COMPARATIVE STUDY OF REGULATORY REQUIREMENTS AND REGISTRATION PROCESS OF GENERIC DRUGS IN JAPAN AND CHINA

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REVIEW ARTICLE

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ABSTRACT

A Generic Product must meet the standards established by Pharmaceutical Medical Device Agency (PMDA) & China Food and Drug Administration (CFDA) to be approved for marketing in Japan and China respectively. This study covers the introduction to generic drugs, and JAPAN & CHINA regulatory authorities. It also includes the requirements and registration of Generic Drugs in above specified countries. It also includes the checklist for comparative study of regulatory requirements and registration process of generic drugs in JAPAN & CHINA.

JAPAN and CHINA are two different markets which are important to pharmaceutical industry. Japan is under one of the Regulated markets and owning the world's second largest pharmaceutical market. Whereas China is under the Emerging market, but unfortunately these two are un trapped markets in the Pharma hub. So, am enthusiastic to know about Regulatory considerations and Registration process of Generic Drugs.

Keywords: Generic product, PMDA, CFDA, Regulatory requirements, Registration.

INTRODUCTION

Regulatory affairs

The pharmaceutical industry is one of the most regulated industries. No drug would be available in the market until and unless it get approved by Regulatory Authorities. Regulatory Affairs is a specialized profession in the pharmaceutical sector. Regulatory Affairs oversees with laws and regulations pertaining to the development, marketing and of drug products. Regulatory Affairs acts as point of contact between the company, its products and regulatory authorities with respect to registration. (1)

Regulatory Affairs interacts with International and domestic drug regulators [e.g., MHLW (Japan), CFDA (China), EMA (Europe), FDA (United States), CDSCO (India) etc] to assure:

Pharmaceutical Markets

Even though the world Pharmaceutical regulations are in continuous process of harmonization, they can be divided into four major categories based on the region, development strategy, regulations and marketing interest.

- ❖ North America (US, Canada)
- ❖ Europe (Europe Union, Eastern Europe)
- ❖ Rest of the World (Asia Pacific minus Japan, ANZ, GCC, LATAM, CEE, CIS,MCC)
- ❖ Japan

LATAM-Latin America; CEE-Central East Europe; CIS-Common Wealth of Independent States; ANZ-Australia, New Zealand; ROW-Rest of World; GCC-Gulf Cooperation Council.

Based on the economy and regulatory control of the countries, these are grouped into Regulated markets or Emerging markets. They not only differ by their region, but also in various other aspects like: how they regulate the pharmaceuticals, the different guidelines for registering the drugs, requirements to maintain the registrations, registration fee and patent regulations.

A. Regulated Markets: These are the markets which have stringent regulation and standardized processes for drug approval.

Table 1: List of Regulated Markets

S.NO.	REGION	AUTHORITY
1.	US	FDA [Food Drug Administration]
2.	EU UK	EMA [European Union Medical Agency] MHRA [Medicines and Health Care Products Regulatory Agency]
3.	JAPAN	Pharmaceuticals and Medical Device Agency [PMDA]

B. Emerging Markets: These are the markets in which the regulations are not as stringent as that of regulated markets and their process are not standardized. (2)

Table 2: List of Emerging Markets

S.NO.	REGION	AUTHORITY
1.	BRAZIL	National Health Surveillance Agency (ANVISA)
2.	CHINA	Chinese Food and Drug Administration (CFDA)
3.	RUSSIA	Association of International Pharmaceutical Manufacturers.
4.	INDIA	Central Drugs Standard Control Organization (CDSCO)

Introduction to Generic Drug

A generic drug is a pharmaceutical product, usually intended to be interchangeable with a new drug (an innovator product) that is marketed after the expiry date of the patent or other exclusivity rights. A generic drug is defined as a "drug product that is similar to quantitative and qualitative composition of brand / reference listed drug product in dosage form, strength, route of administration, performance characteristics, and intended use." Generic drugs are marketed under a non-proprietary or approved name rather than a proprietary or brand name.

