ejpmr, 2023, 10(10), 106-114

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

REGULATORY REQUIREMENTS AND FILING PROCEDURE OF DMF IN INDIA IN COMPARISON WITH BRAZIL

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Article Received on 01/09/2023 **Article Revised on 22/09/2023** **Article Accepted on 12/10/2023**

ABSTRACT
The master file is an essential regulatory document that plays a crucial role in the pharmaceutical industry, Ensuring the confidential report of important information related to the manufacturing, quality and safety of drug products DMF plays an important role in the drug approval process such as ANDA (abbreviated new drug applications) and provide a good welfare to both drug manufactures and regulatory agencies, thereby ensuring the successful development and approval drug products.

KEYWORDS: DMF (drug master file), pharmaceutical industry, ANDA (abbreviated new drug applications), regulatory agencies.

INTRODUCTION

Drug Master File

A Drug Master File (DMF) is a confidential document submitted to regulatory authorities by pharmaceutical manufacturers, containing comprehensive information about the quality, safety, and manufacturing processes of components used in pharmaceutical products. These components can include active pharmaceutical ingredients (APIs), excipients, packaging materials, and more. The purpose of a DMF is to support the regulatory approval process by providing regulators with the necessary data to assess the component's compliance with regulations without revealing proprietary details to the drug product applicant. This mechanism streamlines the regulatory process and ensures the confidentiality of sensitive manufacturing information.

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. CDSCO's primary responsibility is to ensure the safety, efficacy, and quality of drugs, medical devices, cosmetics, and diagnostics available in the Indian market.

- **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.

