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DRUG REGULATIONS AND REGISTRATION IN JAPAN

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ABSTRACT

Japan has the second largest individual market in the world. Japan market generates about 67% of the Asia - pacific market. Total market value in 2005 was $65.5billion USD. Unlike rest of the countries Japan has few barriers to consider like ICH does not cover all of Japan drug development, language barrier, J-GCP is followed here leading to many operational differences and barriers. The procedures followed in USA & EUROPE countries do not work here. This project is intended to describe the necessary regulatory hurdles and regulations required that are need before one can introduce a pharmaceutical product into Japan market.

Keywords: ICH, J – GCP, WHO, MAA.

INTRODUCTION

Drug Registration

Drug registration is a system that subjects all pharmaceutical products to pre-marketing evaluation, marketing authorization, and post-marketing review to ensure that they conform to required standards of quality, safety, and efficacy established by national authorities. The outcome of the drug registration process is the issuance or the denial of a pharmaceutical product marketing authorization or license.

The registration process entails the steps described in the following diagrams. The first, "Assessment of Applications for New Marketing Authorizations," provides a global description of the registration process. Not all the areas of assessment (i.e., those indicated in boxes in the chart) are relevant for all drug products. For example, safety and efficacy assessment is required for new chemical entities (NCE) only; interchangeability applies only for generic products; and not all countries include price as part of the assessment of an application for MA. The second chart describes assessment of imported well established products.

Decisions on applications are made on the basis of assessment reports prepared by qualified staff. To carry out drug registration a DRA may:

- Prepare its own reports, Apply a combination of the above options, which is the most frequent case.
- An assessment report may include:
- A brief outline of the information provided in the application.
- The reasons for any disagreement with the applicant's proposals.
- A summary and evaluation of information on interchangeability (when applicable), with recommendations and reasons.
- A proposal of final decision.

If the DRA finds that the information submitted is incomplete or does not agree with statements, conclusions, or proposals made by the applicant, an appropriate letter is usually sent to the applicant. In general, such letters are requests for additional information or explanation on specific issues. They are referred to as the "correspondence loop" in the first chart. Relying on a scientific report prepared by another national authority may entail starting a correspondence loop, if the data set submitted is not the same as the one submitted to the other regulatory authority.

When assessing imported products, it is recommended that a WHO-type certificate with approved product information be obtained in all cases, together with

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assurance by the applicant that the product to be supplied is identical in all aspects of manufacturing and quality to that approved in the exporting country. As presented in the second chart, it will also be necessary to consider whether the proposed product information is appropriate in the importing country. Refer Chart No: 1 and 2.

Drug development and registration in Japan:

The responsibility for the regulation of pharmaceuticals is situated within the Pharmaceutical Affairs Bureau (PAB) of the Japanese Ministry of Health and Welfare. The scientific evaluation of the application is undertaken by a series of committees consisting of independent senior members of the medical and scientific community whereas all communication between them and the pharmaceutical company is conducted through PAB offices (Koseisho). As in the U.S., the Japanese drug application covers product quality, safety, and efficacy, but the actual data requirements differ between the two countries. Some of these differences have a basis in Japanese regulations whereas others emulate from demands set by senior members of the medical fraternity who carry great sway in Japan. These cause concern to international pharmaceutical companies since they may require studies to be duplicated with consequent delays. Moves toward the achievement of global harmonization of regulatory requirements with the associated benefits of reducing the numbers of animals sacrificed in the total development program and of important new medications reaching patients earlier are discussed.

A regulatory process, by which a person/organization/sponsor/innovator gets authorization to launch a drug in the market, is known as drug approval process. In general, a drug approval process comprises of various stages: application to conduct clinical trials, conducting clinical trials, application to marketing authorization of drug and post-marketing studies. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs. This article will focus the similarities and differences in drug approval process of various regulatory bodies.

In the present scenario, countries have different regulatory requirements for approval of a new drug. The single regulatory approach for marketing authorization application (MAA) of a new drug product applicable to various countries (on the basis of single dossier) is utmost difficult. Therefore, the knowledge of exact and detailed regulatory requirements for MAA of each country should be known to establish a suitable regulatory strategy [1].

