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(REVIEW ARTICLE)

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Regulatory requirement and filling procedure of drug master file in India under central drug standard control organization (CDSCO) in comparison with South Korea

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Abstract

The Drug master file (DMF) is a type of Confidential file that submitted to regulatory authorities about the ingredients, process, packing and storage of any drugs intended to human use. Drug master file plays an important role in production of drug. The Indian regulatory agency is a CDSCO that manages and encourage DMFs in India and in South Korea MFDS manages the DMFs. Unveiling the difference in regulatory requirements and filling procedure of DMF in India and South Korea as per CDSCO and MFDS respectively. Make certain the Protection, Grade, and Effectiveness of Drug Products.

Keywords: Drug master file; CDSCO; CTD; QOS; MFDS; Comparative Study

1. Introduction

1.1. Drug Master File

An important piece of information about facilities, procedures, or ingredients used in the production, packing, or storage of any drugs intended for human use is submitted to the Food and Drug Administration (FDA) in the form of a Drug Master File (DMF). While filing a DMF is not required, the manufacturer may choose to submit one anyway. Generally speaking, DMFs are filed in support of any of the following: an export application; an IND; a new drug application; an NDA; an ANDA; an IND; an ANDA; or any other DMF. An approved or disapproved DMF does not serve as a replacement for an IND, NDA, ANDA, or export application. An IND, NDA, or export application review process is the exclusive means of examining a DMF's technical contents.

Due to differences in Regulatory Requirements and filling procedure of Drug Master File in India and South Korea, so maintain the drug quality, safety, efficacy of drugs so that DMFs are essential.

1.2. Regulatory authority of India:

1.2.1. CDSCO (Central Drug Standard Control Organization.)

As India's top regulatory body for drugs and medical devices, the Central Drugs Standard Control Organization (CDSCO).It functions within the purview of the Indian government's Ministry of Health and Family Welfare. Making sure those medications, medical equipment, cosmetics, and diagnostics accessible in the Indian market are Protection, effectual, and of high standard is CDSCO's main duty

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1.2.2. Functions

- It makes policies and procedures for uniform discharge of the giving of Drugs and Cosmetics Act, 1940 and Rules, 1945.
- It aid in setting and discharge of yardstick of drugs, cosmetics and medical devices.
- This organization engages in coordination and communication with global institution such as World health organization (WHO) , United state food and drug administration (USFDA) ,European Medicines Agency (EMA) ,Pharmaceutical and Medical Devices Agency (PMDA) of Japan , European Directorate for the quality of Medicines and Healthcare (EDQM) , South Asian Association for Regional Cooperation (SAARC) , WHO Regional Office for South East Asia (SEARO) , BRICS Nations (Brazil ,Russia ,India ,China ,South Africa).
- As the central license approving authority (CLAA) ,it oversees the import of medications, grants approval for novel medications and clinical trials, arranges meetings with the Drug consultative committee (DCC) and Drugs Technical Advisory board (DTAB) and authorizes specific licenses.
- Together with zonal office it conducts inspections and works with state drug controllers to coordinate measures.
- It utilizes port office to oversee the quality monitoring of imported medications.
- It keeps up drug testing labs for testing samples.
- Maintaining Statistics: The CDSCO Maintains Statistics regarding the import and export of drugs and cosmetics
- Preparing Reports: The CDSCO prepares monthly, quarterly, annual reports.
- Drawing Samples: The CDSCO draws the samples from the ship in and market oversees consignments