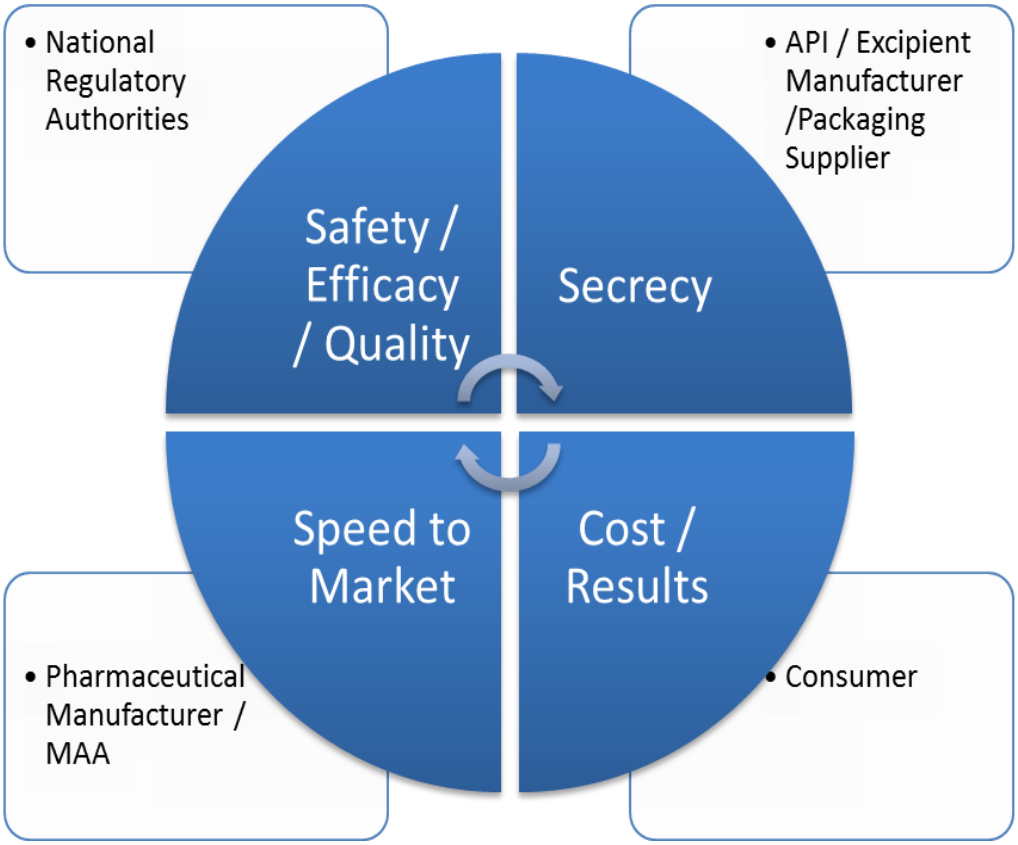
- **Key Responsibilities**

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.
- Quality Control: CDSCO monitors and enforces Good Manufacturing Practices (GMP) to ensure that pharmaceutical products meet established quality standards.
- Safety Monitoring: CDSCO tracks and investigates adverse drug reactions (ADRs) and takes necessary actions to mitigate risks associated with drugs and medical devices.
- 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.
- 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.

- Enforcement: CDSCO has the authority to take enforcement actions, including recalls, suspensions, and penalties against entities found violating regulatory norms.
- 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.



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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. A DMF declared by the company provides in detail the manufacturing place, physiochemical properties, toxicological studies of bulk drug and formulation, Pharmacodynamic /kinetic, therapeutic classes, dosage form, strength, route of administration, Labelling and packaging, etc. Suppose any foreign manufacturer wants to be obtained 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.

Types of Drug Master File

- 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.

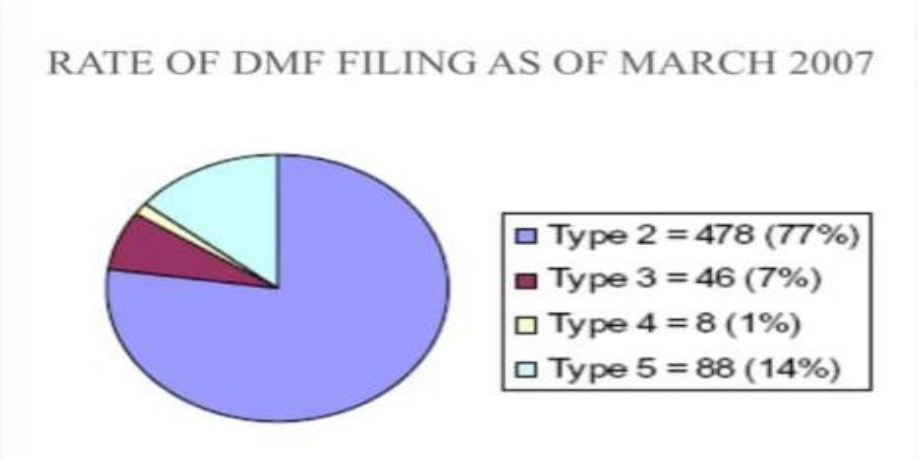
Type II:- Also known as an "Active Pharmaceutical Ingredient (API) DMF," this type contains confidential information about the quality, manufacturing, and controls of the active ingredient of a drug product. It's submitted by the manufacturer of the API to provide regulatory authorities with information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

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.

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.

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.