Comparison of Innovator and Generic Drugs

Table 3: Comparison of Innovator and Generic Drugs

S.NO	PARAMETERS	INNOVATOR DRUG	GENERIC DRUG
1.	Active ingredients	Same	Same
2.	Safety and efficacy	Same	Same
3.	Quality and strength	Same	Same
4.	Performance and standards	Same	Same

Generic drugs are drugs manufactured and marketed without a brand name. In practice, generics are often marketed as equivalents to branded drugs. Generic drugs are generally much cheaper than their branded counterparts for a number of reasons. First, drug development is extremely time consuming and costly. On average, new drug companies spend about $5 billion to discover, develop, manufacture and register a new drug. They then have to charge fairly high prices to recoup their investment and actually make a profit. Generic manufacturers, however, don't have to spend nearly as much on drug development. Generic drugs are effective, but much cheaper than brand-name drugs. Generic medicines play a key role in ensuring the affordability and sustainability.

Generic drugs are usually cheaper than the innovator drugs because of the following reasons:

1. No cost of identification and isolation of New Chemical Entity (NCE),
2. No cost of research and development,
3. Minimum marketing cost because branded drug is already approved as safe and effective. (3)

5.	Costs/prescription	Highly expensive	Less expensive
6.	Inspection of manufacturing facilities	Yes	Yes
7.	Reviews reports of adverse reactions	Yes	Yes
8.	Review on Drug Labeling	Yes	Yes
9.	Extensive research and development investments	Yes	No
10.	Clinical trials(4 phases)	Yes	No
11.	Review to show active ingredient is equivalent to original	---	Yes
12.	Extensive marketing and advertising	Yes	No
13.	Patent protection	Yes	No
14.	Product development time	12 to 15 yrs	2 to 4 yrs

Role of Regulatory and Stages involved in Development of Generic Drugs

Obtaining regulatory approval, in minimum time will be the goal for all drug development projects. Drug development is a complex global undertaking, very expensive and, by its nature, risky. Given the inherent risk of international drug development, even with high quality drug candidates, decisions taken during development will impact the overall success of the program. Ensuring these decisions are optimally considered will have significant impact on the likelihood of success and overall cost of the endeavor. It is critical for a company to utilize all the expertise in a multidisciplinary team to increase the efficiency and effectiveness of the development program. Regulatory affairs has a unique position in global development teams as the pivot between the technical data generating groups on the development side and the commercial, medical, and marketing functions which will support the medicinal product in the marketplace. Taking maximum advantage of this position, the regulatory expert can provide critical tools to a development team to help unlock the inherent value in a development candidate. (4-8)

JAPAN – (An Attractive Market for Pharma)

Japan will remain an important market for the pharmaceutical industry. It is the world's second largest pharmaceutical market and presents a number of opportunities, including an aging population, together with a relatively low barrier to reimbursement compared to many EU markets. Indeed, the Japanese reimbursement system is streamlined compared to the complicated processes companies need to go through in other countries, with pharmaco-economics rarely used to make listing decisions. Moreover, Japan has a much lower penetration of generics compared to most of the major markets which is advantageous for the big Pharma. (9, 10)

Japanese Regulatory Authority

Pharmaceutical Medical Device Agency is the regulatory authority of JAPAN.PMDA continues to improve the public health and safety of nation by reviewing applications for marketing approval of pharmaceuticals and medical devices, conducting safety measures, and providing relief to people who have suffered from adverse drug reactions. The Pharmaceuticals and Medical Devices Agency (PMDA) focuses on three key areas Relief services for adverse health effects, Product reviews, Safety measures.

These three encompass the entire life cycle of drugs and medical devices from development through the post-marketing period. This so-called "safety triangle" system, which contributes to public health, is unique to Japan. (11)

Steps involved in Registration of Generic drugs in Japan

Foreign Manufacturer Accreditation

A foreign manufacturer (a person/a company) intending to manufacture drugs, quasi-drugs, or medical devices in foreign countries and export them to Japan, is required to be accredited by the Minister of Health, Labor, and Welfare as an

"Accredited Foreign Manufacturer", specified in Article 13-3 of PAL,(Pharmaceutical Affairs Law) in the same way that a Japanese manufacturer is licensed. The person or the company who intends to apply for the accreditation is hereinafter referred to as an "Applicant".

