

MEDICAL DEVICE APPROVAL PROCESS IN JAPAN

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ABSTRACT

The Ministry of Health, Labor and Welfare (MHLW or Koseirodoshō in Japanese) is in charge of the pharmaceutical regulatory affairs in Japan. Formal approvals and licenses are required to marketing drugs in Japan which are obtained from the MHLW. Japan's Pharmaceutical and Medical Devices Agency (PMDA) has set itself the challenging task of expediting patient access to novel therapies while ensuring these meet international standards of safety, efficacy and quality. One of the biggest hurdles for the government is the "drug lag" problem, whereby many new innovative medicinal drugs do not reach the Japanese market until several years after the United States (US) and Europe (EU). This delay is caused due to the obligation to perform clinical bridging studies in Japan hand since clinical data obtained in non-Japanese trials such as EU and US studies cannot solely be used to obtain market approval in Japan. Japan provides a public medical insurance system, which is carried on as a social insurance system covering all citizens. Through this insurance system, about 30% of the nation's medical expenses are covered by public funds, and all prices for medicine, including medical compensation for doctors and prices for new drugs are substantially controlled by the Japanese government.

Key words: MHLW, PMDA, pharmaceutical affair law, PMS, medical insurance.

INTRODUCTION

Japan is the second largest pharmaceutical market behind the United States and a highly developed country. It has been discovered that Japanese people are using multiple drugs with an especially high use of recently approved drugs. The patient awareness is now similar to that in the Western countries. Medicinal products represent over 20% of healthcare costs with about almost 50% in elderly patients. Therefore Japan becomes more and more attractive for the pharmaceutical industry.

One of the biggest hurdles for the government is the "drug lag" problem, whereby many new innovative medicinal drugs do not reach the Japanese market until several years after the United States (US) and Europe (EU). This delay is caused due to the obligation to perform clinical bridging studies in Japan hand since clinical data obtained in non-Japanese trials such as EU and US studies cannot solely be used to obtain market approval in Japan. On the other hand there are long review periods for clinical trial applications and marketing applications. To minimize this "drug lag" the Japanese government is encouraging pharmaceutical companies to conduct simultaneous clinical development and include Japan in global clinical trials. Pharmaceutical companies also want to develop medicinal products more or less in parallel in the major markets of the US, EU and Japan even this aspect is driven by more commercial considerations. Once the clinical development program is finished and all data are compiled the dossier has to be created to be filed with the respective authorities.

To simplify the general life cycle management a harmonized dossier approach would be of advantage. A harmonized dossier is easier to handle since the same document can be used for all countries. It also facilitates the compliance of the documentation, increases the supply flexibility and facilitates the communication between external and internal regulatory communication units. Once the marketing authorization is granted variations (clinical or quality based) or extension applications update of one dossier is faster than different dossiers.

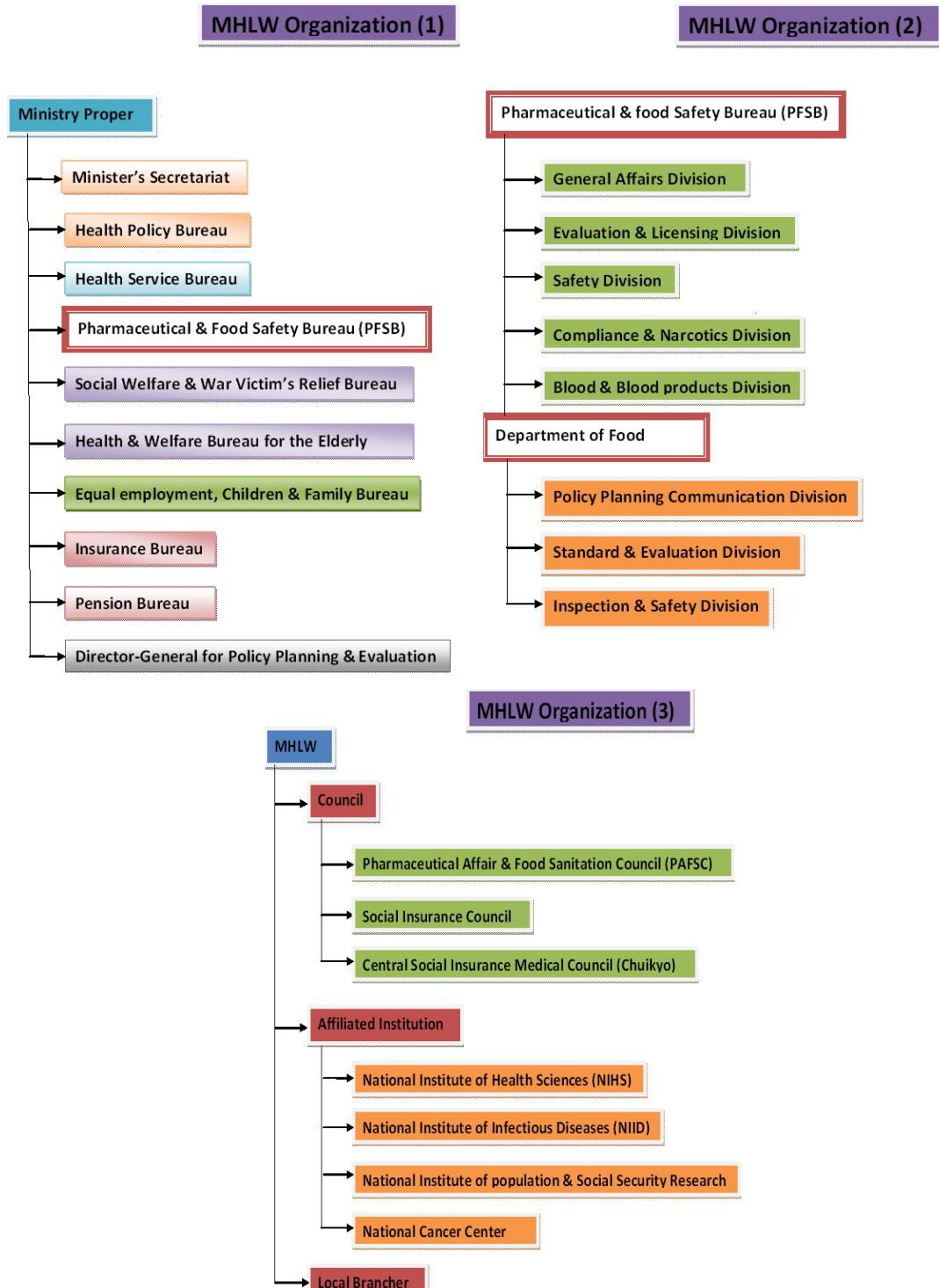
MHLW:

The Ministry of Health, Labor and Welfare (MHLW) is regulatory authority of the pharmaceutical regulatory affairs in Japan. Formal approvals and licenses are required to marketing drugs in Japan which are obtained from the MHLW.

The MHLW was established in January 2001 as part of the government program for reorganizing government ministries. One of the 11 bureaus of the MHLW is the Pharmaceutical and Food Safety Bureau (PFSB). This bureau handles clinical studies, approval reviews and post-marketing safety measures.

Functions of MHLW:

- To give a marketing approval.
- To issue a license for marketing authorization holder.
- To issue a manufacturer license



PHARMACEUTICALS AND MEDICAL DEVICES AGENCY (PMDA):

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

The work of the PMDA can be divided into following categories:

- ADR relief work: Collection, examination and analysis, assessment & provision of ADR information
- Review and Implementation of works, such as examination, data analysis, etc. before administrative measures eg.
 - Scientific review of Pharmaceuticals and Medical Devices application,
 - GLP/GCP/GMP/QMS inspection,

- Clinical trial consultation

The PMDA consists of 22 offices and 2 groups as follows: the Office of General Affairs, Office of Financial Management, Office of Planning and Coordination, Office of Regulatory Science, Office of International Projects and Office of International Liaison, Office of Relief Funds, Office of Review Administration, Office of Review Management, Office of New Drug I, Office of New Drug II, Office of New Drug III, Office of New Drug IV, Office of New Drug V, Office of Biologics I, Office of Biologics II, Office of OTC and Generic Drugs, Office of Medical Devices I, Office of Medical Devices II, Office of Conformity Audit, Office of Safety I, Office of Safety II, Office of Compliance and Standards Officer,

Subjects of GMP Inspection by PMDA

- ❖ Domestic manufacturing sites which are manufacturing following products;
 - New drugs
 - Biological Products
 - Products derived from human blood and human plasma
 - Vaccines
 - Tissue-based pharmaceuticals
 - Radiopharmaceuticals
 - Biotechnology-products
- ❖ Foreign manufacturing sites^{1,2,3,4,5}

PHARMACEUTICAL AFFAIRS LAW:

The objective of the Pharmaceutical Affairs Law is to improve public health through regulations required to assure the quality, efficacy, and safety of drugs, quasi-drugs, cosmetics, and medical devices, and through measures to promote R&D of drugs and medical devices that are especially essential for health care.

Manufacturing and marketing medical devices are regulated by the Pharmaceutical Affairs Law (PAL). The current PAL came into effect in April 2005 after the revision of the Pharmaceutical

Affairs Law was promulgated in 2002. The revision has been undertaken from the viewpoint of international regulatory consistency. Namely,

- (a) Substantial reforms of safety measures for medical devices,
- (b) Revision of the approval and licensing system and enhancement of post marketing safety measures,
- (c) Enhancement of safety measures of biological products. This report highlights the above revised points and explains procedures for manufacturing and marketing medical devices in connection with PAL^{6,7}

Medical device:

An instrument or apparatus intended for use diagnosing, curing, or preventing diseases in humans or animals, or

intended to affect the structure or functions of the bodies of humans or animals.

Classification:

- (1) General medical devices: these are extremely low risk devices and marketing approval not required.
- (2) Controlled medical devices: these are low risk devices and third party certification required
- (3) Specially controlled medical devices: these are high risk medical devices and marketing approval required.

LICENSE FOR MARKETING AUTHORIZATION:

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.

A GMP compliance review is performed to assure that the plant manufacturing the product complies with the manufacturing control and quality control standards. Marketing approval is granted to products meeting these standards. This approval system is the essential basis for ensuring good quality, efficacy, and safety of drugs and related products, which is the principal objective of the Pharmaceutical Affairs Law.

The Pharmaceutical Affairs Law of Japan requires a license for marketing authorization when importing to Japan and selling pharmaceutical products manufactured in other countries.

To receive a license for marketing authorization, the manufacturer/seller must, at the very least, employ the following personnel full time: a General Manufacturing and Marketing Officer, a Quality Assurance Officer, and a Safety Management Officer.

