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REGULATORY REQUIREMENTS AND FILING PROCEDURE FOR DRUG MASTER FILES IN INDIA UNDER THE CENTRAL DRUGS STANDARD CONTROL ORGANIZATION COMPARED TO BRAZIL

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ABSTRACT

The regulatory requirements and filing procedures for Drug Master Files (DMF) in India and Brazil are pivotal for ensuring the safety, efficacy, and quality of pharmaceutical products. Both countries have stringent frameworks to evaluate the quality of drug substances and ensure compliance with relevant standards. In India, the Central Drugs Standard Control Organization (CDSCO) oversees the submission and review process, while Brazil has its own regulatory authorities managing DMF filings. Despite sharing similar goals in safeguarding public health, these two countries have distinct processes, making it essential for pharmaceutical companies to understand the nuances of each system to achieve timely approvals. The quality of Active Pharmaceutical Ingredients (API) is a critical element in the manufacture of safe and effective drug products, and any changes to an approved DMF must be promptly notified, as they can impact drug product applications. Although emerging markets like India and Brazil enforce more stringent API approval requirements compared to established markets, the lack of harmonized guidelines and transparency in these regions presents challenges. This study emphasizes the importance of adherence to local regulatory standards and highlights the

complexities pharmaceutical companies face when navigating the DMF filing procedures in these emerging markets.

INTRODUCTION

Drug Master File

A Drug Master File (DMF) is a type of submission made to the Food and Drug Administration (FDA) to provide important information related to facilities, processes or ingredients used for manufacturing, packaging or storing of any human drugs.[1] Though it is not mandatory to file a DMF, the submission is subject to the discretion of the manufacturer.[2] DMFs are generally filed to supportan Investigational New Drug Application (IND), a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), any other DMF, application of export, or to support any of these.[3]

Central Drugs Standard Control Organization (CDSCO)

The Central Drugs Standard Control Organization (CDSCO) is the apex regulatory authority for pharmaceuticals and medical devices in India. It operates under the Ministry of Health and Family Welfare, Government of India.[4] CDSCO's primary responsibility is to ensure the safety, efficacy, and quality of drugs, medical devices, cosmetics, and diagnostics available in the Indian market.[5]

Regulatory Authority

CDSCO derives its regulatory authority from the Drugs and Cosmetics Act, 1940 and the Drugs and Cosmetics Rules, 1945. These legislations empower CDSCO to regulate the import, manufacture, distribution, sale, and quality control of drugs and medical devices across the country.[6]

Key Responsibilities

- CDSCO's key responsibilities encompass various aspects of pharmaceutical and medical device regulation:
- Approval and Licensing: CDSCO evaluates applications for the approval of new drugs, medical devices, and clinical trials, and grants licenses to manufacturers, importers, and distributors who comply with regulatory standards.[7]
- Quality Control: CDSCO monitors and enforces Good Manufacturing Practices (GMP) to ensure that pharmaceutical products meet established quality standards.[8]

- Safety Monitoring: CDSCO tracks and investigates adverse drug reactions (ADRs) and takes necessary actions to mitigate risks associated with drugs and medical devices.[9]
- Clinical Trials Oversight: CDSCO oversees the conduct of clinical trials in India, ensuring ethical practices, patient safety, and adherence to guidelines.
- Regulatory Guidelines: CDSCO formulates and updates regulatory guidelines, standards, and policies to maintain regulatory coherence and align with international practices.[10]
- Public Awareness: CDSCO educates healthcare professionals, the pharmaceutical industry, and the general public about regulatory requirements, safety concerns, and quality assurance.
- Collaboration: CDSCO collaborates with international regulatory bodies, agencies, and organizations to foster harmonization, share best practices, and enhance regulatory efficacy.[11]
- Enforcement: CDSCO has the authority to take enforcement actions, including recalls, suspensions, and penalties against entities found violating regulatory norms.[12]
- Mission: CDSCO's mission is to ensure that the public has access to safe, effective, and high-quality pharmaceutical products and medical devices. It works towards establishing a robust regulatory framework that promotes innovation while safeguarding public health and patient well-being.[13]