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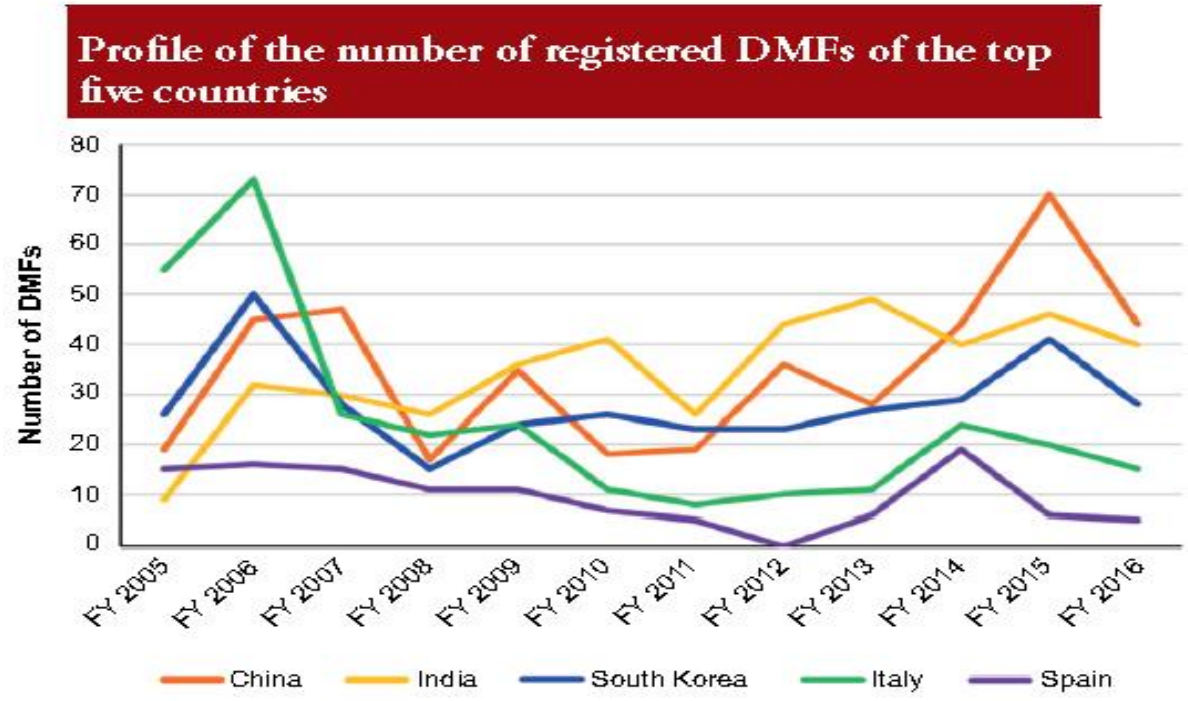

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About the Method

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
- Include information 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.

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.
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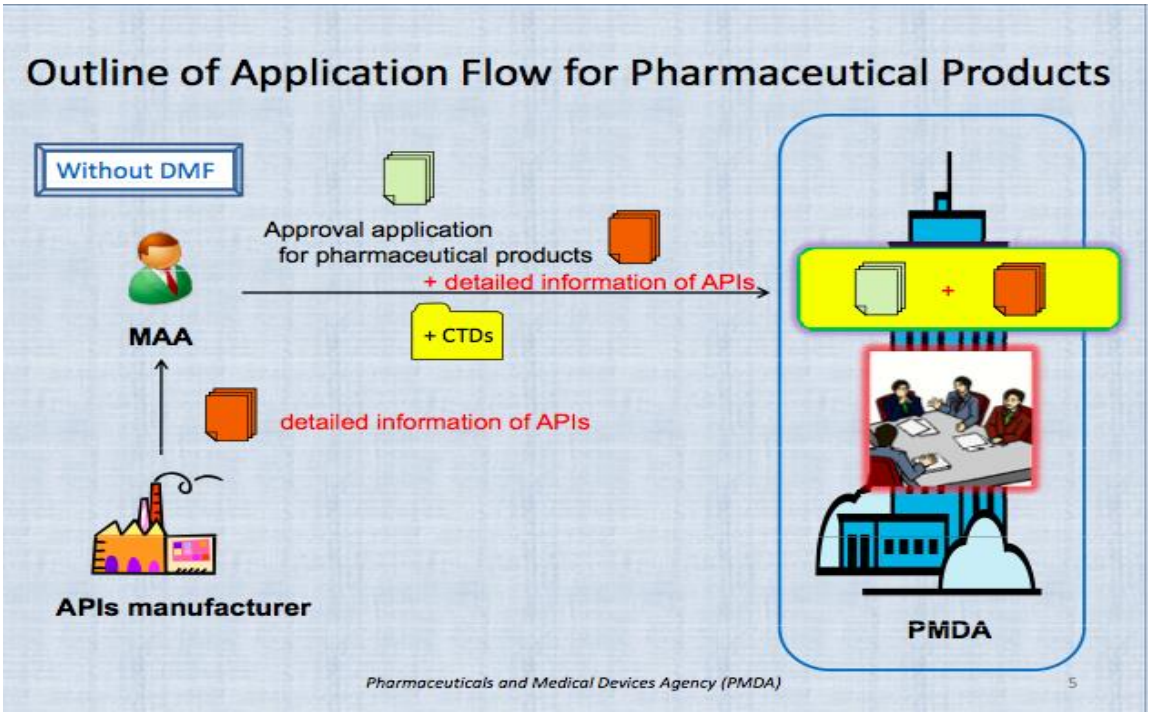