The new drug approval is of two phase process - the first phase for clinical trials and second phase for marketing authorization of drug. Firstly, non-clinical studies of a drug are completed to ensure efficacy and safety, and then application for conduct of clinical trials is submitted to the competent authority of the concerned country. Thereafter, the clinical trials can be conducted (phase I to phase IV). These studies are performed to ensure the efficacy, safety and optimizing the dose of drug in human beings. After the completion of clinical studies of the drug, then an application to the competent authority of the concerned country for the approval of drug for marketing is submitted. The competent authority review the application and approve the drug for marketing only if the drug is found to be safe and effective in human being or the drug have more desirable effect as compare to the adverse effect [2].

Even after the approval of new drug, government should monitor its safety due to appearance of some side effects, when it is used in larger population. The interactions with other drugs, which were not assessed in a pre-marketing research trial and its adverse effects (in particular populations) should also be monitored [3].

1. Pharmaceutical and Food Safety Bureau (PFSB)

The Pharmaceutical and Food Safety Bureau (PFSB) (except for the Department of Food Safety) is one of the 11 bureaus of the MHLW. In addition to polices to assure the efficacy and safety of drugs, quasi-drugs, cosmetics and medical devices, and policies for safety in medical Institutions, the PFSB tackles problems directly related to the lives and heath of the general public including policies related to blood supplies and blood products, and narcotics and stimulant drugs. This new bureau consists of a Secretary-General, Councilor in charge of drugs, five divisions, and one office**.**

These divisions have the following functions

1.1 General Affairs Division

The functions of this division are as follows:

1) Overall planning and coordinating activities for the Pharmaceutical and Food Safety Bureau

2) Matters related to pharmacists

3) Supervision of the PMDA (excluding areas under the control of the Evaluation and Licensing Division and Safety Division, and Compliance and Narcotics Division)

4) Issues related to PFSB not governed by other divisions

Office of Drug Induced Damages

1) Matters related to the relief of damage due to adverse drug reactions handled by the PMDA

2) Measures for handling health injury caused by drugs, quasi-drugs, cosmetics, and medical devices (“drugs, etc.”)

1.2 Evaluation and Licensing Division

The functions of this division are as follows:

1) Technical guidance and supervision concerning the production of drugs, quasi-drugs, cosmetics, and medical devices (“drugs, etc.”)

2) Manufacturing/marketing business licenses and approvals to manufacture and market drugs, etc.

3) Reexamination and reevaluation of drugs and medical devices
4) Business license and approvals to market, rental, or repair medical devices (excluding areas under the control of Health Policy Bureau ["HPB"])

2. Pharmaceutical Laws and Regulations

2.1. Pharmaceutical Laws

Pharmaceutical administration in Japan is based on various laws and regulations, consisting mainly of: (1) the Pharmaceutical Affairs Law, (2) Pharmacists Law, (3) Law Concerning the Establishment for Pharmaceuticals and Medical Devices Organization, (4) Law Concerning Securing Stable Supply of Blood Products, (5) Poisonous and Deleterious Substances Control Law, (6) Narcotics and Psychotropic's Control Law, (7) Cannabis Control Law, (8) Opium Law, and (9) Stimulants Control Law. For the enforcement and management of these laws, detailed regulations are prepared by the government in the form of ministerial ordinances and notices, such as the Enforcement Ordinance and the Enforcement Regulations of the Pharmaceutical Affairs 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 [4].

2.2. 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. 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 the reexamination of new drugs, the reevaluation of drugs, 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 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. In the revised Law, provisions on the enhancement of safety measures for biological products, investigator-initiated clinical trials, and safety reports from medical institutions came into effect on July 30, 2003 (Cabinet Order No. 212, April 23, 2003), and law to establish the PMDA was enacted on April 1, 2004 to revitalize the review system. Provisions related to the manufacturing/marketing approval system, manufacturing/marketing businesses and manufacturing businesses, as well as 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) to revise the OTC drug selling system and strengthen the control of illegal drugs was issued on June 14, 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 addition, a notification was issued to implement registered marketing authorization holder tests to confirm the characters of registered marketing authorization holders who are engaged in the sales of type 2 and/or type 3 drugs (Notification No. 0808001 of the General Affairs Division, PFSB dated August 8, 2007).

The notification was enforced on April 1, 2008. The Pharmaceutical Affairs Law has 11 chapters and 91 articles as follows:

2.3 Licenses for Marketing Businesses and Manufacturing Businesses

1) Licenses for marketing businesses Person wishing to start marketing business for drugs, quasi-drugs, cosmetics, or medical devices must obtain a marketing business license of the prefectural governor depending on the type of business. These licenses are of the following seven types.
(1) Type 1 drug marketing business license: Marketing of prescription drugs
(2) Type 2 drug marketing business license: Marketing of drugs other than prescription drugs
(3) Quasi-drug marketing business license: Marketing of quasi-drugs
(4) Cosmetic drug marketing business license: Marketing of cosmetics
(5) Type 1 medical device marketing business license: Marketing of specially controlled medical devices
(6) Type 2 medical device marketing business license: Marketing of controlled medical devices
(7) Type 3 medical device marketing business license: Marketing of general medical devices.