However, a foreign manufacturer of the drug or medical device, etc. whose marketing approval holder has an effective importing license granted under the old PAL as of April 1, 2005, is deemed to be temporarily accredited under the revised PAL by the end of its effective period. The manufacturer satisfying the above condition is hereinafter referred to as a "Deemed Accredited Foreign Manufacturer".

The Minister of Health, Labor and Welfare has an authority to grant accreditation to a foreign manufacturer, while PMDA examines buildings and facilities of the manufacturing establishment for accreditation. The accreditation is granted for each manufacturing establishment according to the category specified by the Enforcement Regulations. Before applying for accreditation, a Japanese marketing approval holder for an Applicant needs to submit "Business Number Registration Form", reporting information on the applicant's business and manufacturing establishments, in order to obtain "Business Number". (12)

Filing

Generic drugs undergo a rigorous review process by the PMDA to ensure their quality prior to becoming available to patients. Multiple facets of a generic drug's bioequivalence, chemistry, and production are evaluated by the PMDA prior to approval. Critical elements including drug components, drug stability, packaging, manufacturing processes, and facility descriptions must meet all of PMDA's high standards. All the data required is submitted in the paper format to the Regulatory Authority. There is a timeline for generic drug submission. (13)

Time Line for Generic Drug Submission

Table 4: Time Line for Generic Drug Submission

Stages	Cycle 1	Cycle 2
Filing	March 1 to August 31	September 1 to February 28/29
GMP inspection application	by end February	by end August
Replacement of application (equivalency review completion)	by May 25	by November 25
Notification of GMP inspection result	by August 10	by February 10
Approval	by August 15	by February 15
NHI price listing	December	June

GMP Compliance Inspection

GMP Compliance Inspection concerning Pharmaceuticals of Foreign Manufacturers is a inspection on the compliance of manufacturing control and quality control methods at the relevant manufacturing sites with Japanese GMP ("Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs", Ordinance of Ministry of Health, Labor and Welfare, No. 179, 2004), conducted by the Pharmaceuticals and Medical Devices Agency (hereinafter "PMDA"). GMP compliance is a requirement for marketing approval and it includes

a) Inspections that are conducted at the point of application for new marketing approval or of application for partial changes of approved information.

b) Inspections that are conducted every five years following the obtainment of marketing approval. In the case of ethical drugs, packaging, labeling and storage facilities and external testing laboratories are included in the scope of GMP Inspection, in addition to the manufacturing sites of drug products, APIs (Active Pharmaceutical Ingredients) and intermediates. In the case of application for partial change approval, GMP Compliance Inspection is not required if the partial change is

addition, change, or deletion etc. Administration and dosage are indication that will not affect the methods for manufacturing control or quality control. While drug products for over-the-counter drugs are included in the scope of GMP compliance Inspection, APIs for over-the-counter drugs are excluded from the inspection (however APIs of over-the-counter for new marketing approval are in the scope of GMP compliance Inspection).

A marketing authorization holder that applies for the marketing approval of pharmaceutical, or an appointed marketing authorization holder designated by a manufacturer that seeks to obtain foreign restrictive approval, shall file an application with the PMDA for GMP compliance Inspection of foreign manufacturing sites.

Following the application for GMP Compliance Inspection, the applicant shall submit

"Documents pertaining to manufacturing control and quality control of product(s) concerning the compliance inspection" and "Documents pertaining to manufacturing control and quality control of manufacturing sites concerning the compliance inspection", at request of the PMDA. Attached documents for the application of inspection prepared by foreign manufacturers". Even applications and attached documents are concerning foreign manufacturing sites, it should be prepared in the Japanese language. If the attachment includes a large volume of documents written in a foreign language, it is acceptable to prepare only an overview of such documents in Japanese. If GMP Compliance Inspection has been conducted on the same product at the same manufacturing site, based on GMP compliance applied by another marketing authorization holder, and if a copy of the Compliance Inspection Result Notification (no older than two years, in principle) can be provided to the second marketing authorization holder, the second marketing authorization holder does not need to receive the GMP Compliance Inspection concerning the manufacturing site.