A license for marketing authorization may not be granted if the quality management methods and post marketing safety management methods applied with respect to the pharmaceutical product fail to conform to the standards stipulated in the ordinances promulgated by the Ministry of Health, Labour and Welfare. Licenses for marketing authorization are granted by the prefectural government for the location of the office where the General Manufacturing and Marketing Officer is stationed.

Manufacturing License:

When manufacturing pharmaceuticals in Japan, each manufacturing location requires a manufacturing license. As a condition to receiving a manufacturing license, there must be a full-time pharmacologist in each manufacturing location who serves as the Pharmaceuticals Manufacturing Manager (Managing Pharmacist). In addition, the structure and facilities at the location must satisfy criteria stipulated in the ordinances promulgated by the Ministry of Health, Labor and Welfare.

The manufacturing license is issued by the governor of the prefecture in which the manufacturing location is located except in cases requiring particularly high levels of expertise. To manufacture pharmaceutical products, a license for marketing authorization holder must also obtain a manufacturing license. A license for marketing authorization holder may entrust all manufacturing of the pharmaceutical product to a third party, but the party entrusted with manufacture must obtain a manufacturing license. Parties that receive manufacturing licenses may be held criminally accountable and/or may be subject to administrative disposition, including cancellation of licenses, in the event of violations of the Pharmaceutical Affairs Law.

Accreditation of Foreign Manufacturers:

The Pharmaceutical Affairs Law stipulates that when pharmaceutical products are manufactured in other countries for export to Japan, the foreign manufacturer may receive accreditation from the Minister of Health, Labor and Welfare for each foreign location at which pharmaceutical products are manufactured, and in actual practice, foreign manufacturers are required to obtain this accreditation.

Manufacture and Sale Approval:

Parties engaged in manufacture/sale must in principle receive the approval of the Minister of Health, Labor and Welfare for the manufacture and sale of each pharmaceutical product to be manufactured and sold (including import sales) in Japan. Notwithstanding, approval may be revoked in the event of problems with the efficacy or safety of a pharmaceutical product after it has been approved.

Exceptional Approvals for Foreign Countries:

Under the Pharmaceutical Affairs Law, enterprises located in foreign countries may apply for manufacture and sale approval from outside of Japan. For example, a foreign pharmaceuticals manufacturer who wishes to obtain approval for manufacture and sale in Japan may nominate a party to conduct manufacture/sale in Japan and seek approval from the Minister of Health, Labor and Welfare for manufacture and sale by that party. The party nominated to manufacture and sell the pharmaceutical must obtain a license for marketing authorization and must discharge all responsibilities as a manufacturer/seller.

Post marketing Safety:

The pharmaceutical manufacturer/seller and the party obtaining approval under foreign country exceptions are required under the Pharmaceutical Affairs Law to collect and investigate information on side effects and infections resulting from the pharmaceutical product.

Reports must be filed with the Minister of Health, Labor and Welfare in the event that an objective assessment of the information obtained indicates that the pharmaceutical product meets certain criteria stipulated in the ordinances promulgated by the Ministry of Health, Labor and Welfare.^{7,8,9}

JAPAN NEW DRUG APPLICATION (J-NDA) PROCEDURE:

The pharmaceutical administration in Japan consists of various laws and regulations of which the Pharmaceutical Affairs Law (PAL) is a fundamental one consisting of 11 chapters and 91 articles.

Various regulations apply to the development, manufacture, import, marketing and proper use of drugs exists. Some of the main regulations affecting pharmaceuticals are listed below:

- Quality standards and government standards e.g. Japanese Pharmacopeia (JP)
- Classification of drugs e.g. biological products and specified biological products
- Concerning marketing approvals e.g. revision in April 2005
- GMP status e.g. GMP certificate as prerequisite to obtain a manufacturing business license
- Accreditation of overseas manufacturers e.g. accreditation is required to export medicinal products from overseas to Japan
- GLP and GCP standards
- Good Quality Practice (GQP) on marketed products
- Good Vigilance Practice (GVP) on marketed products etc.

Pre-submission Activities

Consultation Meetings

In Japanese culture it is uncommon to make decisions during consultation meetings based on information, which is exchanged in this same meeting by means of discussion or presentation. Usually, in Japan decisions are either made prior to a meeting based on available information or, alternatively, the final decision is taken after the meeting. In case the decision is taken prior to the meeting the outcome is then basically only explained during the meeting. Therefore it is recommended to provide a strategy which allows influencing the thinking of the PMDA prior to the meeting. Prior to the official consultation meeting pre-meetings are taking place to discuss the content of the dossier in advance for review. In 2005 the activities of the PMDA consultation meeting were evaluated to review the timelines of such meetings. New shorter timelines were determined which were again revised in 2008.

Approval Procedure

The PAL's principle objective is to provide an approval system which ensures good quality, efficacy and safety of the medicinal products to be marketed and used for healthcare in Japan.