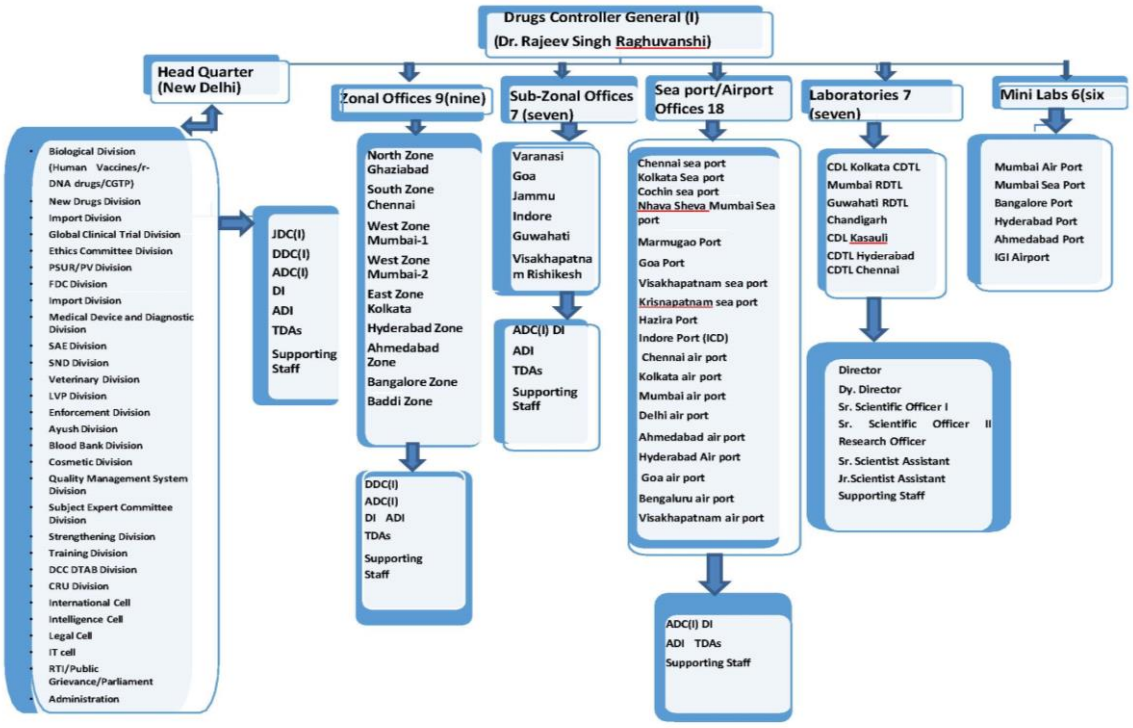

Figure No. 01: Flowchart of CDSCO.[14]

Drug Master Filing in India

There are no drug master file guidelines issued by the Indian regulatory authorities Central Drug Standard Control Organization (CDSCO). In India, generally United States' DMF format is used to submit confidential information to drug substances and drug products to regulatory authorities. A DMF may be filed for a bulk drug and formulation.[15] A DMF declared by the company provides in detail the manufacturing place, physiochemical properties, toxicological studies of bulk drug and formulation, Pharmacodynamics /kinetic, therapeutic classes, dosage form, strength, route of administration, Labeling and packaging, etc. Suppose any foreign manufacturer wants to be obtained.[16]

A drug marketing license in India for a drug product manufactured in a foreign country. In such a case, the manufacturer should submit all chemistry manufacturing and controls (CMSs) information on drug products in Indian CTD format to CDSCO. If foreign drug products, Drug substances, intermediates, etc. accepted DMF by USFDA, Europe or any other country should be submitted and the application for approval of India's drug products. India continues to lead in the number of DMF filed with the USFDA.[17]

Benefits of DMF services[18]

- ✓ Gives an edge over the competitors
- ✓ Ensures confidentiality of proprietary information
- ✓ Several applicants can refer to the information
- ✓ It will add status to the company and the product
- ✓ Establish a good rapport with customers
- ✓ Improve sales globally
- ✓ It will penetrate the high entry barrier in the US Market

Details of DMF[19]

- Regulatory Authority: Central drug and standard control organization(CDSCO)
- Use of DMF in support of application : MAA
- Information provided : API, drug products, flavors, colorants, etc
- Fees of assessment : No fees
- Submission in CTD (common technical document) format : Required in Indian CTD format
- Forms of DMF filling : Not applicable

- Language : English
- Submission of DMF : eCTD format
- Approved/disapproval by Regulatory Authority : Only accepted

Types of Drug Master File[20]

Type I

Type II

Type III

Type IV

Type V

Type I: - This type of DMF contains information related to the raw materials, processes, and manufacturing facilities used in the production of the drug substance or drug product. It's often referred to as a "Reference DMF" and is intended to be used as a supportive document by multiple drug product applicants.[21]

Type II: - Also known as an "Active Pharmaceutical Ingredient (API) DMF," this type contains confidential information about the quality, manufacturing, and controls of the active ingredient of a drug product. It's submitted by the manufacturer of the API to provide regulatory authorities with information while protecting proprietary details.[22]

Type III: - This type contains information about the quality, specifications, and manufacturing of excipients used in drug products. It's submitted by the manufacturer of the excipient and can be referenced by drug product applicants.[23]

Type IV: - This type pertains to packaging materials used for the drug product. It contains information about the quality and suitability of the packaging materials, ensuring they meet the necessary standards for drug storage and stability.[24]

Type V: - This type is used for submitting information about bioequivalence studies and other supporting data related to generic drug products. It's sometimes required for drug product applications that rely on data from another source.[25]

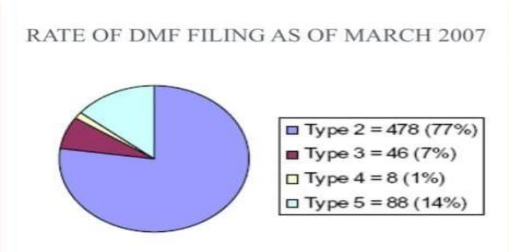

Figure No. 02: DMF filing as per 2007.[26]

METHODOLOGY

Regulatory Requirements for DMF Filling

1. Application Format: The DMF application should be prepared as per the prescribed format outlined by CDSCO. Ensure that the application is clear, concise, and properly organized.
2. Cover Letter: Include a cover letter that introduces the DMF and provides a brief overview of the contents.
3. Administrative Information: Include details such as the DMF number, applicant's name, address, and contact information.
4. Table of Contents: Prepare a comprehensive table of contents that outlines the sections and sub-sections of the DMF.
5. Module Structure: Organize the DMF into modules based on the type of information provided (e.g., Module 1: Administrative Information, Module 3: Quality Information, etc.).
6. Letter of Authorization: If the DMF contains proprietary information, include a letter of authorization allowing CDSCO to review the contents.
7. Quality Overall Summary (QOS) or Executive Summary: Provide an overview of the DMF, including a summary of the information contained in the various modules.
8. Electronic Submission: Submit the DMF electronically through the CDSCO's e-GOV Portal in the specified format.

Submission guidelines and formats:

Module 1: Administrative Information: Include administrative details such as the DMF holder's contact information, regulatory status of the drug, etc.

