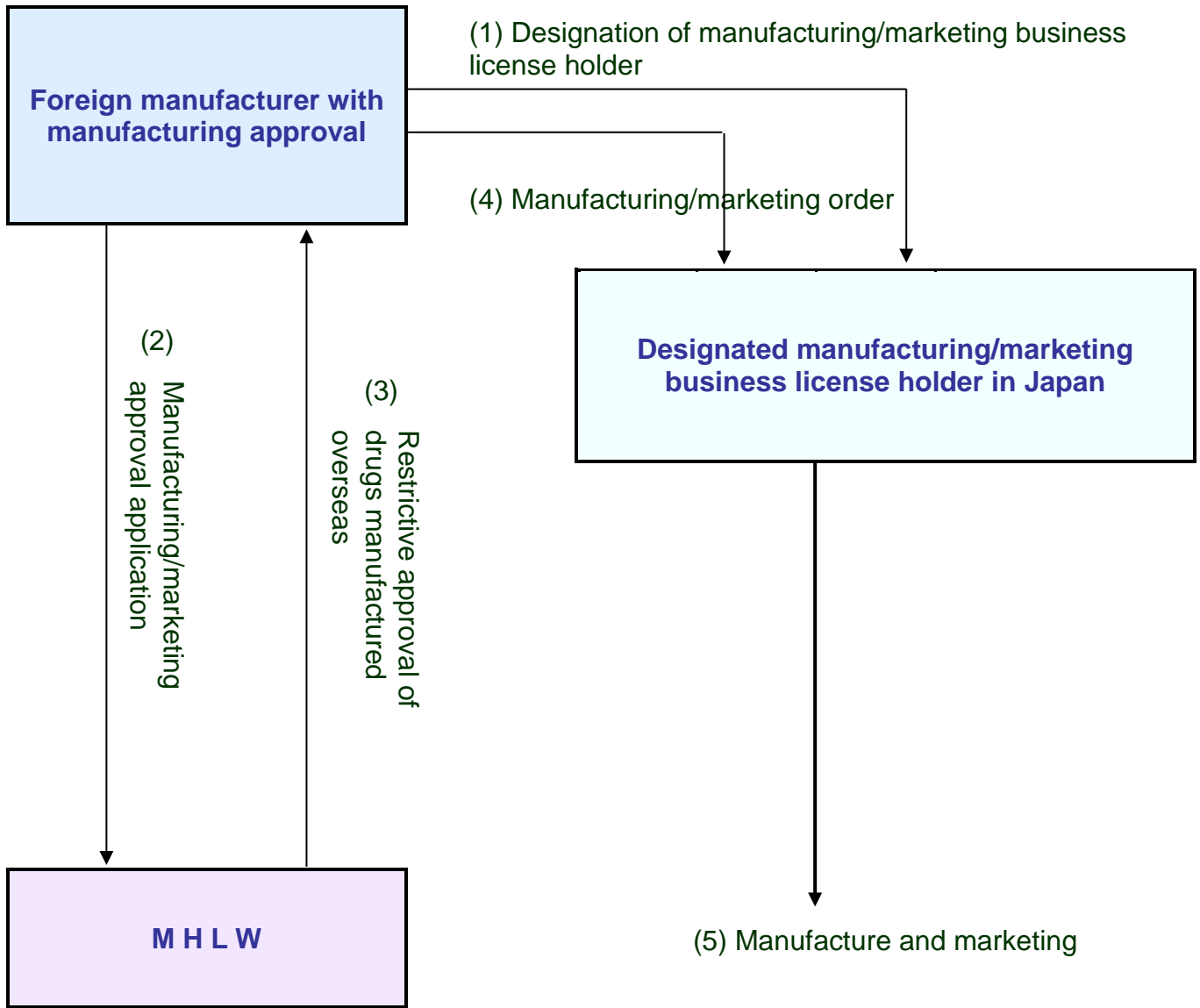


Fig. 6 Procedure for manufacturing and marketing approval of drugs for overseas manufacturers in Japan