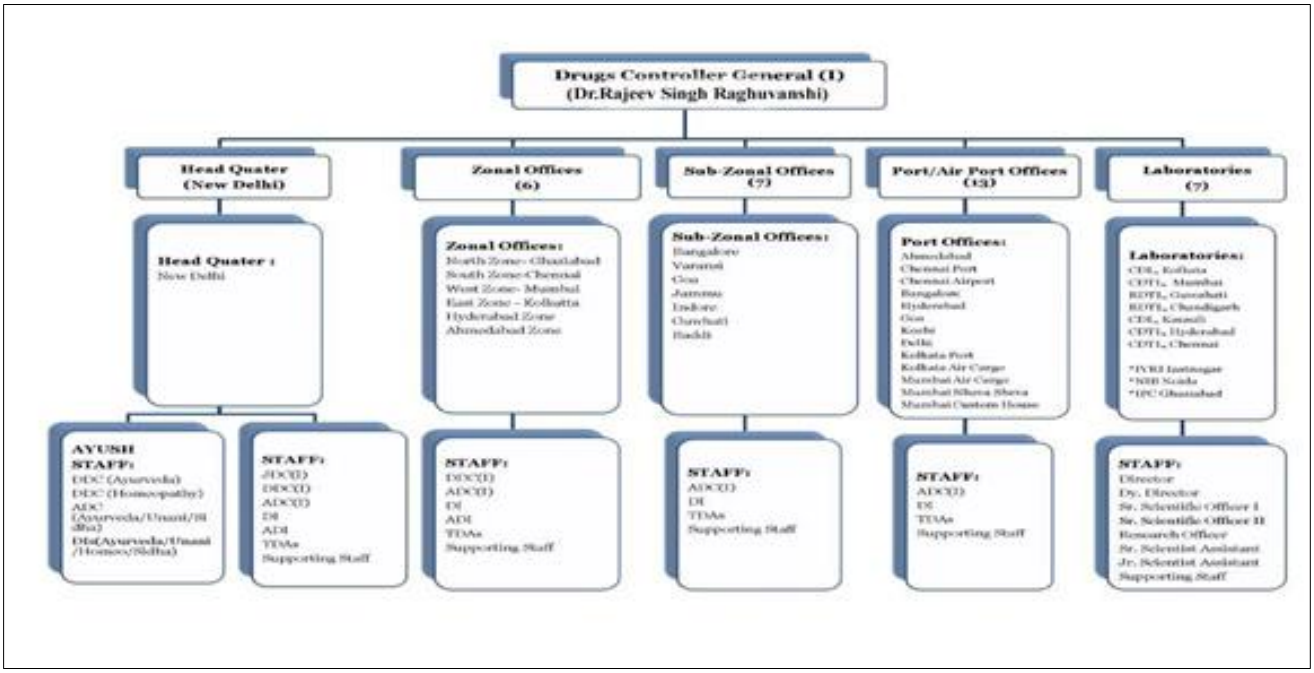

Figure 1 Organization of CDSCO

1.3. Drug master filling in India

The Indian regulatory body, the Central Drug Standard Control Organization (CDSCO), has not released any drug master file guidelines. The DMF format from the United States is typically used in India to provide regulatory authorities with private information about drug substances and drug products. A formulation and bulk drug may be submitted for a DMF. The company has disclosed a DMF that includes comprehensive information about the manufacturing process, physiochemical properties, toxicological studies of huge drug and formulation, pharmacological, therapeutic classes, dosage form, power, route of administration, labeling and packaging, and other related aspects. Let's say a foreign manufacturer wishes to obtain a drug vend Licenses in India for a drug product that was produced abroad. Under such circumstances, the manufacturer is required to provide CDSCO with all Chemistry Manufacturing and Controls (CMSs) data pertaining to pharmaceutical products in Indian CTD format. If foreign pharmaceutical intermediates, substances, products, etc. The applications for the approval of India's pharmaceutical products should be filed along with the approved DMF by the USFDA, Europe, or any other nation. India maintains its top spot in terms of DMF submissions to the USFDA.

1.3.1. Benefits of DMF

- Improves the sales globally.
- The company and the product will gain prestige as a result.
- The data is accessible to multiple applicants.
- Gives Protection over the competitors.
- Secure the confidentiality of proprietary information and maintains the confidentiality for the users.

1.3.2. Details of DMF

- Regulatory Authority:- CDSCO (Central Drug Standard Control Organization).
- Use of DMF in support of application:-MAA (Market Authorization Application).
- Information provided: - API, Drug products, flavors, colorants, Binders etc.
- Fee for assessment:-No fees
- Submission in CTD format:- Indian CTD or eCTD (Common Technical Document.)
- Language:-English.

1.3.3. TYPES OF DMF

- TYPE 1 DMF: - Contains information about Process, procedure, Manufacturing Facilities.
- TYPE 2 DMF:- Contains information about Drug products, Drug Product intermediates.
- TYPE 3 DMF:- Contains information about Packing Materials.
- TYPE 4 DMF:- Contains information about Excepients.
- TYPE 5 DMF:- USFDA Approved reference Materials