Module 2: Quality Overall Summary (QOS): Present a comprehensive summary 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, etc.

Module 5: Clinical Study Reports (if applicable): Include clinical study data, if required, including details on the drug's safety and efficacy 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 applicable): If using information from another company's DMF, provide a letter of access from that company.

Specific requirements for various types of DMF

The specific requirements for various types of Drug Master Files (DMFs) in India under the Central Drugs Standard Control Organization (CDSCO) can vary based on the type of DMF being submitted. Here are some specific requirements for different types of DMFs:

Active Pharmaceutical Ingredient (API) DMF: Detailed information about the API, including its structure, synthesis route, and characterization data.

- Description of the manufacturing process, including equipment, controls, and critical steps.
- Specifications for the API's physical and chemical properties, as well as impurities.
- Validation data for the manufacturing process and analytical methods.
- Stability data to demonstrate the API's stability under various conditions.
- Details on the container closure system used for the API.

Excipient DMF

- Description of the excipient's role in the formulation and its intended use.
- Specifications for the excipient's quality, including physical and chemical properties.
- Manufacturing process details, including controls and critical steps.

- Information on compatibility with the drug substance and other excipients.
- Stability data to demonstrate the excipient's stability in the formulation.

Packaging Material DMF

- Detailed information about the packaging material, including its composition and specifications.
- Description of the manufacturing process for the packaging material.

Compatibility data to demonstrate the packaging material's compatibility with the drug product. Information on the container closure system's integrity and functionality.

Stability data to show that the packaging material does not affect the stability of the drug product.

Biological Product DMF

1. Detailed information about the biological product, including its source, characterization, and manufacturing process.
2. Specifications for the biological product’s quality attribute.
3. Information on the cell lines, expression systems, and purification processes used in production.
4. Non-clinical and clinical data to demonstrate the product's safety and efficacy.
5. Validation data for the manufacturing process and analytical methods.

Combination Product DMF

- Detailed information about the combination product, including the drug components and the medical device.
- Description of the manufacturing process for both the drug and the device.
- Compatibility data between the drug and the device components.
- Data on the functionality, design, and performance of the medical device.

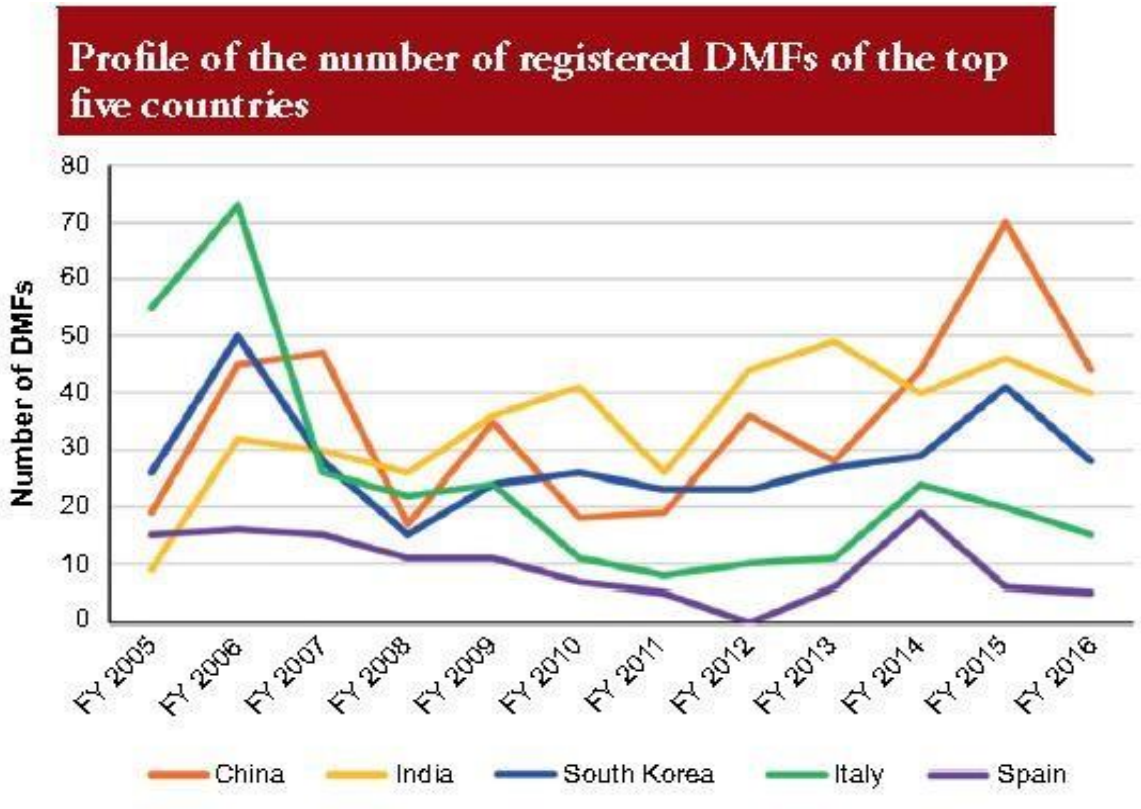

Figure No. 03: Graph showing DMF Filing Of Different Countries.

DMF Filing Procedure

Here's a step-by-step guide to help you prepare and submit a Drug Master File (DMF) in India under the Central Drugs Standard Control Organization (CDSCO):

Step 1: Understand the Requirements

Familiarize yourself with CDSCO's guidelines for DMF submission.

Determine the type of DMF you are submitting (API, Excipient, Packaging Material, 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

Includeinformation about the drug substance's specifications, manufacturing process, and controls.

Describe the manufacturing process and critical steps involved.