The approval review process consists of the following steps:

- ❖ J-NDA evaluation process

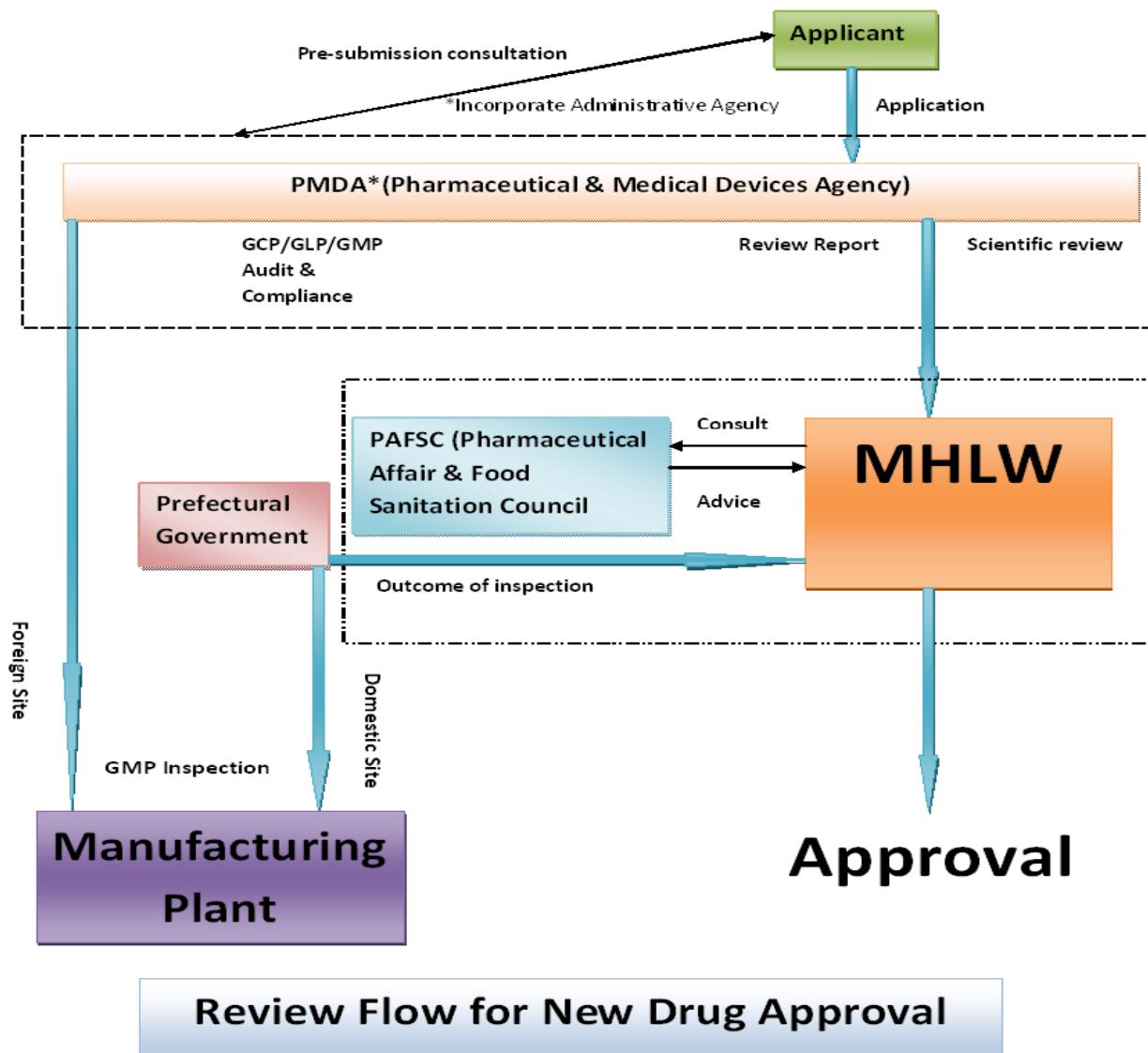
- ❖ Compliance Review (including GCP inspection)
- ❖ GMP inspection (can also be performed as paper audit)