The licensing requirements for drug marketing businesses include the appointment of a general marketing

compliance officer, who is a pharmacist, and compliance with Good Quality Practice (GQP) for quality control and Good Vigilance Practice (GVP) for post marketing safety surveillance. Marketing business license is valid for a period of 5 years after every renewal.

The general 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.

In Office Communication dated April 9, 2007, the Safety Division of the PFSB issued a collection of case reports on pharmaceutical manufacturing and marketing business licenses.

2) Manufacturing business licenses

Persons wishing to establish a business for the manufacture of drugs, quasi-drugs, cosmetics, or medical devices must obtain a manufacturing business license in accordance with the manufacturing category as specified by MHLW ordinance.

2.4 Marketing Approvals

Formal approvals and licenses are required for individual formulations of drugs in order to market the drugs in Japan. Formal approval and/or licenses 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 the ingredient(s) and strength, dosage and administration, indications, adverse reactions, etc.

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 a person who has obtained a marketing business license (marketing authorization holder) for the type of drug concerned and confirmation that the product has been manufactured in a plant compliant with GMP.

2.5 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.

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, MHLW dated July 2, 2009 and "Q&A on GMP for Investigational Products"). Investigational Product GMP Certificates are also issued for investigational products (Office Communication of the Inspection and Guidance Division, Narcotics Division, PFSB, MHLW dated March 30, 2009).

2.6 Drug Master File (MF)

With the amendment of the Pharmaceutical Affairs Law enforced on April 2005, approvals for drug substances that had been necessary in the past were no longer required (except for products listed in the Japanese Pharmacopoeia) and it is possible to omit documentation on drug substances attached to applications if the marketing authorization holder presents a certificate in writing of drug master file (MF) registration.

The MF system aims at protecting intellectual property of relevant information and facilitating review work by allowing a registrant (master file registrant) other than an applicant to separately submit information on quality and the manufacturing method at the time of approval reviews of drug substances to be used in drug products (Notification No. 0210004 of the Evaluation and Licensing Division, PFSB dated February 10, 2005). MF registration is optional. When an overseas drug substance manufacturer submits an MF registration application, it is necessary to appoint a drug substance manager 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 slight MF modification notification must be submitted. However, new registration applications are required in cases where there is concern that the change in registered items will alter the basic nature of registered items.

When an application to change of the MF is submitted, the 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 are slight, the 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 marketing authorization holder or the manufacturing approval holder of the change(s).

When approval applications are filed using MF registration, a copy of the registration certificate and a copy of the contract with the registrant related to MF utilization are required. When inquiries concerning MF registration arise in the course of the review, inquiries directly from the PMDA are made to the registrant or the drug substance manager. When changes are made in the registered contents as a result of the review, the MF registrant must submit an application for a change in registered content or a slight modification notification without delay [5].

3. 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 in 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 Ordnance on Standards for Implementation of Nonclinical Studies on Safety of Drugs" and the amendment was enacted on August 15, 2008. On June 20, 2008, Notification No. 0620059 of the PMDA entitled "Establishment of Guidelines for Drug GLP and Medical Device GLP On-site Inspections" was issued (refer to Section 3.1.4).

4. 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"; Ordinance No. 28, GCP dated March 27, 1997) based on the ICH-GCP Guidelines (E6) (see Chapter 3 for details).

Thereafter, the GCP ordinance was partially revised, and the current GCP is a modification of the Ordinance to Amend the Ordinance on Standards of Clinical Trials of Drugs.

5. Good Post-marketing Study Practice (GPSP)

The GPMSP 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 MHLW dated March 10, 1997).

6. Reexamination and Reevaluation

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. 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 had been six years as a rule, but it was prolonged to eight years as a rule from April 1, 2007 (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. Brand products are protected from generics during this period [6].

7. 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, 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.

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. 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.

Generic drugs will not be approved until the substance (application) patent has expired. Brand products are protected from generics during this period. However, in the past if some of the indications or dosage and administration of brand products were patented, partial approvals were not granted because of patent protection, but with Notification 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.

8. MARKETING APPROVALS

8.1 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 Pharmaceutical Affairs Law.