Provide detailed specifications for starting 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.

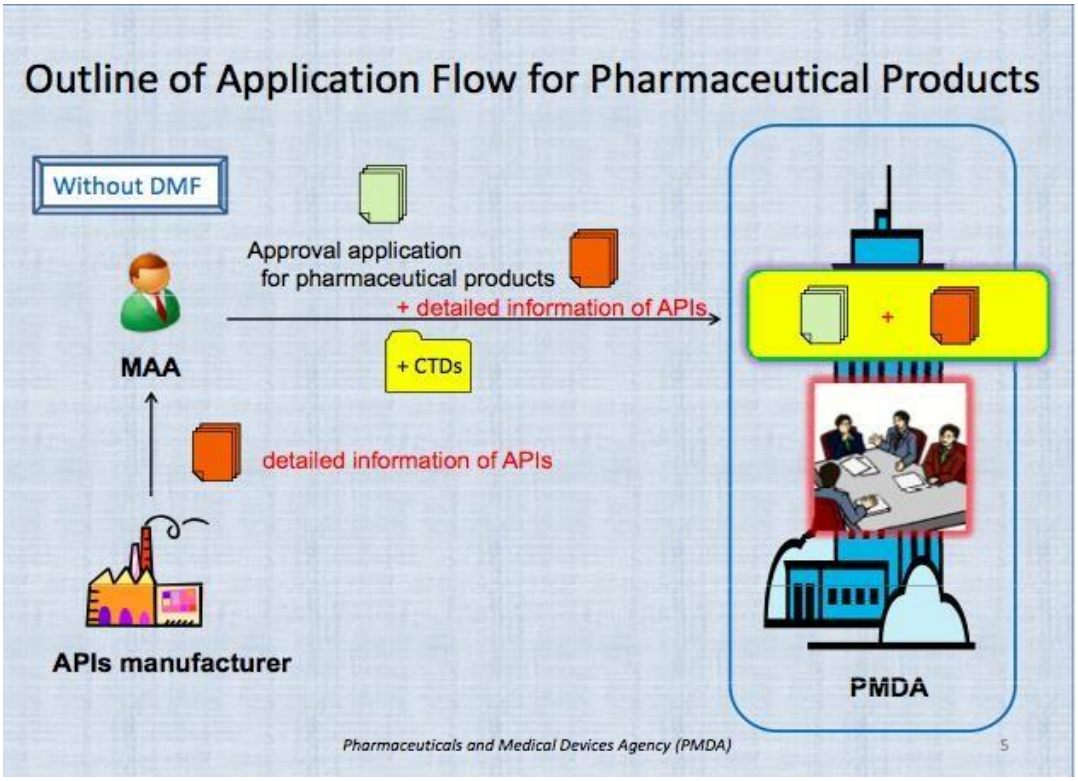

Fig. 04: Outline of application flow for pharmaceutical products without DMF.

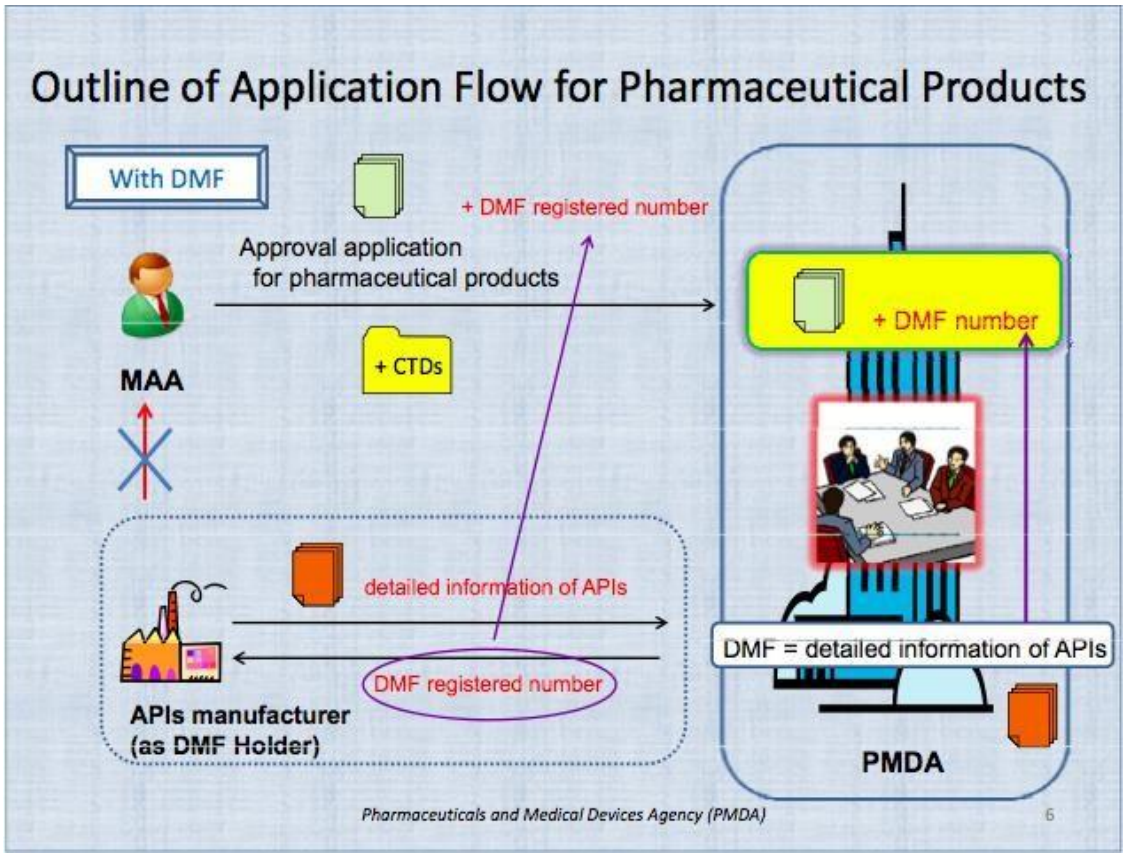

Fig. 05: Outline of application flow for pharmaceutical products with DMF.