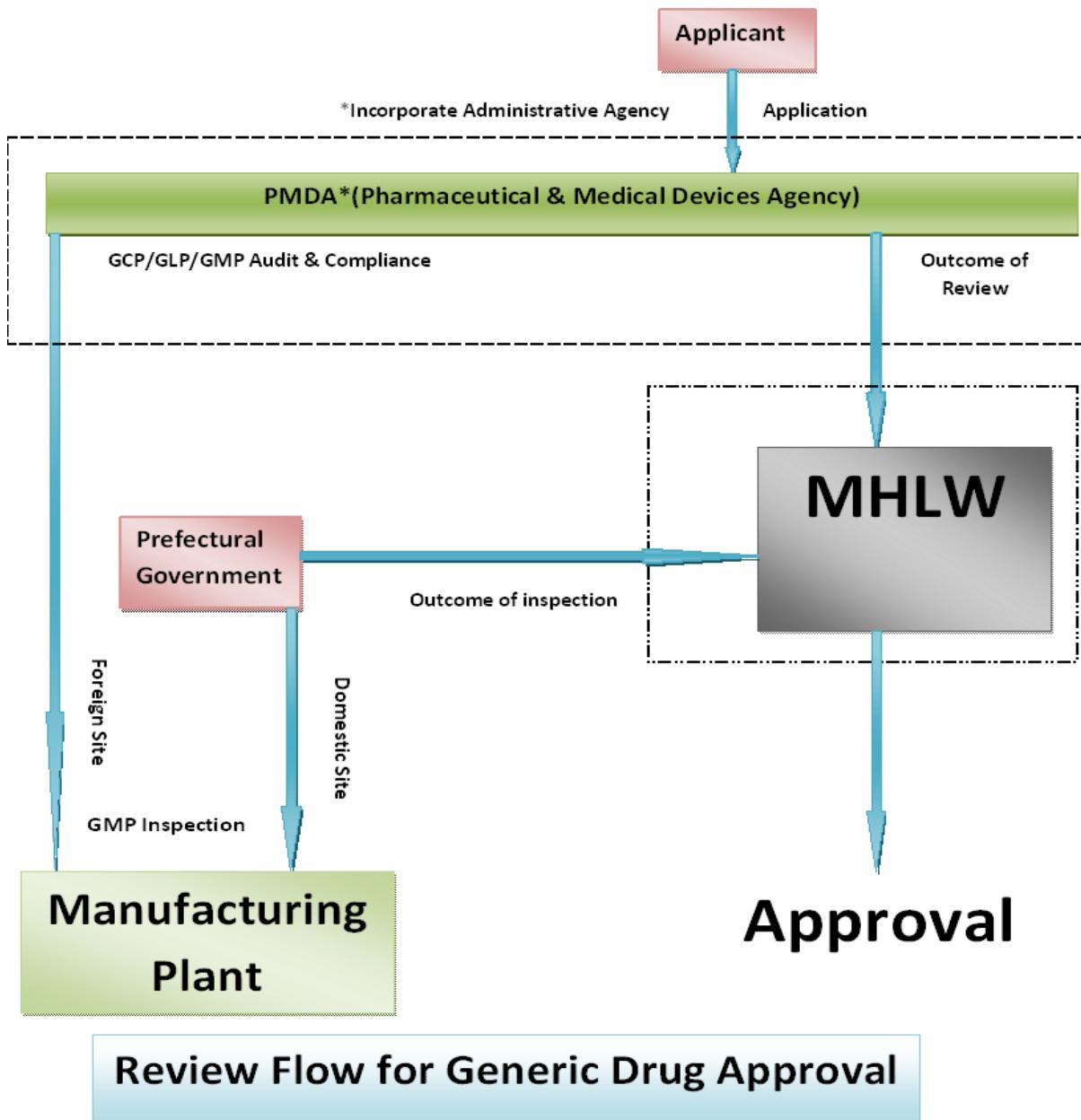
Priority Review Designation

NDA approvals reviews are normally processed in the order the application forms are received. For medicinal products considered to be especially important from a medical standpoint such as new drugs treating serious diseases and meeting especially high medical need, priority review can be granted (for orphan drugs priority review is automatically granted).

Criteria for priority review are severity of the target indication (disease with important effect on patient's survival (fatal disease), progressive and irreversible disease with marked effect on daily life) and medical efficacy (no existing treatments available, superior to currently available therapies with regard to efficacy, safety and quality of life).

Products of priority review are given priority at each stage of the review process as much as possible. The process of the MHLW could therefore be shortened from 12 months to 6 months which results in a total of 12 – 18 months approval period. When a drug product subject to priority review is approved this fact is made public.





Accreditation:

A foreign manufacturer who intends to export medicinal drugs into Japan is required to be accredited by the MHLW as an “Accredited Foreign Manufacturer”. The applicant is required to submit an “Application for Accreditation” that is addressed to the minister and an “Application for Accreditation Examination” to the chief executive of the PMDA (16). Among the documents which have to be attached to the accreditation application (all documents have to be translated into Japanese) is a medical certificate from a physician which indicates whether or not the applicant (e.g. the CEO of a company) has mental disorders or is addicted to narcotics, cannabis, and opium or stimulant drugs. The application should be submitted at latest when the NDA is

submitted. The accreditation process takes about 5 months. The accreditation needs to be renewed every 5 years.

Post Authorization Activities:

Information concerning the new drug approval prepared from the review data (final evaluation report) 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 the medical institutions.

The PMDA request the applicant to provide a masking proposal of the evaluation report and a masking proposal for the data that summarizes non-clinical and clinical results.

Masking of quality data is not necessary since they are not included in such publication report. Information related to the quality of the medicinal product is provided in the information to the doctors. The summary data should be published within 3 months after approval at the latest.^{10,11}

DATA REQUIRED FOR APPROVAL OF APPLICATIONS (DOSSIER CREATION):

The dossier has to be created according to the ICH guideline for Common Technical Documents (CTD) and follows the CTD structure. Therefore the dossier exists of Module 2 with the summary documents for quality, non-clinical and clinical, Module 3 including the quality data, Module 4 the non-clinical data and Module 5 the clinical data, respectively. In addition regional information e.g. labeling information is provided in Module 1.

In Japan Module 3, 4 and 5 can be submitted in English whereas Module 1 and 2 have to be translated into Japanese. Module 1 contains in Japan the so called "Application Approval Form" (AAF) listing product formulation, relevant manufacturing information, shelf life and storage condition as well as the specification and test methods.

Module 1

Module 1 contains the following information:

- NDA application form (including AAF and position paper for priority review, if applicable)
- Certificates (GLP, GCP statements, expert statements)
- Patent status information
- Discovery, research and development history
- Conditions of use in foreign countries (including labeling information)
- List of other drugs with similar pharmacological action
- Draft package insert
- Documentation of non-proprietary name
- Summary of data on designation e.g. powerful drug
- Draft protocol for post-marketing surveillance
- List of attached documents (Module 3, 4 and 5)
- Others:
 - ❖ Application form for accreditation and registration of foreign manufacturers
 - ❖ Application form for GMP inspection
 - ❖ List of laboratories conducting GLP studies
 - ❖ GCP compliance report
 - ❖ Application form for document review

Application Approval Form (AAF)

The AAF describes critical aspects of the drug. It is attached to the license upon approval. The "approved" items

described are binding. They determine a regulatory commitment and are the basis of post-approval changes. Topics which are not mentioned in the AAF may be changed without regulatory consequence.