- Article 14, Paragraph 1 of the Pharmaceuticals Affairs Law (Approval of marketing of drugs) a person intending to market a drug, for each product, obtain marketing approval of the Minister of Health, Labor and Welfare.

- Article 14, Paragraph 6 of the Pharmaceuticals Affairs Law A person who wishes to obtain the approval or who has been granted the approval specified in Paragraph 1 for a drug shall be subjected to a document inspection or an onsite inspection by the Minister to determine whether the method of manufacturing control or quality control in the manufacturing plant complies with the specifications specified by MHLW ordinance before approval and during a period specified by cabinet order not exceeding 3 years after the approval was granted.

- Article 14-2, Paragraph 1 of the Pharmaceuticals Affairs Law (Inspections by the PMDA) Tentative translation (as of October 7, 2008). The Minister of Health, Labor and Welfare may have the PMDA conduct the inspection of drugs as specified in Paragraph 1 and Paragraph 6 of the previous Article.

- Article 21 of the Pharmaceutical Affairs Law Enforcement Ordinance (Period of Inspection for Standards for Methods of Manufacturing Control or Quality Control) The period specified by the government ordinance pursuant to the provisions of Article 14, Paragraph 6 of the Law shall be five (5) years.

- Article 50, Paragraph 1 of the Pharmaceutical Affairs Law Enforcement Regulations (Application for GMP Compliance Inspection) Application for the inspection specified in Article 14, Paragraph 6 of the Law shall be made by submitting an application using Form No. 25 to the Minister of Health, Labour and Welfare.

- Article 50, Paragraph 2 of the Pharmaceutical Affairs Law Enforcement Regulations. The following documents shall be attached to the application specified in the preceding paragraph.

1. Documents on the manufacturing control and quality control of the product subject to the GMP Compliance Inspection

2. Documents on the manufacturing control and quality control of the manufacturing site subject to the GMP Compliance Inspection

❖ Article 50, Paragraph 3 of the Pharmaceutical Affairs Law Enforcement Regulations. In the application of the provisions of Paragraph 1 to cases where the Minister has decided to have the PMDA conduct the GMP Compliance Inspection pursuant to the provisions of Article 14-2, Paragraph 1 of the Law, in the same paragraph to the Minister shall read to the PMDA.

❖ Article 51 of the Pharmaceutical Affairs Law Enforcement Regulations (Notification of GMP Compliance Inspection Results) Notification of the results of the GMP Compliance Inspection from authorized compliance to the marketing approval holder licensing authorities or to the approval authorities shall be made by submitting a notification using Form No. 26. (12)

Raw Data Compliance Inspections

- The range of documents to be submitted will be decided by PMDA.
- Documents in electronic media (e.g. CD-ROM) may be accepted.
- Written instructions on necessary documents and how to submit (hard copy or electronic file) will be given by PMDA after equivalency review has been completed, approximately 3 months before approval.
- Target of data compliance inspection

1. Data concerning specifications and test methods for drug substance and drug product
2. Data concerning stability testing
3. Data concerning bioequivalence
4. Data concerning other tests for scientific evaluation.

If a GMP Compliance Certificate (original only), issued by the authorities covered by the MRA or MOU, the submission of 2 to 5 and 9 to 12 of the above listed documents are not required. "MRA" stands for "Mutual Recognition Agreement". The MRA countries are as follows (Only referring to processes for pharmaceuticals as preparations excluding sterile drugs and biopharmaceuticals). (14- 16)

Drug Marketing Approval

The Pharmaceutical Affairs Law of Japan requires a license for marketing authorization when importing to Japan and selling pharmaceutical products manufactured in other countries. The holder of the license for marketing authorization may entrust import services to third parties who have not received licenses for marketing authorization when importing pharmaceuticals from other countries. However, the first purchaser of the pharmaceutical product in Japan must be the license for marketing authorization holder. Schemes in which the party entrusted with import services initially purchases the pharmaceutical product and then sells it to the license for marketing authorization holder are not allowed. However, the first purchaser of the pharmaceutical product in Japan must be the license for marketing authorization holder. Schemes in which the party entrusted with import services initially purchases the pharmaceutical product and then sells it to the license for marketing authorization holder are not allowed. Parties that receive licenses for marketing authorization 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. (17)