8.2 Marketing Approval Reviews

The surveys and clinical trial consultation services performed previously by the OPSR and the review work undertaken by the Evaluation Center are now undertaken by the independent administrative organization, PMDA (KIKO) established on April 1, 2004. The PMDA covers the entire range of work from clinical trial consultations to approval reviews.

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). From March 19, 2009, the applicant can confirm the status of review progress for each product applied for with the manager of the PMDA review team.

(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 leastthree clinical specialists as experts)
(7) General review conference (main
(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."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 by the National Institute of Health Sciences or by the Infectious Disease Surveillance Center (IDSC) prior to approval. When active ingredients, dosage, administration route, and indications are the same as those of approved drugs (so-called "generic drugs").

Common Technical Document (CTD)

CTD format for submissions was formally adopted in Japan on 21st June 2001 (notification number 899) and it's use became mandatory on 1st July 2003.

Pre-CTD, the Gaiyo was a summary document forming part of the submission containing approximately 200-300 pages and contained 7 sections:

- Origin or background of Discovery – A
- C&P General (B), Stability (C)
- Preclinical (toxicity, pharmacology, kinetics) – D, E and F
- Clinical (kinetics, efficacy) – F and G

Modules 2 to 5 of an NDA dossier must be submitted in CTD format. Module 2 replaces the Gaiyo and must be written in Japanese. The interpretation of the clinical data should focus on the Japanese component of

the global program, with the bridging study providing a link to the foreign safety and efficacy data, which will be included in sections 2.5 (clinical overview) and 2.7 (clinical summary). Module 5 can be written in English and must cover

- Efficacy from studies considered pivotal to the submission
- AEs and SAEs from all studies
- Cases of abnormal laboratory test results
- Figures showing laboratory test changes

Foreign data should be used as appropriate.

For JNDAs you can use a mixed format i.e. cross-reference to a pre-CTD submission. Unlike the US and EU, CTD format will not be required in Japan for generics or OTC products. To date there have been 72 J-CTD submissions

- 27 for new chemical entities
- 4 were e-CTDs

The key focus has been on Module 2, especially clinical and quality issues. CTD format for submissions will be required for

- NCEs
- Biological products
- New dosage forms or doses
- New routes of administration
- New indications

Feedback from the MHLW indicates

- The CTD is about a standardized format, not content
- Content should be easily understandable, focused on the Japanese data and facilitate Japanese review
- Module 2 will be disclosed to the public in the same manner as the Gaiyo it replaces. CMC information is protected; however, the critical overviews for S & E and the summary documents will be released

Planning the Submission

Planning for JNDA submissions has changed over the past few years. Historically, companies would ensure their "Western Development" was complete before thinking about gaining approval in Japan. Even today, it can be difficult to encourage teams to think about Japan at the same time as the West.

Given that Japan is potentially the second biggest market for a new medication, companies really should plan to develop the JNDA at the same time as the Western submissions. Most multinational companies should have development templates that factor Japan into the global planning process. The JNDA timings should be based around the key decision points and/or formal PMDA meetings and sufficient resource will need to be put in place if parallel development is to take place.

Face to face meetings are important, videoconference and teleconference meetings help but they do have limitations. The key clinical sections should be scoped out before discussing the detail. The JNDA team needs to understand the commercial and medical positioning of the product in Japan. With more and more companies adopting a bridging strategy, the use of Western data as pivotal in Japan is becoming widespread. The impact this has on the submission package needs to be considered, as it will be much larger as the requirements for Western certificates increases and the bridging strategy needs to be included.

Japan New Drug Application (J-NDA) Procedure

General Information

The Ministry of Health, Labor and Welfare (MHLW or Koseirodosho 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. 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.

In April 2004 a new independent administrative organization, the Pharmaceutical and Medical Devices Agency (PMDA, SOGO-KIKO) was established through the integration of different pharmaceutical institutes. Appendix 1 depicts the organization of the PMDA. The PMDA provides consultation concerning clinical trials of new drugs and conducts approval reviews of a new drug application (NDA). Therefore they perform GCP compliance review (document review and GCP inspections) as well as GMP inspections. They handle all activities from preclinical stage to approvals and post-marketing surveillance. With the establishment of the PMDA a faster accessibility to better/more effective and safer drugs for the public should be ensured.

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 [7].

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

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-meeting. 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. The timeline for the new procedure and the comparison to the old procedure for consultation meetings are provided in below figure 1.

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. 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. 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, 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.