The AAF contains the following information:

- General information as required e.g. name, dosage and administration, use or indication, storage method and shelf life, specifications and test methods, manufacturing facility, drug substance facility
- Information about ingredients and content Composition: amount of excipients and specifications (JP)
- Specifications and test methods
- Reference substance
- Manufacturing methods
- Manufacturing facility -Drug substance manufacturer, Drug product manufacturer, External testing facilities.

Information listed in the AAF should be a summary of the information in the QOS e.g. manufacturing description and in-process controls and test methods. The information is provided in special format as provided by the PMDA. Summary tables and figures should be included with very brief narratives of the information provided in the QOS. In the manufacturing description the items applicable to minor change notification or partial change application have to be highlighted. On the other hand, specifications and test methods in the AAF should be a copy of the description in the QOS.

Module 2 (QOS)

- (1) Modules 2 to 5 (CTD) table of contents
- (2) CTD introduction
- (3) Quality overall summary
- (4) Nonclinical overview
- (5) Clinical overview
- (6) Nonclinical summary (text and tables)
 - Pharmacology
 - Pharmacokinetics
 - Toxicity
- (7) Clinical summary
 - Summary of bio pharmaceutics and associated analytical methods
 - Summary of clinical pharmacology studies
 - Summary of clinical efficacy
 - Summary of clinical safety
 - Literature references
 - Synopses of individual studies

The QOS of Module 2 is the main review document for the PDMA. In Japan it is expected that the applicant summarizes all critical data from Module 3 together with a sufficient discussion on every critical point for ensuring the quality of the medicinal product. The QOS should be written in a way that it makes it possible for the reviewer to understand the characteristics of the drug within a short time and to review the J-NDA application efficiently.

The QOS should include many figures and tables which summarize the critical data. It contains more detailed information The Pharmaceutical Manufacturers Association of Tokyo, Osaka Pharmaceutical Manufacturers Association and Japan Health Sciences Foundation issued in July 2002 a Mock-up of the Japanese QOS. This document can be used for the dossier preparation. Since companies also intend to prepare global dossiers which are applicable for ICH as well as Non-ICH countries the mock-up document can provide specific Japanese requirements which need to be incorporated. Since the QOS in Japan contains more detailed information compared to the QOS for the EU and US a separate QOS has to be prepared which generally contains much more than 100 pages. Writing the QOS in Japanese style facilitates the review process.

Items listed in the manufacturing process description require appropriate change control and are either subject to partial change application or minor change notification. Partial change application requires review and approval of the PMDA which could take 12-18 months. Minor change notification follows the principle of do and tells (within 30 days). Therefore it has to be carefully considered which items should be highlighted as partial change application and which as minor change notification.

3) Module 3: Quality

(1) Module 3 table of contents

(2) Data or reports

(3) Literature references

4) Module 4: Nonclinical study reports

(1) Module 4 table of contents

(2) Study reports

(3) Literature references

5) Module 5: Clinical study reports

(1) Module 5 table of contents

(2) Tabular listing of all clinical studies

(3) Clinical study reports

(4) Literature references^{12,13,14,15,16,17}

REQUIREMENTS FOR DRUG MANUFACTURING AND MARKETING APPROVALS:

Proper control at the stage of drug manufacture is essential so that drugs can be supplied to patients with good quality. This means that the manufacturers and the buildings and facilities

in the manufacturing plants must be appropriate so that drugs based on the approvals can be produced.

The manufacturing process as a whole must be controlled on the basis of scientific principles, and it is also necessary to assure the quality of drugs manufactured by taking measures to prevent errors during processing. When it is not found that the methods of manufacturing control or quality control at a manufacturing plant conform to the standards, the Minister of Health, Labour and Welfare cannot grant a manufacturing and marketing license. And when the buildings and facilities of a manufacturing plant do not conform to the standards, the Minister of Health, Labor and Welfare or prefectural governor can choose not to grant a license.

The requirements for manufacturing control and quality control methods for drug substance should be referred to the Guidelines on GMP for Drug Substance (ICH Q7A, currently Q7) which concretely specifies 20 requirements concerning manufacturing and control of drug substance, including quality control, buildings and facility, validation, as agreed in the ICH5 held in San Diego, California, USA in November 2000. The following sections outline the GMP regulations:

1) Required documentation:

According to the GMP regulation, all of the operations in the plants must be divided into operations for manufacturing control and those for quality control, and various types of documentation are required, including standard operating procedures for standardization of all work conditions (drug product standards, manufacturing control standards, manufacturing hygiene control standards and quality control standards), documentation required for actual operation procedures based on these standards (manufacturing instructions and test and self-inspection protocols), records of the results of all of these operating procedures (records related to manufacture, records of manufacturing hygiene control, and records of tests and self-inspections), and records of storage and distribution.

Additional documents should be compiled if they are considered necessary for proper manufacturing control and quality control. These documents must be retained for designated time periods from the date of preparation. When damage to the health of patients or other users of biological products (biotechnological technology-derived and of biological origin) occurs, records must be retained for the period required to clarify the cause of this damage.

2) Personnel organization:

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

designated in each plant under the Pharmaceutical Affairs Law.