Requirements for Registration of Generic Drugs in Japan (18)

Table 5: Requirements for Registration of Generic Drugs in Japan

Item Description	JAPAN (Pharmaceuticals and Medical Devices Agency)
Regulatory Filing pathways	Only 1 filing pathway for generic drug products
What product changes are we allowed to still qualify as a generic drug product? 1. Must we have the same formulation? 2. What excipients can we change? 3. Can we use a different form of the API? 4. Can we change the strength of the product? 5. Must the pharmaceutical form be the same? 6. Must we have the same container closure system?	 Yes None No No Yes Yes
Duration of Data Exclusivity for innovator	8 Years
Specific dates for submission of application?	Yes.15th January;15th July
Approval timelines	12 months
Duration of License validity	5 Years
Have ICH guidance been adopted?	Yes
What Pharmacopoeial standards are accepted?	JP only. If not applicable, others will be accepted but not acknowledged. Equivalency must be established.
Format of Dossier for submission to RA	Not CTD for generics; CTD for new drugs. Documents required are: Specific method/ Specification documents for DS, DP. List of reagents and their preparation methods, Excipients, PH adjusting solutions, container/ closures must comply with all JP requirements. Justifications for all differences between submitted product and innovator are mandatory.
CPP Requirements	
CPP from major markets/countries required	No
Can>1 API manufacturer be registered	Yes; complete DP stability data (3bxs/ presentation, triplicate tested) using each source is required.
API manufacturer accreditation required?	Yes also DMF registration needed
Requirements for site accreditation	Complete forms1-8 incl. site aerial photograph, signed docs from senior QA and mfg
Procedure for site accreditation	Yes; specifics forms to complete
Time line for site accreditation	5 months
Stability data required	Yes
Drug substance requirements per ICH	API stability data is not required
How many batches required per presentation?	3 batches per presentation, tested in triplicate. Triplicate testing is not required for commercial batches Raw data from stability trials is to be submitted during Raw data compliance/questions time. This includes all test results, chromatograms and photos of TLC's.
Pilot scale or commercial batch scale?	As per ICH

Which stability temperature conditions are required? Long term Intermediate Accelerated	 >12 months - 6 months
Bioequivalence study data required?	Not required for IV products

CHINA - Growing and Distinctive Pharmaceutical market

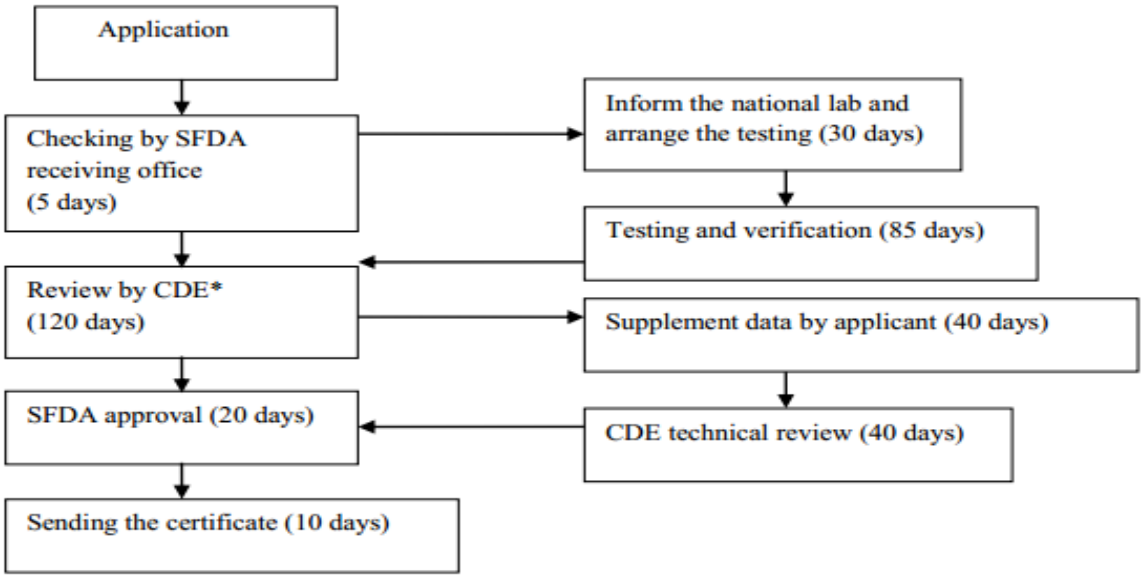
China is one of the largest pharmaceutical markets in the world, but the status is arguably due to the size of its population, as the market is not yet mature. The combined forces of economic and demographic development, government stimulus, and enhanced health awareness among the public, market consolidation, and improving R&D capability may help the country to grow into a more sophisticated market within the next decade. (19)

