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Comparative Study of Active Pharmaceutical Ingredients Related Regulatory Requirements in Japan, Saudi Arabia and India

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ABSTRACT

Pharmacological activity of any finished pharmaceutical product is a direct effect of an Active Pharmaceutical Ingredient (API) used. It is mandatory to provide the details of an active ingredients during the registration of any finished pharmaceutical products. From several decades, United States Food and Drug Administration (USFDA) had an extensive and complex set of API requirements. Europe had also given importance of API since 1990. Nowadays, various pharmaceutical industries started their own API manufacturing facilities instead of importing the same from other manufacturers. Furthermore, many industries also started outsourcing the production of API to contract manufacturers located all over the world. These put the highlight on the study of API related requirements, either submitted alone as Drug Master Files (DMFs) or in Dossier of Finished Pharmaceutical Product. The current review study provides the insights of the different pharmaceutical legislations and requirements of an API in Japan, Saudi Arabia and India, which will help the pharmaceutical industries to understand the requirements related to API when registering in the proposed countries.

Keywords
Active Pharmaceutical Ingredient (API), Regulatory requirements, DMF, Japan, Saudi Arabia, India

INTRODUCTION

Marketing authorization of a pharmaceutical product is very crucial part. There are billions of dollars spent for clinical trials to prove the safety and efficacy of the product. This efficacy of product is due to the presence of active pharmaceutical ingredient (API) and to receive a marketing authorization of finished pharmaceutical product, it is mandatory to provide the information regarding the API used in the product. Till now, no country has made it necessary to register the API in respective country, but during the review of finished pharmaceutical product, all the details of API are reviewed thoroughly by the drug regulatory authorities [1], [2]. Current review article describes the requirements of API which need to be provided during finished product marketing authorization application in the countries Japan, Saudi arabia and India.

JAPAN

According to Market Research Future Analysis, API market in Asia-Pacific is growing at a rapid pace. This market is estimated to grow at a CAGR of 8%-10% from 2017 to 2023. Japan holds the lion share in the Asia-Pacific API market. In 2017, Japan's market for APIs is the largest in Asia, with a value of US$ 15.6 billion. According to the Japan Pharmaceutical Manufacturers' Association (JPMA), export business in Japan has increased by 142% in the span of 10 years. Larger share lies in Innovator APIs and demand for biotech drug sector is continuously in demand [3]. Furthermore, foreign API manufacturers have a very good sales opportunities in Japan.

The regulatory body which controls the pharmaceuticals in Japan is known as Pharmaceuticals and Medical Device Agency (PMDA). The Drug Master file (DMF) which voluntarily submitted for review of drug substance related information to the regulatory authority is submitted to the

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Master File Management Group, Administration Division I, Office of review Administration, PMDA.
The Drug Master File is called as Master File in Japan.
The foreign manufacturer of API can also apply for Master file (MF) registration to PMDA. But it is necessary to obtain a foreign manufacturer accreditation, because the MF application form requires accreditation category, accreditation number as well as date of accreditation. In addition to these, manufacturer code for the foreign manufacturer and manufacturing site are also required. Therefore, it becomes necessary that both the codes must be registered in advance. Furthermore, foreign manufacturer cannot apply directly to PMDA. They need to appoint "In-Country Caretakers (ICC) of DMF" in Japan. When a foreign drug manufacturer registers for MF, the cover page of application form can be completed with its name and address written in their own language and a handwritten signature of the representative is accepted instead of seal. Application form must be submitted with the handwritten signature of the representative of the foreign drug manufacturer. One should note that application form with the signature and seal of their in-country caretaker is not acceptable in Japan [3], [4].

Documents Requirements
The requirements included in Master file are similar to ICH M4 guideline - Drug Substance part requirements. All these registration documents should be submitted in Japanese which includes mainly the name of the drug substance, manufacturing site information, manufacturing license number and category, name and address of the ICC, detailed information about API like manufacturing method, manufacturing process control, quality control aspects, specifications and test methods, storage methods, non-clinical studies (for new APIs), safety information as well as stability studies [6]. Stability studies conditions for proposed countries are described in Table I, II and III [7]-[9].

Table I. General Stability Conditions in Japan, Saudi Arabia and India.