Timelines and Expected Response Time

The timelines for DMF submission and the response times from the Central Drugs Standard Control Organization (CDSCO) can vary. Here's a general overview:

- DMF Submission Timeline

The timeline for preparing and submitting a DMF depends on the complexity of the submission and the completeness of the documents.

Aim to submit the DMF well in advance of the anticipated marketing authorization application, as it can take several months for CDSCO to review the DMF.

- Response Time for Acknowledgment

After submitting the DMF through the e-GOV Portal, you should receive an acknowledgment of receipt from CDSCO. This typically occurs within a few weeks.

- Initial Review Timeline

CDSCO initiates the review process after acknowledging the DMF submission.

The initial review may take several months, during which CDSCO assesses the completeness of the submitted documents.

- Clarification and Query Response

If CDSCO identifies any deficiencies or requires additional information, they will issue queries or requests for clarification.

You should respond to these queries promptly to avoid delays in the review process.

- Final Review and Approval Timeline

Once all queries are satisfactorily addressed, CDSCO will conduct a final review of the DMF.

The timeline for the final review can vary but generally takes a few months. Upon successful review, CDSCO will issue an approval letter or notification.

It's important to note that these timelines are approximate and can vary based on factors such as the type of DMF, the complexity of the submission, CDSCO's workload, and any additional information requested during the review process. It's recommended to plan ahead and be prepared for potential delays in the review process.

Confidentiality and Intellectual Property

CDSCO is committed to maintaining the confidentiality of proprietary and sensitive information contained in DMFs. Here are some points to consider:

- Confidential Information: CDSCO recognizes that certain information in the DMF may be proprietary and sensitive, such as detailed manufacturing processes, formulations, and analytical methods.
- Letter of Authorization: If your DMF contains confidential information, include a letter of authorization allowing CDSCO to review the confidential data while ensuring its protection.
- Reviewers' Obligation: CDSCO reviewers are bound by regulations and ethical guidelines to maintain the confidentiality of the information provided in DMFs.
- Data Protection: CDSCO takes measures to safeguard confidential information and prevent unauthorized disclosure.
- Non-Disclosure Agreements: In certain cases, applicants may consider entering into non-disclosure agreements with CDSCO to further protect confidential information.

Amendments and Updates to DMF

Procedure for Making Changes to a Submitted DMF:

- Identify the Need for Amendments: Determine the need for amendments based on changes to the drug substance, manufacturing process, quality data, or any other relevant information.
- Classify the Amendments: Classify the amendments as either "major" or "minor" based on CDSCO's guidelines.
- Prepare the Amendment Submission: For minor amendments, prepare the revised sections of the DMF affected by the change.
- For major amendments, provide a comprehensive explanation of the changes and their impact on the DMF.
- Compile Additional Data: Include any additional data, test results, validation reports, or other relevant documentation supporting the amendments.
- Submit the Amendment: Upload the revised sections or comprehensive amendment document through CDSCO's e-GOV Portal. Provide a cover letter explaining the purpose of the amendment and the changes made.
- Review and Clarifications: CDSCO will review the amendments and may issue queries for clarification or additional information.

- Respond Promptly: Respond to CDSCO's queries or requests for additional information promptly to avoid delays in the review process.

Review and Approval: CDSCO will review the amendments and assess their impact on the DMF. Once satisfied, CDSCO will either approve the amendments or request further actions.

Timelines for Updating DMF Information

- Minor Amendments: The timeline for CDSCO's review of minor amendments can vary but generally takes a few months. CDSCO may issue queries or clarifications during the review process.
- Major Amendments: Major amendments often involve a more extensive review process due to the significant impact on the DMF.The review timeline for major amendments can be several months.
- Post-Approval Changes: After CDSCO's approval of the amendments, the updated information is incorporated into the DMF. It's important to ensure that the DMF remains accurate and up-to-date with the approved amendments.
- Annual Updates: CDSCO requires annual updates to DMFs to ensure that the information remains current and reflective of any changes in the manufacturing process or specifications.
- Renewals: Along with annual updates, DMF holders need to renew their DMFs periodically to maintain their validity.

Handling of Confidential Information in the DMF

a) Confidentiality Protection: CDSCO recognizes the need to protect confidential and proprietary information in the DMF. CDSCO reviewers are obligated to maintain the confidentiality of sensitive information in accordance with regulatory and ethical guidelines.

b) Letter of Authorization: If your DMF contains confidential information, include a letter of authorization allowing CDSCO to review the confidential data.

c) Reviewer Access: Only authorized CDSCO reviewers involved in the evaluation process have access to the confidential information contained in the DMF.