J-NDA evaluation process

With the agreement reached on the CTD guidelines of the ICH, new guidelines for preparation of approval application data were issued. Applications using the CTD format became obligatory for new products filed after July 2003 (electronic specifications for the CTD have been applied to application submitted in eCTD format since April 2005).

The standard processing period by the MHLW is about 12 months. The applicant normally needs another 6 - 12 months to respond to the inquiries (Question and Answer session: Q&A) which sums up to a maximum period of about 18 - 24 months from the application to the approval. Marketing approval cannot be obtained without accreditation approval and GMP inspection report. There is a defined timetable for the various meetings at the authorities. Pharmaceutical manufacturers outside Japan can apply directly under their own name for marketing approval. Nevertheless they have to identify a licensed manufacturer (e.g. subsidiary company) who will release and distribute the medicinal product to the Japanese market.

General Information

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. A detailed description is provided below (Section 3.3.1). After the Q&A session and the expert meeting Module 1 and Module 2 have to be revised accordingly and resubmitted. The following sections are focusing on Module 1 and Module 2, especially on quality overall summary (QOS), and the main differences between the dossier to be submitted in the EU compared to Japan, since Module 3 is identical for the EU and Japan.

Content of Module 1 and Module 2 (QOS)

Module 1

EU-MAA

Module 1 contains general information such as the application form, labeling information, information on the expert, pharmacovigilance system and risk management plan. No information with regard to the manufacturing or process controls and specifications are given in this Module for an EU MAA.

J-NDA

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 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.

9. Japanese Pharmacopoeia and Other Standards

9.1 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 Pharmaceutical Affairs Law after hearing opinion of the Pharmaceutical Affairs and Food Sanitation Council (PAFSC). The JP is a book of drug standards specified and published by the Ministry.

Since it was first published in June 1886, the JP has been revised several times. The Pharmaceutical Affairs 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 5years 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.

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) Characteristics and the role of the JP

The JP is a publication that contains the specifications required to assure the quality of drugs in Japan in accordance with the scientific and technological progress and medical demand at the time. It includes the specifications and test methods to assure the overall quality of drugs in general, and to clarify the role of standards to evaluate the quality of medically important drugs.

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 and it also serves to publish and explain information on drug quality for the general public. The JP contributes to the smooth and efficient promotion of government policy and the maintenance and assurance of international coordination related to drug quality.

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.

(4) Selection of products for entry in the JP

Items selected for entry in the JP must be those important in healthcare that must be entered as soon as possible after marketing based on the necessity of the drug in medical practice, wide application, and experience of use.

10. Process from Development to Approval

New drugs are defined as drugs with ingredients, dosage, administration route, or indications, which are clearly different from those of drugs, which have already been approved for manufacture and marketing or those listed in the JP. Applications for approval to manufacture and market new drugs must be submitted to the Ministry of Health, Labour and Welfare with results of nonclinical and clinical studies required showing the quality, efficacy, and safety of a new drug attached to the approval

application form (Article 14-3 of the Pharmaceutical Affairs Law [PAL]).

10.1 Development of New Drugs

It is important to prepare data for the review process during the course of drug development. Results to show quality, efficacy, and safety of new drugs must be obtained in nonclinical and clinical studies.

The nonclinical studies include physicochemical studies and animal studies on pharmacology, pharmacokinetics, and toxicity. The clinical studies usually consist of Phase I, II and III studies (or human pharmacology, therapeutic exploratory, therapeutic confirmatory and therapeutic use categories). On starting each phase of clinical studies, it is necessary to adequately confirm the safety of the drug product from the results of nonclinical studies or results of previous clinical studies.

The Pharmaceutical Affairs Law specifies that the data submitted to obtain approvals must be obtained and compiled according to the standards specified in its Article 14.

10.2 Reviews and Guidance by the PMDA (KIKO)

The PMDA conducts advice, guidance, and reviews from the development to the approval review stage of new drugs. This includes reviews of compliance with quality standards, reviews of clinical trial protocol notifications, and guidance and assistance by means of consultations on nonclinical studies and clinical studies.