Country	Long- term Stability Testing		Accelerated Stability Testing	
	Storage Condition	Minimum Time period	Storage Condition	Minimum Time period
Japan	25°C ± 2°C/ 60% RH ± 5% RH or 30°C ± 2°C/ 65% RH ± 5% RH	12 months	40°C ± 2°C/ 75% RH ± 5% RH	6 months
Saudi Arabia	30°C ± 2°C/ 65% RH ± 5% RH	12 months	40°C ± 2°C/ 75% RH ± 5% RH	6 months
India	30°C ± 2°C/ 65% RH ± 5% RH	12 months	40°C ± 2°C/ 75% RH ± 5% RH	6 months

Table II. Stability Conditions for the APIs to be kept in Refrigerator.

Country	Long- term Stability Testing		Accelerated Stability Testing	
	Storage Condition	Minimum Time period	Storage Condition	Minimum Time period
Japan	5°C ± 3°C	12 months	25°C ± 2°C/ 60%	6 months

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			RH± 5% RH	
Saudi Arabia	5°C ± 3°C	12 months	30°C ± 2°C/ 65% RH± 5% RH	6 months
India	5°C ± 3°C	12 months	25°C ± 2°C/ 60% RH ± 5% RH	6 months

Table III. Stability Conditions for the APIs intended for storage in a Freezer.

Country	**Long- term Stability Testing**	
	Storage Condition	**Minimum Time period**
Japan	-20°C ± 5°C	12 months
Saudi Arabia	-20°C ± 5°C	12 months
India	-20°C ± 5°C	12 months

For any kind of change in Master file should also becommunicated with PMDA. Aspects related to minor or major changes are covered in the guideline "Master File System for Drug Substances".

MF Review Process

Usually, review of DMF is performed at the time of the review process of the pharmaceutical products. At the time of DMF registration, PMDA only checks completeness and correct format (Module 3: in English or Japanese).

Apart from this, the Japanese DMF system allows API manufacturers to register their products directly with the regulatory authority. This system is similar to that of US DMF system. When multiple drug manufacturers in Japan want to use the same API for their finished drug products, the API manufacturer does not need to turn over sensitive information in support of the finished drug registration. Instead, the PMDA uses the information from the API DMF to approve finished drug applications [10]. Key steps of DMF approval process in Japan is shown in Fig. 1 [3], [6].

SAUDI ARABIA

API segment in the Saudi pharma market is niche with a large area of potential room for investment, targeting both generic as well as innovative APIs. More importantly, Saudi Arabia has a wide range for untapped API portfolio that can be produced locally with full compliance international IP treaty such as the Patent Cooperation Treaty [11]. With increase in demand for API, Saudi arabia regulatory authority has also created guidelines for active ingredients. "Drug Master File: Guidance for Submission" is a guideline given by Saudi Food & Drug Authority to the applicant or DMF holder to assist them regarding submission of DMF to the authority. This guideline applies to drug substance, its intermediates and other materials used in their preparation.

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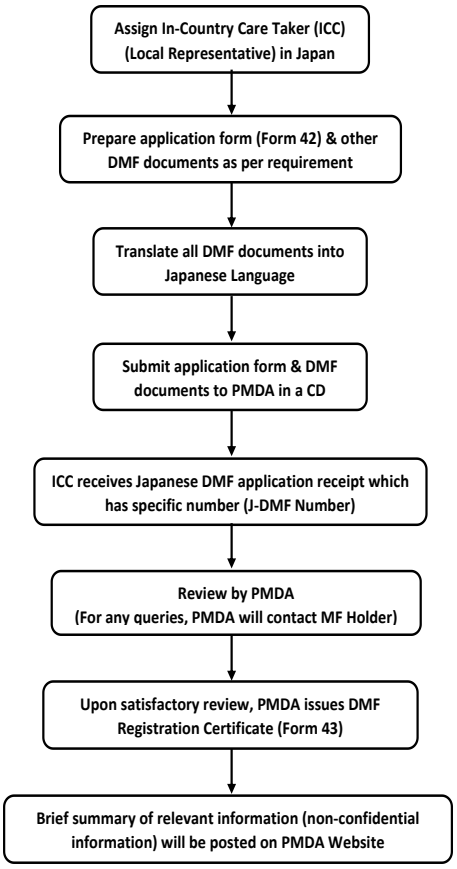