2. Methodology

2.1. Regulatory Requirements of DMF Filling

2.1.1. Submission Guidelines and Formats

- Application Format:-The DMF applications should be prepared as per the prescribed format outlined by CDSCO .Ensure that the application is clear, concise and properly organized.
- Cover letter:-Include a cover letter that introduces the DMF and provide a brief overview of the contents.
- Administrative Information:-Include details as the DMF number, Applicant name, Address and Contact Information.
- Table of contents:-Prepare a comprehensive table of contents that outlines the sections and sub-sections of DMF.
- Module Structure:-Organize the DMF into modules based on the rather information provided.
- Letter of Authorization:-If the DMF contains proprietary information, include a letter of authorization allowing CDSCO to review the contents.
- Quality Overall Summary (QOS) or Executive Summary:-Provide an overview of the DMF, including a summary of the information contained in the various modules.
- Module 1 :-Administrative information: Include administrative details such as the DMF holder's contact information, regulatory status of the drug.
- Module 2 :- Quality Overall Summary: Present a comprehensive synopsis of the drug substance, its manufacturing process, controls, and specifications.
- Module 3 :-Quality information: Include detailed information about the drug substance's quality attributes, specifications , and testing methods.
- Module 4:- Non-Clinical Study Reports: Provide relevant non-clinical data including studies on safety, pharmacology, toxicology.
- Module 5:- Clinical Study Reports: Include clinical study data, if required, including details on the drug's well-being and effectiveness in human trials.
- Module 6:- Overall Conclusions: Summarize the data presented in the DMF and draw conclusions about the drug substance's quality and safety.
- Module 7:-Appendices: Include any additional supporting documentation, such as certificates of analysis, validation reports, etc.
- Module 8:-Letter of Access: If using information from another company's DMF, provide a letter of access from that company.

- Electronic Submission:-Submit the DMF electronically through the CDSCO's e-GOV Portal in the specified format.

2.1.2. DMF Filling Procedure

Here's a step-by-step guide to help you prepare a Drug Master File.

Step 1:-Understand the Requirements:

- Familiarize yourself with CDSCO's guidelines for DMF submission.
- Determine the type of DMF you are submitting(API,Excipient,PackagingMaterial,etc)

Step 2:- Gather Documentation:

- Collect all necessary documents, including administrative information, quality data, manufacturing details, stability studies, and any additional data relevant to your type of DMF.

Step 3:- Organize the DMF:

- Divide the DMF into modules based on CDSCO's guidelines.
- Prepare a table of contents to help reviewers navigate the DMF easily.

Step 4:- Compile Administrative Information:

- Complete the DMF application form with accurate details.
- Prepare a cover letter introducing the DMF and its purpose.

Step 5:- Prepare Quality Information:

- Include information about the drug substance's specifications, manufacturing process, and controls.
- Describe the manufacturing process and critical steps involved.
- Provide detailed specifications for staring materials, intermediates and finished products.
- Include stability data to demonstrate the product's shelf life.

Step 6:- Include Non-Clinical and Clinical Data (if applicable)

- Include non-clinical study reports, summarizing safety, pharmacology, and toxicology data.
- If relevant, provide clinical study reports to support safety and efficacy claims.

Step 7:- Create an Executive Summary:

- Prepare an executive summary or Quality Overall Summary (QOS) to provide an overview of the DMF contents.

Step 8:-Address Confidentiality:

- If proprietary information is included, draft a letter of authorization allowing CDSCO to review confidential data.

Step 9:- Review and Verify:

- Thoroughly review all documents for accuracy, consistency, and compliance with CDSCO guidelines.

Step 10:-Prepare Electronic Submission:

- Format the DMF in accordance with CDSCO's electronic submission requirements.
- Prepare the electronic files and documents for upload.

Step 11:- Submission through e-GOV Portal:

- Access CDSCO's e-GOV Portal for DMF submission.
- Fill in required information and upload the prepared electronic files.

Step 12:- Monitor and Respond

- Monitor the status of your DMF submission on the e-GOV Portal.
- Address any queries or requests for additional information from CDSCO promptly.

Step 13:- Prepare for Review

- Be ready to provide clarifications or additional information as requested by CDSCO reviewers.

Step 14:- Follow Up

- Monitor communications from CDSCO regarding the review process.

2.2. Regulatory Authority of South Korea

2.2.1. South Korean Agency: - MFDS

The South Korea's regulatory system is diverse, and oftentimes challenging to navigate. The South Korea's regulatory agency, The Ministry of Food and Drug Safety (MFDS), has its own sets of regulations and customary manner of conducting business. Thus, determine the most effective and efficient strategy to obtain approval for your pharmaceutical products without sufficient knowledge and experience with the South Korean regulatory authorities can become costly and exhaustive.