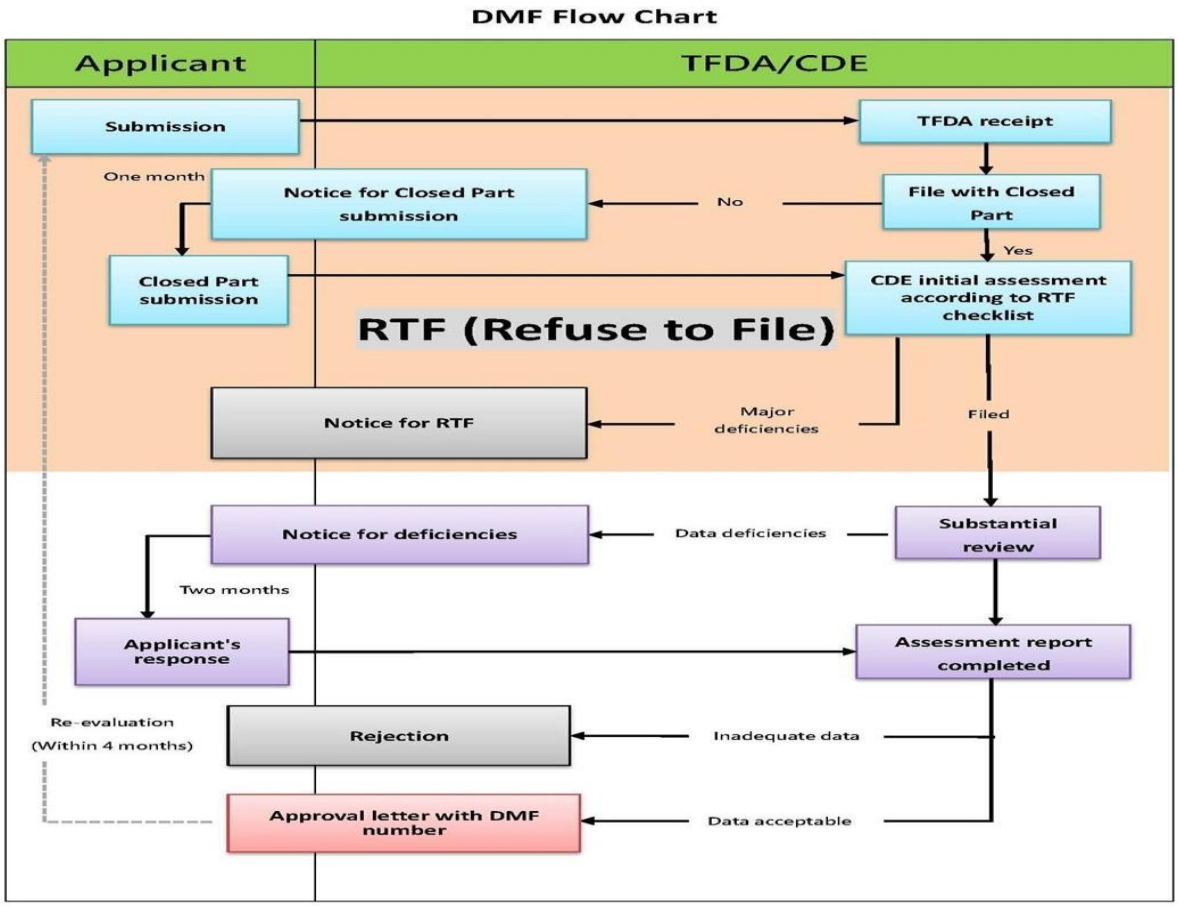

Figure No. 06: DMF Flowchart.

Fees and Charges

- Fees associated with Drug Master File (DMF) submission and processing in India under the Central Drugs Standard Control Organization (CDSCO) can vary based on the type of DMF and the services required. Here's an overview of the fees and charges:
- DMF Submission Fees: There is typically an initial fee for submitting a DMF to CDSCO. The fee amount varies based on the type of DMF and the nature of the submission.
- Review Fees: CDSCO charges review fees for processing and evaluating the DMF submission. The review fees can vary based on the complexity of the DMF and the type of submission (new DMF, amendment, renewal, etc.).
- Amendment Fees: If you make amendments to an existing DMF, there may be additional fees associated with the review of these changes. The fee amount can depend on the significance of the amendments.
- Annual Maintenance Fees: CDSCO requires DMF holders to pay annual maintenance fees to keep their DMFs active and updated. The annual maintenance fee is usually lower than the initial submission and review fees.

- Other Charges: Additional charges may apply for specific services, such as expedited review requests, additional queries, or any special requests related to the DMF.

Post-Approval Obligations

Here's an overview of the post-approval obligations associated with Drug Master File (DMF) submissions in India under the Central Drugs Standard Control Organization (CDSCO), including post-approval changes and reporting requirements, as well as annual updates and renewals:

- Post-Approval Changes and Reporting Requirements:
- Change Notification: As a DMF holder, you are required to promptly inform CDSCO of any significant changes to the drug substance, manufacturing process, or other relevant information.
- Notify CDSCO of these changes using the appropriate channels specified by the organization.
- Types of Changes: Changes that may require notification to CDSCO include modifications to the manufacturing process, specifications, changes in starting materials, or significant changes affecting the quality or safety of the product.
- Submission of Updated Information: If the changes are substantial, you may need to provide updated data, documentation, and relevant information to support the changes.
- Assessment and Approval: CDSCO will assess the changes and determine if they have an impact on the quality, safety, or efficacy of the product.
- Approval may be required before implementing certain changes.

Annual Updates and Renewals

- Annual Updates: CDSCO requires DMF holders to provide annual updates to maintain the currency and accuracy of the information in the DMF. These updates ensure that the DMF reflects any changes that have occurred over the year.
- Content of Annual Updates: Include any changes to manufacturing processes, specifications, stability data, or other relevant information that have occurred since the last submission.
- Annual Update Deadline: Annual updates are usually required within a specified timeframe from the anniversary date of the initial DMF submission.
- Renewals: DMFs need to be renewed periodically to ensure their validity. Renewal processes and timelines can vary, so refer to CDSCO guidelines for specifics.