Fig. 1 Key Steps of DMF approval process in Japan*Documents Requirements*

Saudi Food & Drug Authority requires only electronic form of DMF and this soft copy is required in duplicate. No hard copy of DMF needs to be submitted. All the information and documents supporting the DMF application should be written in English or in Arabic language. If any other language containing documents are attached, then they should be translated in English language by authorized translation office. The required documents are same as mentioned in ICH CTD guideline Drug substance part. According to the guideline "The GCC Data Requirements for Human Drugs Submission" documents required for Marketing authorization in relation to active substances are as follows:

Module 1:
- Certificate of Analysis (COA) of Drug substance
- LOA or acknowledgement to DMF

Module 2:
- Quality Overall Summary (QOS) of quality information of drug substance mentioned in Module 3

Module 3:
Drug substance information in Module 3 can be submitted in one of the following options:
- Certificate of Suitability (CEP) or
- Drug Master File (DMF) or
- Complete information on the "3.2.S Drug Substance" section of ICH CTD guideline

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1. Certificate of Suitability (CEP):

A complete copy of CEP containing all the annexures should be provided in Module 1. Applicant should also submit following details along with the CEP:

- General Properties (For properties not mentioned in CEP or Ph. Eur. Monograph; eg. Solubility & polymorph)
- Elucidation of Structure & other characteristics (eg. Study of polymorph)
- Specifications (For tests not mentioned in CEP or Ph. Eur. Monograph; eg. Polymorph and particle size distribution)
- Analytical Procedures and Validation (For tests not mentioned in CEP or Ph. Eur. Monograph)
- Batch Analysis (Results of 3 batches)
- Reference Standards &/or Materials
- Container Closure System &
- Stability

2. Drug Master File (DMF) & 3.2.S Drug Substance" section of ICH CTD guideline:

Full details of Chemistry, Manufacturing and Quality Control (CMC) of drug substance should be provided in DMF. These details should include all the requirements mentioned in ICH CTD Module 3 Drug substance Part. This part contains General Information, Manufacture & Characterization of Drug Substance, Control of Drug Substance, Reference Standards, Container Closure & Stability related information. For the stability of drug substance, GCC guidelines for "Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products (FPP)" should be referred.

DMF Review Process

DMFs are accessed only when specific drug product application is reviewed. DMFs are processed in sequence according to date of receipt. Only complete DMF application will be assigned with a DMF number. Upon receipt of the DMF application, letter of acknowledgement is mailed to DMF owner or agent within 10 days. If any queries raised by regulatory authority during review of DMF, it will be communicated to respective parties. For queries related to Open part, Finished Pharmaceutical Product Manufacturer will be informed, whereas the queries related to Restricted part are communicated with DMF owner or to their applicant.

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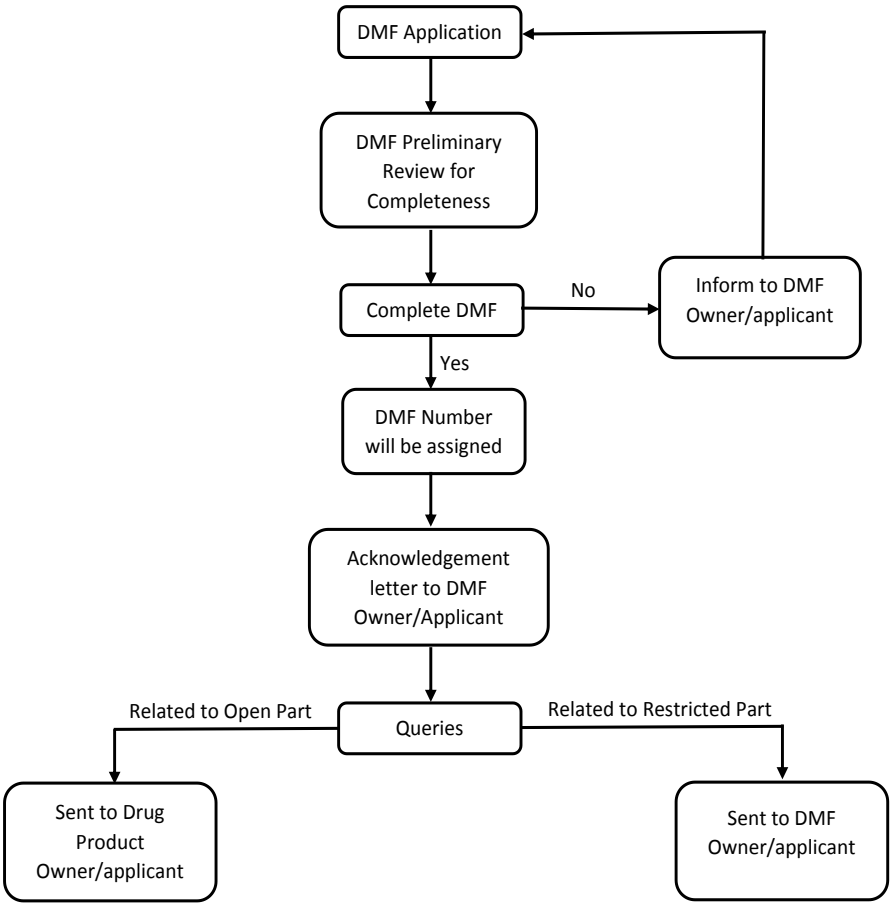