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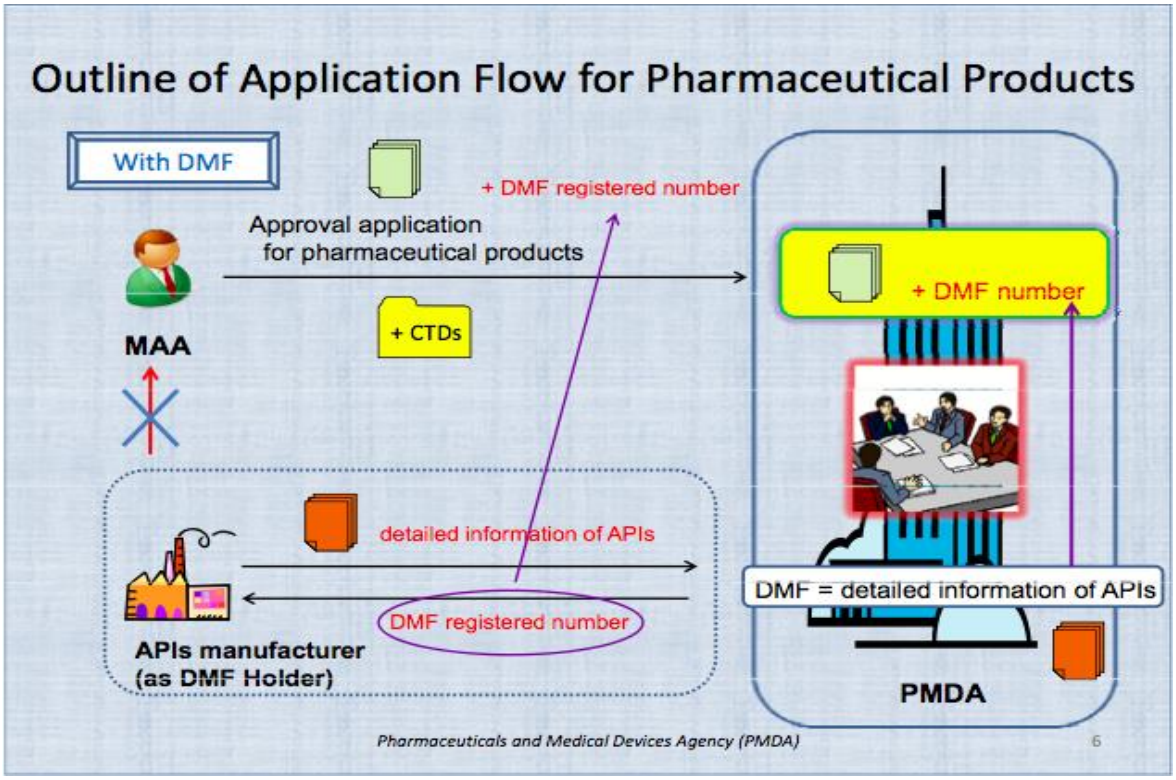