- Maintaining Compliance: It's crucial to stay proactive in fulfilling post- approval obligations to ensure the regulatory compliance of your DMF. Failing to provide timely updates or notifications of changes could lead to delays in the approval process for drug products that reference your DMF. Regularly review CDSCO guidelines and notifications to stay updated on any changes to post-approval obligations and requirements. Keep records of all communications, updates, and changes made to the DMF to demonstrate compliance with CDSCO's guidelines and requirements. Effective communication with CDSCO and a commitment to maintaining accurate and up-to-date information will contribute to the success of your DMF submission and the products that rely on it.

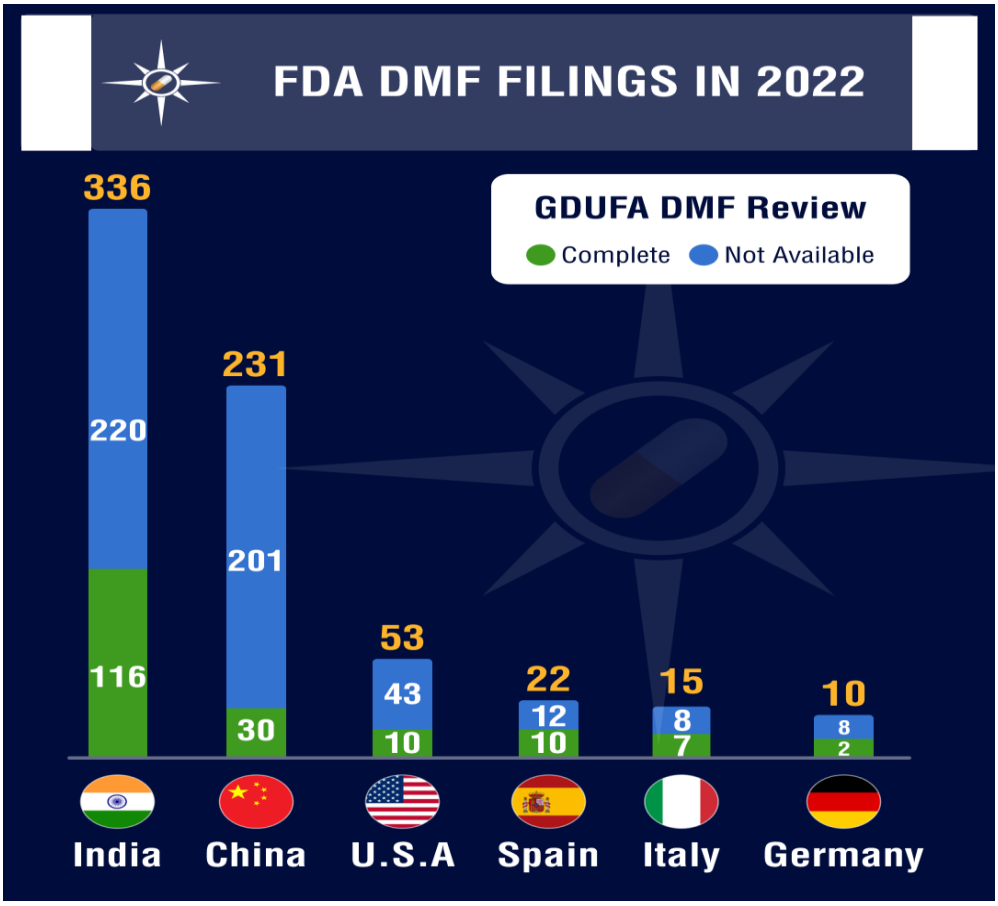

Fig. 07: DMF filings in 2022.

Regulatory requirements of Brazil

Brazilian agency: ANVISA

The Brazilian Health Surveillance Agency, commonly known as ANVISA, abbreviated from Portuguese "Agencia Nacional de Vigilancia Sanitaria," is the food and drug regulatory agency in Brazil. ANVISA was created in 1999 and is linked to the Ministry of Health. It is characterized by its administrative independence, financial autonomy, and the stability of its

directors. In the federal public regulatory structure, the agency is connected to the Ministry of Health. ANVISA's primary goal is to protect and promote public health, by exercising health surveillance over products and services, including processes, ingredients, and technologies that pose any health risks.

ANVISA's vision is to achieve legitimation in society as an integral part of the Brazilian Unified Health System, via a nimble, modern, transparent, and domestic and international benchmark in health surveillance and regulation. ANVISA's mission is "to protect and promote public health and to intervene in the risks caused by the production and use of products regulated by health surveillance. This mission must be carried out in coordination with states, municipalities and the Federal District, according to the Brazilian Unified Health System principles, to improve the quality of life of the population."

The agency is also responsible for health control in ports, airports, and borders, as well as for establishing relations with the Ministry of International Affairs and with foreign organisms and institutions to deal with international affairs regarding health surveillance.

ANVISA was accepted as a new regulatory member of the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). As part of the objective to extend its global outreach, ICH, in November 2016, welcomed ANVISA from Brazil and the Ministry of Food and Drug Safety (MFDS) from South Korea as the first new regulatory Members, together with the Biotechnology Innovation Organization (BIO) as a new industry association Member. There are now 13 members and 22 observers.