Fig. 2 DMF review process in Saudi Arabia.

India

In India, the active pharmaceutical ingredient (API) industry market size was valued at 735 billion Indian rupees in the year 2019. Indian pharmaceutical industries have shown a steady growth for API since 2016. Based on forecasted values, the API market size is expected to increase further by almost 9% percent in between the years 2020 to 2024. As the Indian market size for API is increasing, the regulatory requirements are also becoming stringent. There is no particular guideline available for Drug Master File Submission. Drug Master File may be filed for a bulk drug or a formulation [2].

Documents Requirements

For the import and registration of bulk drug, Central Drug Standard Control Organization (CDSCO) of India has given guideline "Guidance Document on Common Submission Format for Import and Registration of Bulk Drugs and Finished Formulations in India." This guideline describes mainly three kind of documental requirements for registration of API, namely legal documents, administrative requirements and technical documents.

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Table IV. Comparison of DMF's of Japan, Saudi Arabia and India.

DMF Related Requirements	Japan	Saudi Arabia	India
Regulatory Authority	Pharmaceuticals and Medical Device Agency (PMDA)	Saudi Food & Drug Authority (SFDA)	Central Drug Standard Control Organization (CDSCO)
Guidelines given	"Master File System for Drug Substances" & "Guidance on Drug Master File System in Japan"	"Drug Master File: Guidance for Submission"	"Guidance Document on Common Submission Format for Import and Registration of Bulk Drugs and Finished Formulations in India"
Drug Master File (DMF) is called as	Master File	Drug Master File	Drug Master File
Types/Parts	2 Parts: 1. Disclosed (Open) Part 2. Restricted (Closed) Part	2 Parts: 3. Applicant's Part (AP) 4. Restricted Part (RP)	2 Parts: 1. Applicant's Part (AP) 2. Restricted Part (RP)
Language	English or Japanese	Arabic or English	English
Soft Copy/Hard Copy Requirement	Flexible Disk	Only Soft Copy (CD or DVD) is required. Cover letter & letter of access required in Hard copy.	Soft Copy/Hard Copy
No. of copies	2 Copies	1 Copy	2 Copy
Website of regulatory authority	https://www.pmda.go.jp/english/	https://www.sfda.gov.sa/en/Pages/default.aspx	https://cdsco.gov.in/opencms/opencms/en/Home/
DMF Update Requirement	Any kind of change should be notified to regulatory authority	Updated every 5 years, if no change – letter indicating the same should be submitted	Any kind of change should be notified to regulatory authority
Types of DMF	4 Types: 1) Drug substances, intermediates, and pharmaceutical product Materials. 2) New excipients and new pre-mix excipients with a different composition ratio from the existing ones 3) Materials for medical devices	3 types: 1) Drug Substances or Intermediates in the production of Drug substances 2) Container Closure System & Components 3) Excipients	5 Types: 1) Type I: Manufacturing Site, Facilities, Operating Procedures 2) Type II: Drug Substances, Drug Substance Intermediate and Material Used in DMF; their production or Drug