Chart 1. Assessment of Applications For New Marketing Authorizations

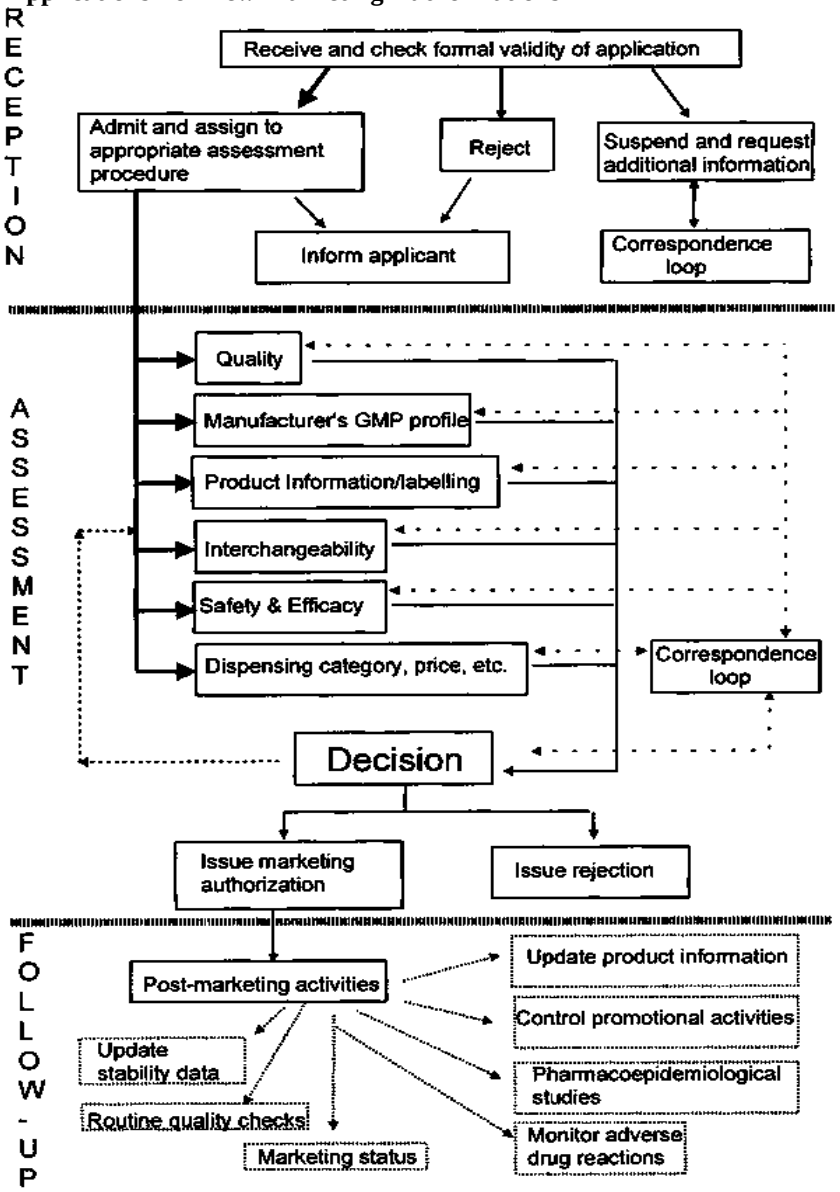


Chart 2. Decision Chart for Marketing Authorizations Using Who-Type Product Certificate