Chinese Regulatory Authority

The Regulatory Authority of People Republic of China is State Food and Drug Administration (CFDA) former it is termed as (SFDA). In March 2013, the regulatory body was re branded and restructured as the China Food and Drug Administration, elevating it to a ministerial-level agency. The CFDA replaced a large group of overlapping regulators with an entity similar to the Food and Drug Administration of the United States, streamlining regulation processes for food and drug safety. The China Food and Drug Administration is directly under the State Council of the People's Republic of China, which is in charge of comprehensive supervision on the safety management of food, health food and cosmetics and is the competent authority of drug regulation in mainland China.

Steps involved in Registration of Imported Drugs in China

Clinical Trial Application



Flow chart 1: imported drug registration process (Before clinical study)

Generic product registration can be carried out by an agent in china. Overseas manufacturers of pharmaceutical products without legal representation in China are thus required to apply for product registration through agent services. An application is submitted to the CFDA, there by the review process is done by CDE (Center for Drug Evaluation). (20, 21)

General requirements for application dossiers

1. The first page of the dossiers shall be a directory for application items, which shall be arranged in order as per the "Provisions for Drug Registration" (SFDA Order No. 28). Each dossier shall indicate on its cover: the name of the drug and application item, document item number, and the name, phone number and address of contact person and the applicant.
2. All documents in the dossier shall be printed or copied in A4 size paper. The content shall be complete, standardized, clear, without alteration, and the data must be real and reliable.
3. The documents shall be put in portfolio envelope(s), on which the application classification, registration category, drug name, the envelope number of set X, the total number of envelopes in the set, original or copy, the contact person, phone number and the name of registration application agent shall be indicated.
4. Two sets of complete application dossiers (at least one set is in the original) and one set of review documents in hard copy shall be submitted for registration application. Four application forms (1 in the original and 3 in hard copy) shall be separately put into each set of dossier (the original application form and a hard copy shall be put in the set of the dossier in the original).
5. "Import Drug Registration Application Form": the drug registration application form submission program could be downloaded from CFDA website (www.cfda.gov.cn); the application form shall be filled in as required, printed and saved, and shall be signed by the overseas applicant, and signed & sealed by its domestic agent.
6. When mailing or submitting the application dossiers, the electronic version of the application form shall be sent to the following e-mail address dedicated for drug registration: slzx@cfda.gov.cn.
7. The data checking code on the electronic and paper application form should be identical.
8. Foreign language materials shall be translated into Chinese. (22)