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	4) Containers/packaging materials		Product. 3) Type III: Packaging Materials 4) Type IV: Excipient Colorant, Flavor, Essence or material used in their preparation 5) Type V: FDA Accepted Reference Information
Guideline for DMF for Biosimilars	-	Drug Master File Requirements for the Registration of Biosimilars	-
Guideline for Stability Study of APIs	As per ICH Q1A(R2) Guideline	Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products (FPP)	As per Appendix IX of Schedule Y of Drug & Cosmetic Act
Fees for DMF	No fee	No fee	Yes

1. Legal Documents:
- Authorization Letter (according to Rule 122A)
- Power of Attorney (POA) (For Foreign Companies)
- Notarized/Appostilled/Attested GMP (Good Manufacturing Practice)
- Certificate or COPP (Certificate of Pharmaceutical Product) as per World Health Organization (WHO) or Proof of DMF approval by NRA and/or CEP (EDQM certificate) for each drug issued by National Drug Regulatory Authority of the Country of Origin
- Notarized/Appostilled/Attested Free Sale Certificate/Certificate of Foreign Government/Certificate of Marketability for each drug issued by National Drug Regulatory Authority of the Country of Origin
- Notarized/Appostilled/Attested Manufacturing License or Market Authorization Certificate
- Notarized/Appostilled/Attested Product Permission

2.Administrative Documents &/or Requirements:
- Cover letter
- Form 40
- Prescribed Fee
- DMF approval number for already approved bulk drug in EU/USA

3. Technical Documents:
- Plant Master File (PMF) (in soft copy)
- Drug Master File (DMF) (in soft copy)

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- Label Submission (ass per Rule 96 of the Act)
- The technical requirement of API related documents during Bulk product submission or medicinal product submission are same as per ICH CTD guideline which are highlighted in details in the guideline, namely "Guidance for Industry on Preparation of Common Technical Document for Import/Manufacture and Marketing Approval of New Drugs for Human Use".

Apart from the guideline for registration of API, CDSCO also gives details regarding the requirements for Import of any bulk drugs in India. As per the same, common requirements to get the import license for bulk drugs are Cover Letter, Authorization Letter, Application Forms (Form 8 & Form 9), Prescribed fees, Valid copy of Registration Certificate in Form 41, Other required documents as per Registration Certificate (If applicable) etc. [13]. DMF for OTC products and Compendia excipients are not reviewed by CDSCO [14].

DMF Review Process

DMF owner/Applicant will file for DMF application to CDSCO. This application is filled in two copies to regulatory authority. Information of DMF is verified for its completeness by CDSCO and all the required information will be entered in DMF database. Upon such entry, DMF number will be assigned & acknowledgement letter will be sent to DMF holder. This DMF will not be reviewed until drug product manufacturer files for NDA or ANDA. This NDA/ANDA application quotes DMF number as supportive documents for drug substance information. Upon receipt of Letter of Authorization, DMF will be reviewed by regulatory authority. DMF holder should abide by all the obligations made to regulatory authority during application. One can determine the status of DMF by symbols like A for Active status, I for Inactive, N for not assigned DMF number and P for Pending filling review.

If no communication with the regulatory will be made by DMF holder for more than 3 consecutive years, then regulatory body will issue a termination letter to DMF holder. Regulatory body shall send a reminder letter called overdue notice letter (ONL) to DMF holder, if there is no response from the holder within 90 days, one copy will be send to federal center and the other will be destroyed. Nowadays, electronic submission of DMF is also possible [12].

Comparative Study of DMF Requirements

There are various similarities and differences in the requirements of DMF application to Japan, Saudi Arabia and India. Table IV describes the comparative study of these requirements in proposed countries.

CONCLUSION

Drug Master File (DMF) is a document which contains complete information of an Active Pharmaceutical Ingredient (API). The Drug Master File may be utilized either by the DMF holder who develops the file, or by one or more other parties like finished product manufacturer, who utilize this file in support of their product's application to regulatory authority. A complete DMF contains detailed information regarding the drug substance's chemistry, manufacture, purity, stability, impurity profile, packaging etc. It consists of open (non- confidential) and closed (confidential) parts. It is not mandatory to file the drug master file in any of proposed countries. This comparative study shows that there is a vast difference in the requirements of documents to be submitted to the regulatory authorities. Not only the technical documents but the legal documents requirements are different too. Furthermore, the review processes are also diverse in

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proposed countries. From this study, it can be concluded that not only drug product requirements but the documents requirements for DMF submission also needs harmonization in future.

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