3) Manufacturing control:

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

- To prepare and preserve manufacturing instructions.
- To manufacture products based on the manufacturing instructions.
- To prepare and preserve records related to product manufacture for each lot.
- To check packaging materials for products for each lot, and to prepare and preserve records related to the results thereof.
- To appropriately store and circulate products by lot and packaging materials by control unit, and to prepare and preserve records thereof.
- To check the cleaning of buildings and facilities, and to prepare and preserve records relating to the results thereof.
- To inspect and maintain buildings and facilities on a regular schedule, and to prepare and preserve records thereof. Further, to carry out appropriate calibration of measuring instruments, and to prepare and preserve records relating to the results thereof.
- To check that manufacturing control has been appropriately conducted on the basis of records relating to manufacturing, storage and distribution, as well as to sanitation control.

4) Quality control:

- The manufacturer, etc. must assure that the duties set forth below are carried out systematically and appropriately by the quality department in compliance with standard operating procedures.
- To collect samples required for the testing and inspection of products, etc. for each lot and of packaging materials for each control unit, and to prepare and preserve records thereof.
- To conduct testing and inspection of the samples collected for each lot or for each control unit, and to prepare and preserve records thereof.
- To store samples of products consisting of an amount two or more times greater than the amount required for testing and inspection for each lot under appropriate storage conditions for a period of one year longer than the expiration period or the shelf-life from the date of manufacture for the product concerned.
- To inspect and maintain on a regular schedule the facilities and implements relating to testing and inspection, and to prepare and preserve records thereof. Further to carry out appropriate calibration of measuring instruments relating to testing and inspection, and to prepare and preserve records related to the results thereof.

- To evaluate the test results of the samples collected, and to notify the manufacturing department in writing of the results thereof.
- Further, manufacturers, etc. makes use of the tests and inspections performed in the import source country, they must assure that the quality department carries out the duties set forth below:
- To confirm at on a regular schedule that that the product, etc. is manufactured in accordance with appropriate manufacturing procedures.
- To confirm on a regular schedule that the manufacturing plant of an overseas manufacturer conforms to the standards relating to manufacturing control and quality control in that country, and to prepare and preserve records thereof.
- To confirm the records of tests and inspections carried out by the foreign manufacturer, and to prepare and preserve records thereof.

5) Documents concerning procedures for validation:

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

6) Validation:

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

The validation plan and results must be reported in writing to the quality control unit. The manufacturer, etc. must take appropriate measures when improvements are required in manufacturing control or quality control based on the results of the validation. Records of the measures taken must be prepared and retained.

7) Change control:

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

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

8) Deviation control:

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

- To record the details of the deviation.

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

9) Information related to quality and handling quality defects:

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

- To elucidate the causes of items relating to the quality information concerned, and in cases in which improvements related to manufacturing control or quality control are required, to take the requisite measures.
- To prepare and preserve a record specifying the nature of the quality information concerned, the results of the elucidation of causes, and the measures for improvement, and to promptly and in writing notify and obtain confirmation from the quality assurance department.
- In cases in which the manufacturer, etc. has identified a quality defect or the risk thereof, to assure that the manufacturing control manager notifies quality department in writing on the basis of the standard operating procedures.

10) Product recalls:

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

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

11) Self-inspections:

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

- To undertake their own self-inspections of the manufacturing control and quality control in the plant concerned periodically.
- To report the results of these self-inspections in writing to the manufacturing control manager.
- To prepare and retain records of the results of self inspections.

- The manufacturer must take appropriate measures when improvement is required in manufacturing control or quality control based on the results of the self-inspection. Records of the measures taken must be prepared and retained.

12) Education and training:

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

To systematically educate and train the workers in terms of manufacturing control and quality control.

- To report the status of implementation of education and training in writing to the manufacturing control manager.
- To prepared and retain records of the conduct of education and training.
- To provide personnel engaged in manufacture or testing and inspection with education and training in hygiene control, microbiology, and other matters requisite for the manufacture of sterile products.
- The manufacturer shall provide education and training on microbiology, medicine and veterinary medicine for employees engaged in manufacture or testing of biological products.
- The manufacturer shall provide education and training on the measures required to prevent contamination by microorganisms for employees engaged in work in sterile areas or in areas handling pathogenic microorganisms.

13) Management of documents and records:

The manufacturer, etc. must assure that, with respect to the documents and records specified under 1) through 12) above, a previously designated person.^{18, 19, 20}

POST-MARKETING SURVEILLANCE OF DRUGS:

Post-marketing surveillance (PMS) to assure the efficacy and safety of drugs after they go on the market and to establish proper methods of use of drugs consists of three systems:

- ADR collecting and reporting system
- reexamination system, and
- reevaluation system