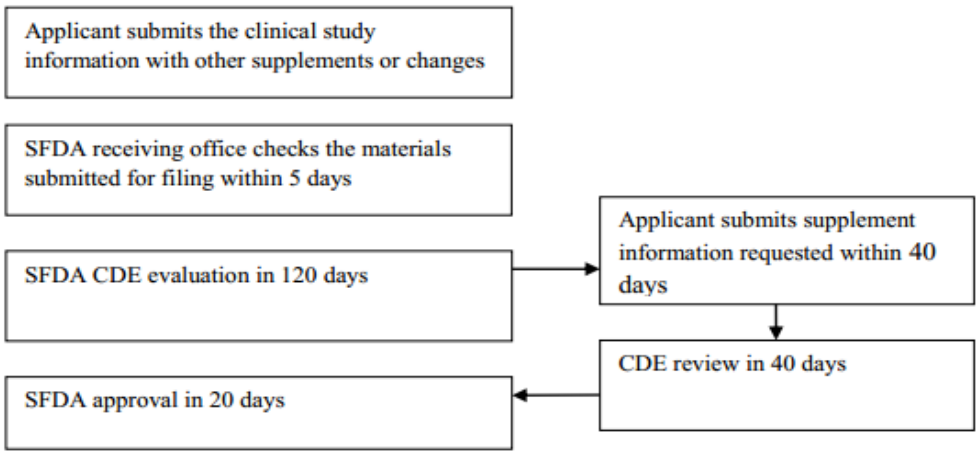
Clinical Study

The Centre for Drug Evaluation will carry out a technical review of the test report and overall documentation which usually takes from 40 to 160 days to complete, depending on the product. The review report will be sent to the CFDA with recommendation on whether the product is subject to a clinical trial or bioequivalence study in China. Further information can be found in the Measures of the Administration of Drug Registration which outlines the requirements for clinical studies. If the Centre for Drug Evaluation deems that no clinical study is needed, the application will enter the final registration phase. In summary, the clinical study can be divided into 4 phases; however it is beyond this document to give a comprehensive introduction to clinical trials in China. Generally, phase I of the study needs between 20 to 30 subjects, phase II is approximately 200 subjects, phase III is 300 subjects, and phase IV is conducted as a post-marketing study investigating around 2000 subjects. For class III pharmaceutical products, a study with 100 pairs of subjects is required. For a bioequivalence study, generally 18-24 subjects are needed. Once the applicant receives approval for the clinical study, the applicant is free to choose the hospitals where the clinical study will be conducted from a list of designated clinical research hospitals or medical institutions listed on the CFDA website. It is a requirement that the clinical study needs to be conducted at a minimum of two different hospitals. The clinical study should be conducted in compliance with Good Clinical Practice (GCP).

All the pharmaceutical products used for the clinical study need to be tested, either by self-testing by the manufacturer or contracted to a designated testing laboratory coordinated by the NIFDC. After completing the clinical study, the clinical study plan, trial protocol, the approval documents by the Ethical Committee, together with patient consent forms and study report will form part of the drug registration application. It is difficult to give general statements about the timeframe for a Chinese clinical trial, as this will depend on availability of subjects, nature of disease, schedule of the hospital, etc. After completing the clinical study and pharmaceutical registration test, the applicant will need to fill in the drug registration form again and submit all documentation to the SFDA. The SFDAs Drug Evaluation Centre will review and evaluate all the submitted information. In some cases, the Drug Evaluation Centre will involve external experts in the evaluation of the pharmaceutical product. Once the Drug Evaluation Centre has passed its final

judgment, the file is transferred to the SFDA for final approval. It is ultimately the decision of the SFDA to make its administrative decision for granting certification of the product or not. If the application is not approved, the applicant can apply for re-evaluation within 60 days. The pharmaceutical registration certificate is valid for 5 years and re-registration should be applied for at least 6 months prior to the certificate expiring. Re-registration should be submitted with all information of post-approval assessments in terms of the safety, efficiency and quality of the product done or collected within the 5 year validity period. In addition to the testing fee for the pharmaceutical registration test, and expenses for clinical trials, the drug registration fee amounts will be paid directly to the SFDA. (23-26)

Imported drug License



Flow chart 2: Imported drug registration process (after clinical study)

The first step in this process is to submit an application to the CFDA for a Clinical Trial Application (CTA). The CFDA will conduct a preliminary review of the submission package and then transfer the dossier to the Center for Drug Evaluation (CDE). Reviewers with background in pharmaceuticals, pharmacology and clinical study will run a technical review, while local sample testing will also be conducted in parallel. Few CTAs would pass through the CDE review in one single round. However, most applications will receive supplement notice(s) in writing to request additional information for further assessment. In such case, CDE will allow a 4-month period for applicant to gather and submit additional requested information to CDE. This entire CTA step usually takes at least 125 working days.