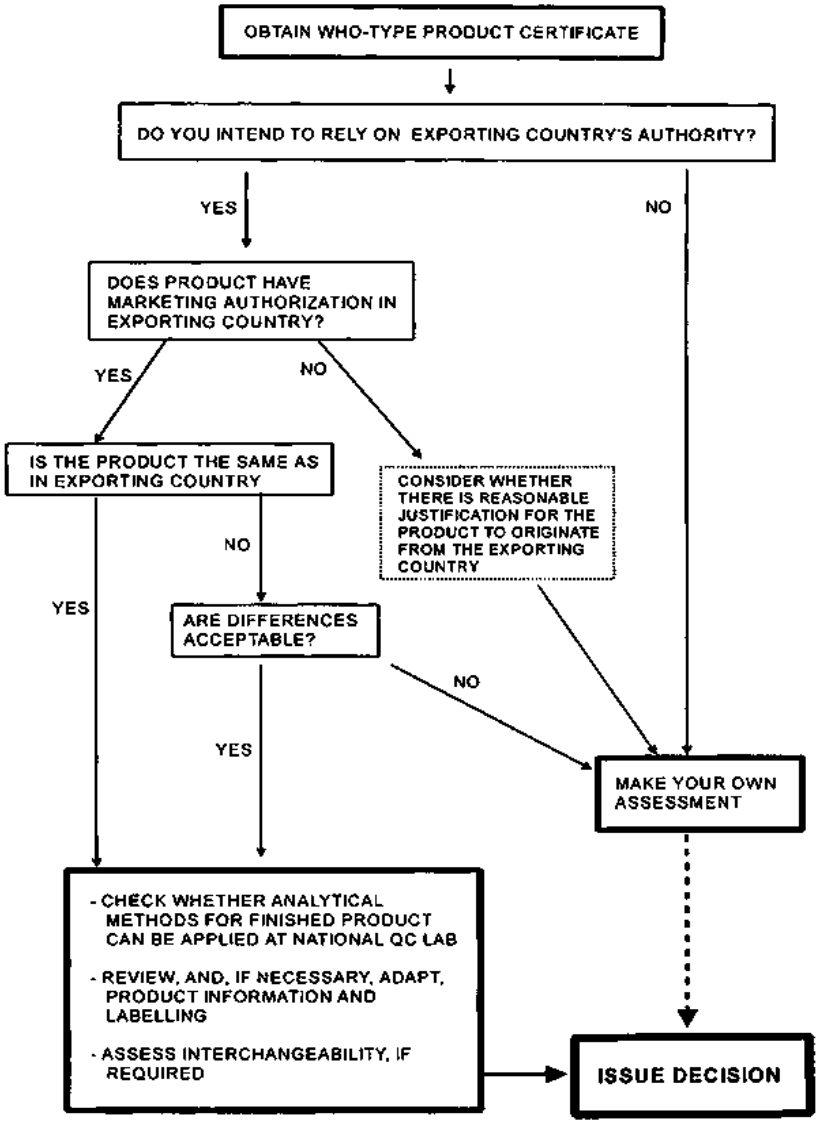


Chart 3. CTD for Japan

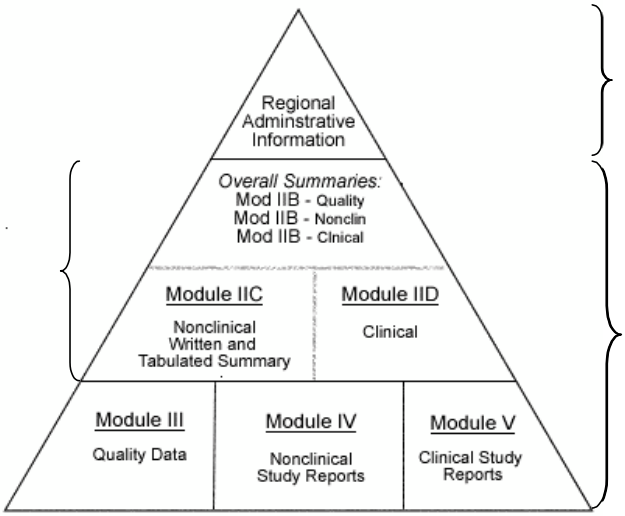


Figure 1. NDA review process

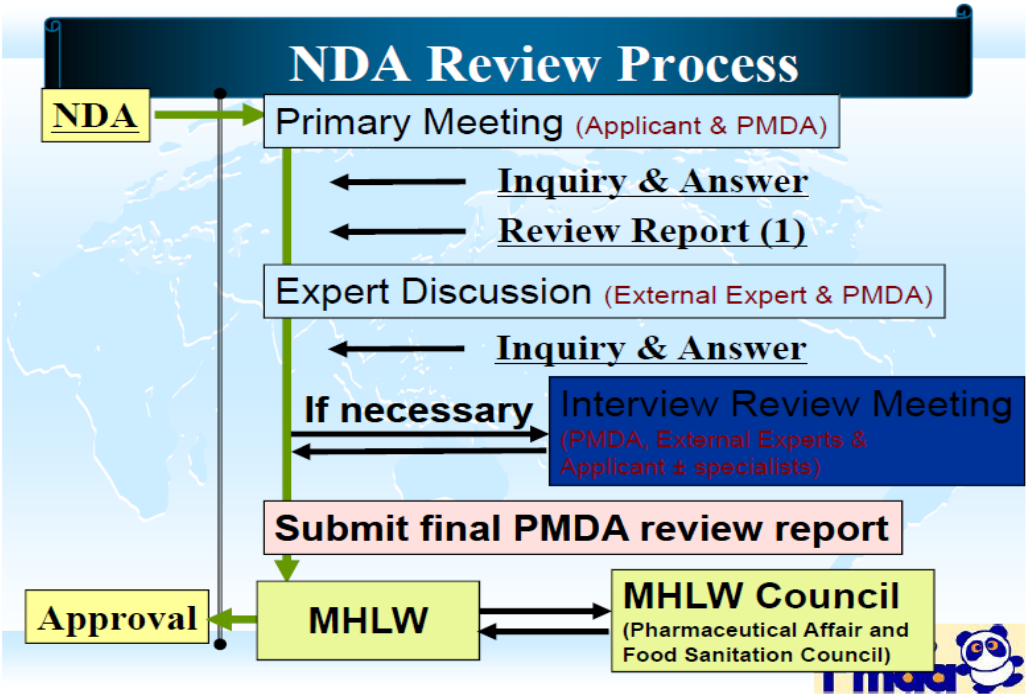
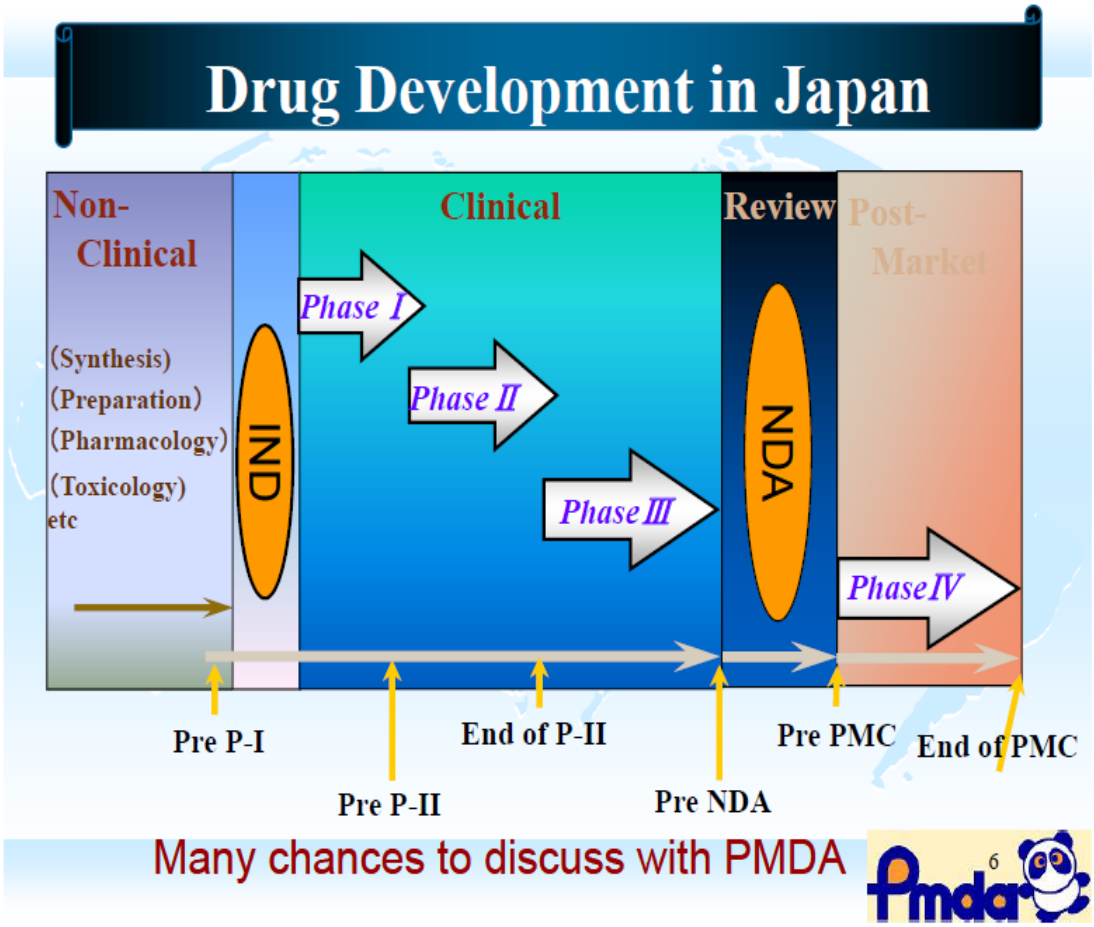


Figure 2. Drug Development in Japan



CONCLUSION

The study was conducted with an objective to chalk out the regulatory framework for CTD submission and its guidelines according to JAPAN. The major emphasis has been provided to regulatory guidelines for drug registration process in JAPAN. Literature review was done mainly on collection of the JAPAN legislations and concentrating on their CTD submission procedures. Generally speaking, the NDA approval in the JAPAN for your new product is exercisable once you have a careful preparation.

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