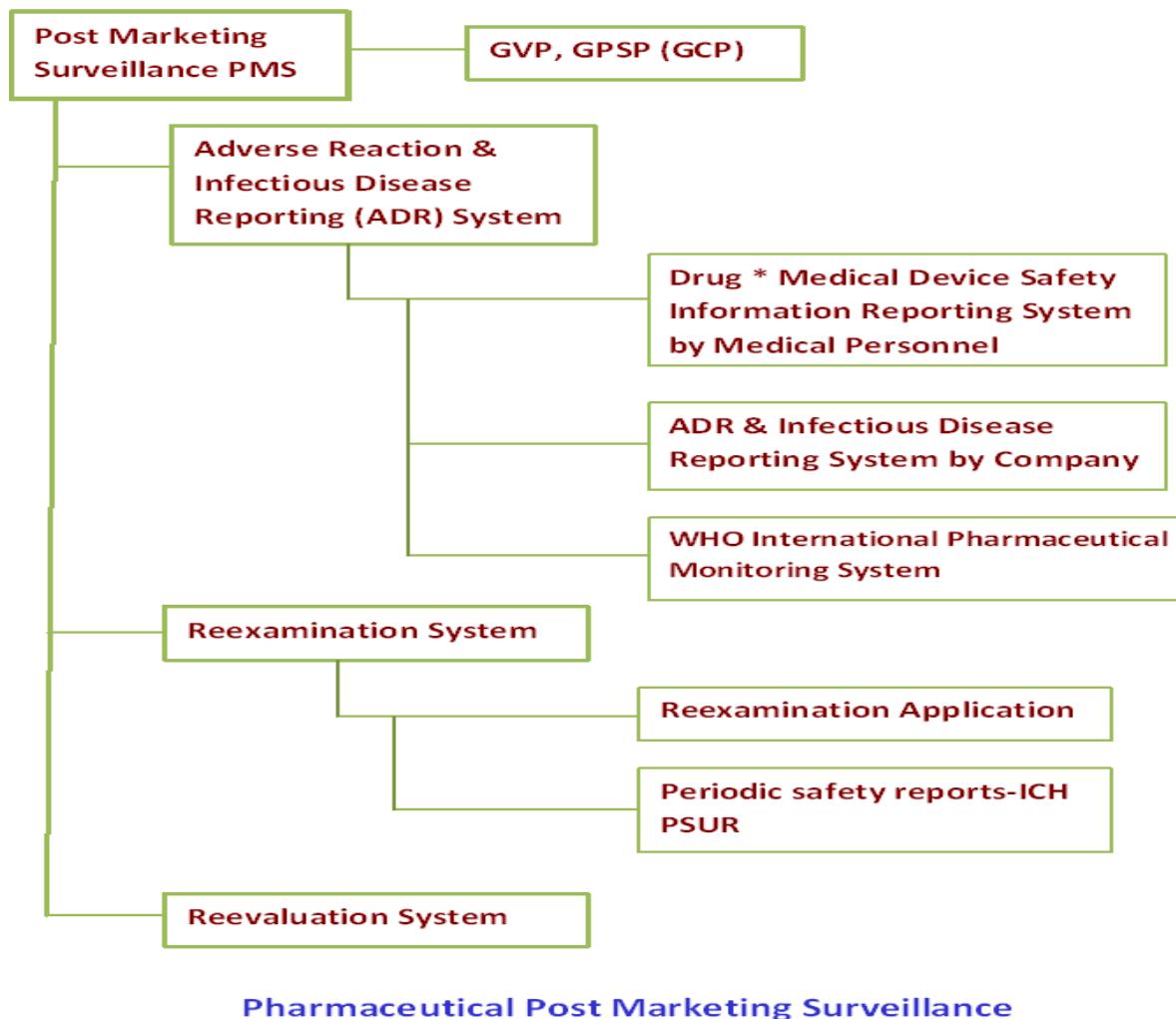
❖ **ADR collecting and reporting system:** Programs for collecting and reporting safety information on drugs such as adverse drug reactions include an adverse drug reaction reporting system undertaken by pharmaceutical companies, the drug and medical device safety information reporting system undertaken by medical personnel, and the WHO International Drug Monitoring Program whereby drug safety information is exchanged among various countries.

❖ **Reexamination system:** The drugs subject to reexamination include products designated by the MHLW at the time of marketing approval as drugs with, for example, active ingredients, and quantities of ingredients, dosage and

administration, and/or indications that are distinctly different from drugs that have already been approved.

been approved, is reconsidered on the basis of the current status of medical and pharmaceutical sciences.^{21,22}

- ❖ **Reevaluation system:** The reevaluation of drugs is a system whereby the efficacy and safety of a drug, which has already



MEDICAL INSURANCES YSTEM:

Japan provides a public medical insurance system, which is carried on as a social insurance system covering all citizens. Through this insurance system, about 30% of the nation's medical expenses are covered by public funds, and all prices for medicine, including medical compensation for doctors and prices for new drugs are substantially controlled by the Japanese government. Recently, because the nation's medical expenses are expected to increase along with the aging of Japanese society, policies for constraining the nation's medical expenses have been adopted, which have significantly affected Japan's pharmaceutical market.

The Japanese government determines prices reimbursed by public medical insurance for each of preparations and standards of all drugs prescribed by doctors. The reimbursement price of each drug is reviewed every two

years and almost all reimbursement prices of drugs are reduced, including those of new drugs immediately after their release onto the market.

This system is called the "Drug Pricing System" and under the system, expenses for drugs covered by medical insurance are constrained and as a result, the size of the Japanese pharmaceutical market has been kept at a certain level in recent years. On the other hand, among major advanced nations, only Japan has a system in which the prices of new drugs immediately after their release onto the market are reduced through political action.²³

CONCLUSION:

Japan has made significant progress in reforming and modernizing its drug and medical device approval process in recent years. Although approval times continue to lag behind those of other developed countries, the government has set ambitious goals and the PMDA and MHLW have made

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marked improvements. These gains, along with Japan's position as the world's second largest medical market, continue to make Japan a desirable place for foreign pharmaceutical companies and medical devices makers to do business.