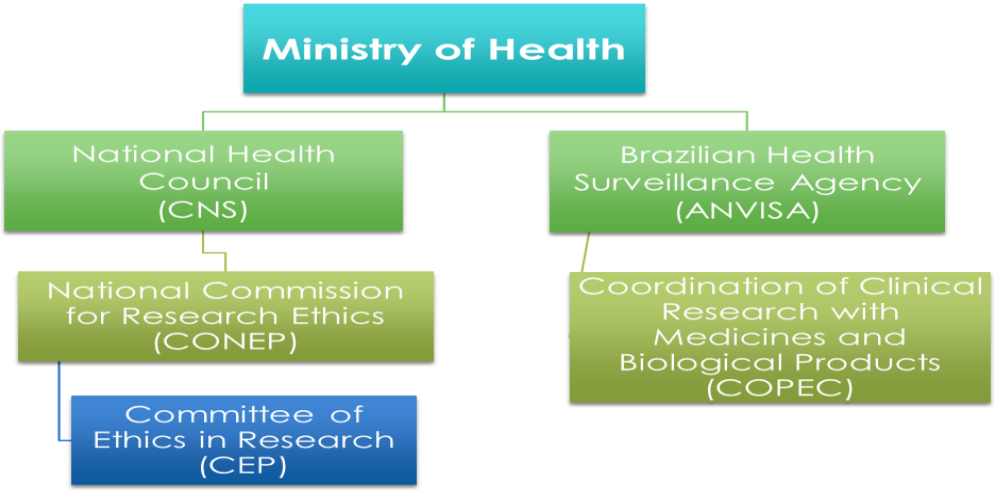

Figure No. 08: Flowchart Of Comparison.

Table No. 01: Regulatory Requirements of DMF Filing between India and Brazil.

	Regulated Market	**Emerging Market**
	India	**Brazil**
Authority	CDSCO	ANVISA
CTD-Modules	5 modules to be submitted	Only 3 modules to be submitted
Applicant part(AP)/ Restricted party(RP)	AP is submitted to the customer and is forwarded to CDSCO RP is submitted to CDSCO directly as a supporting document for the given Applicant DMF number.	AP is submitted to the customer and is forwarded to ANVISA RP is submitted to ANVISA directly as a supporting document for the givenapplicant DMF number.
Filing (eCTD/PDF)	eCTD and PDF	PDF/CD
Review time	Takes several months for CDSCO to review the DMF.	2-3 months for initial queries.Based on queries asked, it takes more one than one year for Approval.
Fee	fees can vary based on the complexity of the DMF and the type of submission	The fees vary depending on the type of authorization, on the product and on the company's corporate size.
Pharmacopoeia	Indian Pharmacopeia	European Pharmacopoeia (EP) USP based on applicant'srequest.
Module 1	Contains general information such as Cover letters ,Query letters ,GMP certificate, Application forms , a brief description of the drug and the therapeutic class to which it belongs , regulatory status in other countries etc.	LOAs if required Cover letters Query letters GMP certificate Application forms – customer-specific
Life cycle management (amendments/ annual reports	Any changes in the DMF are reported to the customer and submitted as amendments. No annual reports.	Any changes in the DMF are reported to the customer and submitted as amendments. No annual reports.

Table No. 02: Comparison of contents in DMF: - Drug Substance.

	India	**Brazil**
Description of Manufacturing Process and Process Controls.	Process flow diagram Raw material batch records, manufacturing steps, recovery solvents, recovery of material, reprocessing steps	Batch sizes of the final API% yield Description of alternate process, recovery solvents, recovery of material, reprocessing steps, blending of Batches if applicable.
Elucidation of Structure and other Characteristics	Possible isomers, structural, geometric, optical data, Refractive index and Chirality Polymorphs synthetic routespectral data Chemical structural data etc.	Possible isomers – structural, geometric, optical data. Structural elucidation of working standard. Description of the method used to employ Particle size distribution. Refractive index and Chirality. Potential to form polymorphs, describing its features and other polymorphs related to the API

Impurities	Genotoxic impurity, residual impurities	Genotoxic impurity (if absent justification). Carry over studies
Validation of analytical procedures	Should be carried out in accordance with the ICH Q2(R1) guidelines	Should be carried out in accordance with the
Reference Standards	Indian PharmacopeiaValidation Data IR spectrum and CoA of working standard	Reference standard CoAs – even though it is a pharmacopeiaproduct Validation data Structural elucidation (SE) data
Container Closure System	Primary packing material and secondary packing material. Storage conditions. In-house test reports and supplier CoA of packing material. Compliance certificate of packing materials.	Material safety data sheet(MSDS)

Table No. 03: Comparison of contents in DMF: - Stability Test.

	India	**Brazil**
Stability summary and conclusion	Stability protocol, studies, conditions, re-test period , confirmation of stability compliance with guidelines	Forced degradation (3.6lux hours in photolytic studies) study reports and conclusions. Photo stability study reports as per ANVISA guidelines
Post-approval stability protocol and stability commitment	CDSCO will assess the changes and determine if they have an impact on the quality, safety, or efficacy of the product.	Retest period Commitment. Zone IV b 12 months or 24 months or till not meet the Specification.
Stability data	Follows ICH Q1 A Guidelines Zone IVb (30ºC ± 2 ºC / 75% RH ± 5% RH) stability data A microbiological test must be routinely carried out and the absence must be justified.	Zone IVb (30ºC ± 2 ºC / 75% RH ± 5% RH) stability data. A microbiological test must be routinely carried out and the absence must be justified. Photo stability study in accordance with RDC 45/2012. Intermediate stability studies are not required.

CONCLUSION

The quality of drug substances or Active Pharmaceutical Ingredients plays an important role in the manufacturing of effective and safe drug products. Hence, the registration requirements for API should be provided completely in detail and the approval of an API dossier (Drug

Master File) must be achieved with utmost care and confidentiality. DMF is a critical document, which is used to support drug product application. Any changes in the approved DMF must be notified as it affects the drug product application as well. Based on the current study, it is clear that the emerging markets possess more stringent requirements for API approval as compared to the regulatory market but the dispute is that the emerging markets do not have harmonized guidelines and are not transparent enough.

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CONFLICT OF INTEREST: No.

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