It is formerly known as the Korea Food and Drug Administration. Its renamed on March 12th2013.Its a government agency responsible for the promoting the public health by secure the welfare and effectiveness of Foods ,Drugs ,Pharmaceuticals , cosmetics , in south Korea.

The head quarter is located in OSANG HEALTH TECHNOLOGY administration complex in CHEONGJU, NORTH CHUNGCHEONG province.

In April 1996, Korea food and Drug Administration, was and its six regional offices were established.

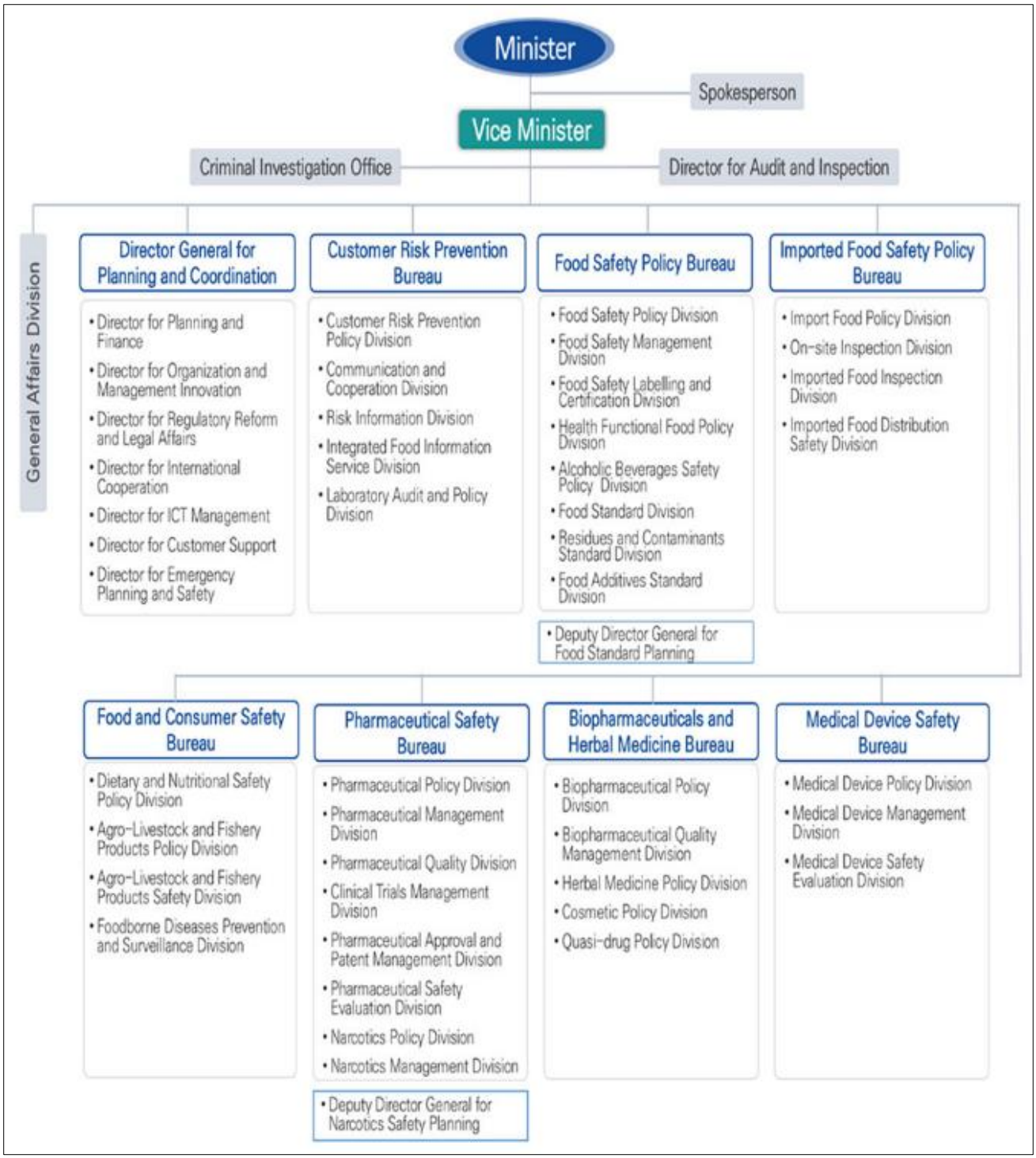

Figure 2 Flow chart of MFDS

2.3. Comparative analysis of Regulatory Requirements and Filling procedure of DMF in India and South Korea

Table 1 Comparative analysis of Regulatory Requirements and Filling procedure of DMF in India and South Korea.