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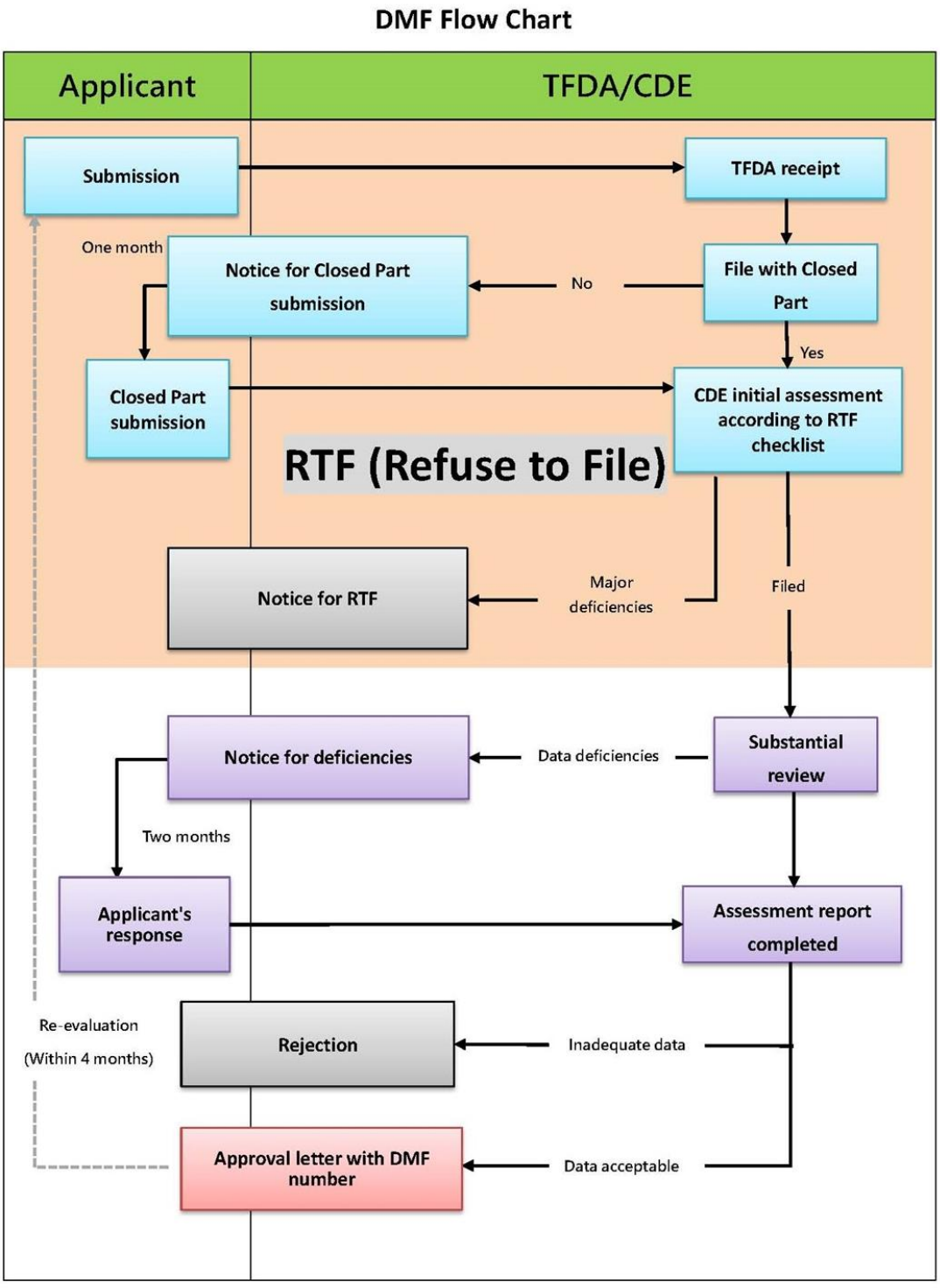
Amendments and Updates to DMF

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 chan 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.



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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.

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.

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 part (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 given applicant 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's request.
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.	1. LOAs if required 2. Cover letters 3. Query letters 4. GMP certificate 5. 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.

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 route spectral 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 impurtites	Genotoxic impurity (if absent justification). Carryover 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 RDC Resolution No. 166.
Reference Standards	Indian Pharmacopia Validation Data IR spectrum and CoA of working standard	Reference standard CoAs – even though it is a pharmacopeia product 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)

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 study reports and conclusions. Photostability 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 IVb 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. Photostability 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.

ACKNOWLEDGEMENT

The authors are wish to thank the management, facility of Sree Siddaganga College Of Pharmacy, Tumkuru ,

Karnataka for providing facilities to carry out this research

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