The second step in drug registration is Production Application (or Imported Drug License Application), which involves submitting a clinical report and other relevant dossiers to obtain an imported drug license. The process itself is basically the same as the CTA step. This second step will take approximately 145 days. (27)

Requirements for Approval of Imported Drugs in China (28)

Table 6: Requirements for Generic Imported Drug Submission in China

Dossier Format	Regional specific, Recently initiated CTD format (still in initial phase)
Data Exclusivity for Innovator products	6 years
Efficacy	Clinical Trial is Mandatory
Reference product	Chinese Reference product
Impact of patents on Submission Time Line	Submitted before 2 years of patent expiry
Certificate of pharmaceutical product	Required for Submission

DMF		Yes
Stability Batches		3 BATCHES
Stability Condition	AT	40°C ± 2°C ;75%RH ± 5%RH
	LT	25°C ± 2°C ;60%RH ± 10%RH
Stability Data Required at the Time of Submission		AT = 6months LT = minimum 12 months
Photo stability study		Required on one batch
Finished product Batch Testing Before Approval		3 batches samples with quantity equivalent to 3 times the analysis
Registration Validity Term		Valid for 5 years

COMPARISON OF DISTINGUISHING PARAMETERS AND REQUIREMENTS FOR GENERIC DRUG APPROVAL PROCESS IN JAPAN AND CHINA (Checklist)

Table 7: Comparative Study of Requirements and Registration process of Generic drugs in Japan and China

PARAMETERS		JAPAN	CHINA
Regulatory Authority		Pharmaceuticals and Medical Devices Agency (PMDA)	State Food and Drug Administration (CFDA)
Web Address		http://www.pmda.go.jp/english/	http://eng.sfda.gov.cn/
Climatic Zone		Climatic Zone **II**	Climatic Zone **II**
Language		written in any language, but their Japanese translations are required	All information should be provided in Chinese and original language
Dossier Format		No need of CTD for generics	Regional specific, Recently initiated CTD format (still in initial phase)
DMF Type		DMF registration needed	DMF registration needed
Reference Product		Japanese Reference Product	Chinese Reference product
Validity of License		5 Years	Valid for 5 years
Time period for Registration		24-30 Months	NA
Application Forms		Form No.18, Form No.16-2	NA
Exhibit Batches		As per ICH	3 Batches Samples
Stability Studies Batches		3 Batches per presentation, tested in triplicate	3 Batches
Testing Frequency	Accelerated	6 months	6 months
	Long term	>12 months	minimum 12 months
Stability Conditions	Accelerated	40°C ± 1°C ;75%RH ± 5%RH	40°C ± 2°C ;75%RH ± 5%RH
	Long term	25°C ± 2°C ;60%RH±10%RH	25°C ± 2°C ;60%RH±10%RH
Data Exclusivity		8 Years	6 Years
Type of Submission		eCTD	Paper
BA / BE Studies		Bio wavier statement is provided for IV products instead of BA/BE	Clinical trials in China is Mandatory

SUMMARY

Regulatory Affairs is a specialized profession in the pharmaceutical sector. It oversees with laws and regulations pertaining to the development, marketing and of drug products. Regulatory Affairs acts as point of contact between the company, its products and regulatory authorities with respect to registration. A generic drug is defined as a "drug product that is similar to quantitative and qualitative composition of brand / reference listed drug". A Generic Product must meet the standards established by Pharmaceutical Medical Device Agency (PMDA) & China Food and Drug Administration (CFDA) to be approved for marketing in Japan and China respectively. This study covers the introduction to generic drugs, and JAPAN & CHINA regulatory authorities. It also includes the requirements and registration of Generic Drugs in above specified countries. It also includes the checklist for registration of generic drugs in JAPAN and comparative study of regulatory requirements and registration of generic drugs in JAPAN & CHINA.

CONCLUSION

From the study we understood the regulations and requirements for generic drug registration in JAPAN and CHINA. A Generic Product must meet the standards established by Pharmaceutical Medical Device Agency (PMDA) & China Food and Drug Administration (CFDA) to be approved for marketing in Japan and China respectively. Hence, we concluded the study by preparing a checklist which identifies the Registration requirements for generic drugs in JAPAN. We also compared the similarities and differences in the regulatory requirements for registration of generic drugs in JAPAN and CHINA. Since JAPAN & CHINA are the untrapped markets in the Pharma sector, but there will be more scope for marketing of generic drugs in future. So this made us to carry out a dissertation work on those two countries.

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CONFLICT OF INTEREST

Author declares that there are no conflicts of interest.

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