Contents	**India**	**South Korea**
Market	Regulated Market	Emerging Market
Country	India	South Korea
Authority	CDSCO (Central Drug Standard Control Organization)	MFDS(Ministry of Food and Drug)
CTD-Modules	5 Modules are submitted	3 Modules are submitted
Applicant Part(AP)/ Restricted Part(RP)	Once the Customer receives the AP, Then it is sent to CDSCO. With the Applicant DMF is provided, Restricted portion is directly submitted to CDSCO as the supporting document.	Once the Customer receives the AP, Then it is sent to MFDS. With the Applicant DMF is provided, Restricted portion is directly submitted to MFDS as the supporting documents.
Filling(eCTD/PDF)	eCTD and PDF	PDF/CD
Review Time	Takes Several Months for CDSCO to review the DMF.	A month for the first questions. Approval takes longer than six to eighteen months, depending on the questions asked.
Fees	Fees may differ according to the type of submission and how complicated the DMF is.	The agent pays authority about $200 USD.
Pharmacopeia	Indian Pharmacopeia	USP/EP based customer requirements. Generally speaking, innovators DMF is or may prefer in Korea.

Table 2 Comparative analysis of Regulatory Requirements and Filling procedure of DMF in India and South Korea

Module 1	Contains general information such as Cover letter, Query letter, GMP certificate, Application form, a brief description of the drug and the therapeutic class it which belongs, regulatory status in other country.	The agent receives the applicant portion of DMF and files it with necessary forms or applications at the authority. The company provides cover letters for RP submissions to the agency.
Life Cycle Management(amendments/annual reports)	Any modifications to the DMF are submitted as amendments and communicated to the client .Not on annual report.	Significant alteration:-Inform and carry out modifications. The deadline for submitting annual report December or January.

2.4. Comparison of contents in DMF Drug Material

Table 3 Comparison of contents in DMF Drug Material

Contents	India	South Korea
Description of Manufacturing Process and Process controls	Process flow Diagram, Raw material batch records, Manufacturing steps, recovery solvents, recovery of materials, reprocessing steps.	Same as India
Elucidation of Structure and other Characteristics	Possible isomers, structural, geometric, optical data Refractive index and Chirality. Polymorphs synthetic route spectral data. Chemical structural data etc.	Details regarding polymorphic forms and limitations on alternative polymorphic forms. Despite being a pharmaceutical product Structural Elucidation (SE) is need.
Impurities	Genotoxic impurity, residual impurities.	Every chromatogram for every carryover including batch analysis for every study. With the exception of class 3rd solvent, a skip lot test for genotoxic contaminants and solvents is necessary.
Validation of analytical procedures.	Must be carried out In accordance with the ICH Q2 (R1) guidelines.	Same as India
Reference Standards	Indian Pharmacopeia Validation Data Infrared Spectrum and CoA of working standard	Same as India
Container Closure System	Primary fill up materials and Secondary fill up materials and Tertiary fill up materials. Storage State In house test details and supplier CoA of fill up material. Assent proof of fill up materials.	Material safety data sheet (MFDS)

2.5. Stability Data

Table 4 Stability Data

Contents	India	South Korea
Stability And the its synopsis	Stability protocols, studies,conditions,re-test period, confirmation of stability Compliance with guidelines.	Same as India
Post-approval stability protocol and stability commitment	CDSCO will assess the changes and determine if they have an effect on the grade, welfare, or value of the product.	Same as India

Stability data	Follows ICH Q1 A Guidelines. Zone IVb (30° C ± 2 °C/ 75% RH ± 5% RH) stability data. It is necessary to regularly perform microbiological tests and provide justification if they not.	For both the accelerated and Long term stability studies, each stability stations raw data and chromatogram. No need exists for intermediate stability. It is not necessary to do forced degradation studies.

3. Conclusion

The production of safe and effective pharmaceutical products is significantly influenced by the quality of the active pharmaceutical ingredients or drug substance. Therefore, it is imperative that an API log(Drug Master File) be approved with the greatest care and discretion. The Drug Product Application or Request is supported by the DMF, which is an essential document. Since the approved DMF has an Impact on the drug implementation as well, any changes must be reported. The present study establishes that emerging markets have stricter requirements for API approval than the regulatory market; however, there is disagreement regarding the lack of harmonized guidelines and transparency in these markets.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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