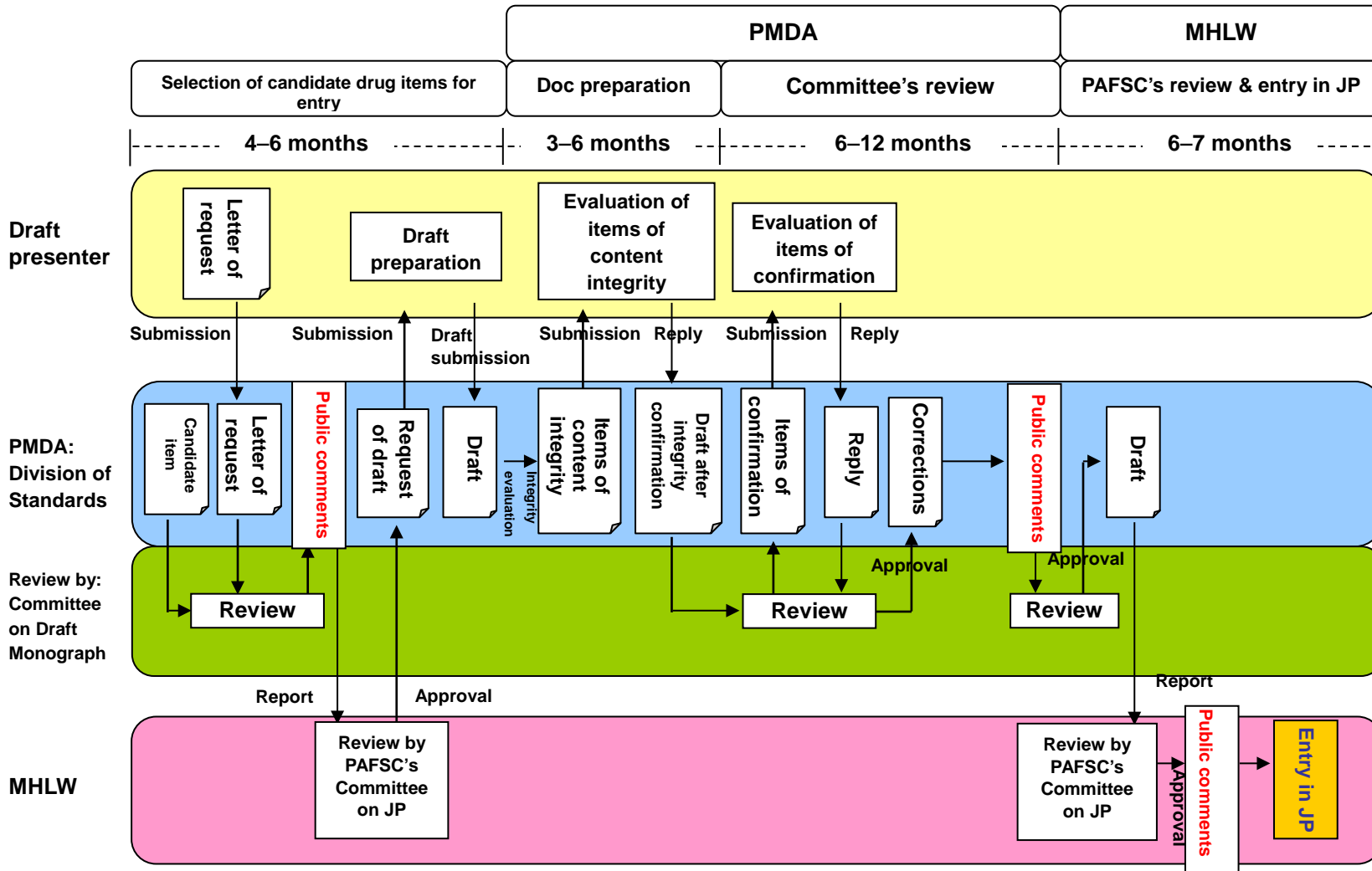


Fig. 7 Flowchart of Drug Listing in Japanese Pharmacopoeia

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 and powdered opium	Opium and powdered opium obtained by concentration and processing of the liquid extract from the opium poppy. Opium and powdered opium processed as drugs are not controlled by the Opium Law but regulated as narcotics under the narcotics and psychotropics classification.
Stimulants	Stimulants are drugs specified as drugs which are habit-forming, can cause severe damage when abused and have potent stimulant effects. The stimulants specified in the Stimulants Control Law include phenylaminopropanes (amphetamines), 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
Evaluation and Licensing Division	<ol style="list-style-type: none"> 1. Items related to business licenses for manufacturing of drugs, quasi-drugs, etc. 2. Items related to manufacturing/marketing approvals (notification) for drugs, quasi-drugs, etc. 3. Items related to attached documentation for new drug manufacturing/marketing approval applications 4. Items related to compliance of drugs with GLP Ordinance (Standards for Conduct of Nonclinical Studies on the Safety of Drugs) 5. Items related to certification of pharmaceutical products (drugs) 6. Items related to statements of approval and licensing status of pharmaceutical products 7. Items related to clinical trial protocol notifications for drugs
Medical Device and Regenerative Medicine Product Evaluation Division	<ol style="list-style-type: none"> 1. Items related to business registrations for manufacturing of medical devices 2. Items related to manufacturing/marketing approvals (notification) for medical devices 3. Items related to business registrations and licenses for manufacturing of extracorporeal diagnostic medicines and regenerative medicine products 4. Items related to manufacturing/marketing approvals (certification/notification) for extracorporeal diagnostic medicines and regenerative medicine products 5. Items related to attached documentation for manufacturing/marketing approval applications for regenerative medicine products 6. Items related to compliance of regenerative medicine products with GLP Ordinance (Standards for Conduct of Nonclinical Studies on the Safety of Regenerative Medicine Products) 7. Items related to certification of pharmaceutical products (extracorporeal diagnostic medicines and regenerative medicine products) 8. Items related to statements of approval and licensing status of pharmaceutical products (extracorporeal diagnostic medicines and regenerative medicine products)
Safety Division	<ol style="list-style-type: none"> 1. Items related to business licenses for manufacturing/marketing of drugs, quasi-drugs, medical devices, extracorporeal diagnostic medicines and regenerative medicine products (Note: The certificate is issued by other division in case the certification is originally requested as an attachment to the application to such division.)
Compliance and Narcotics Division	<ol style="list-style-type: none"> 1. Items related to compliance of drugs and quasi-drugs with GMP requirements (except for items related to certification of pharmaceutical products) 2. Items related to compliance with requirements of Ministerial Ordinance on QMS for Medical Devices and In Vitro Diagnostics 3. Items related to compliance with requirements of Ministerial Ordinance on GCTP for Regenerative Medicine Products 4. Items related to compliance of drug manufacturing plants with GMP requirements for investigational products