

**JOURNAL OF DRUG REACTIONS**

An international online peer reviewed, open access Journal  
Content available at [www.cognixpress.in](http://www.cognixpress.in) Online ISSN: 3139-4132

**DRUG MASTER FILE (DMF): A STRATEGIC REGULATORY TOOL FOR PHARMACEUTICAL QUALITY ASSURANCE**

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Article History: 11.04.2026 Received: 14.05.2026 Revised: Accepted: 03.06.2026

**ABSTRACT**

A Drug Master File (DMF) is a confidential regulatory document submitted to regulatory authorities to provide detailed information about the manufacturing, processing, packaging, and storage of drug substances and excipients. It plays a vital role in ensuring drug quality, safety, and regulatory compliance without disclosing proprietary information to applicants. DMFs support pharmaceutical companies in obtaining marketing authorization by allowing regulatory agencies to review critical technical data independently. In global markets, agencies such as the U.S. Food and Drug Administration and European Medicines Agency use DMFs as part of their regulatory framework. Although India does not have a mandatory standalone DMF system, the Central Drugs Standard Control Organization follows structured documentation requirements aligned with international standards like the Common Technical Document (CTD) format. DMFs are classified into different types depending on the content, such as active pharmaceutical ingredients, packaging materials, or excipients. The increasing globalization of pharmaceutical trade, growing regulatory scrutiny, and emphasis on quality assurance have enhanced the importance of DMF submissions. Overall, DMFs contribute significantly to transparency, regulatory efficiency, and the consistent production of high-quality pharmaceutical products worldwide.

**KEYWORDS:** Drug master file (DMF), regulatory compliance, USFDA, eCTD Submission, Pharmaceutical document, regulatory affairs, drug approval process, international Harmonizations, pharmaceutical regulation, quality assurance.

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**1. INTRODUCTION**

A drug master file, or DMF, is a written report that is filed to the Food and Drug Administration that includes private information about the procedures, facilities, or materials that are used in the manufacturing, processing, packing, and storage of one or more human pharmaceuticals [1]. A DMF is created using comprehensive data pertaining to the active pharmaceutical ingredient (API), a finished drug formulation, or a dosing form. It is known as the US-Drug Master File (US-DMF) in Europe and the European Drug Master File (ASMF) in the US. Any human dosage form containing a drug's chemistry, stability, purity, production, packaging, impurity profile, and cGMP status are all covered in detail by the drug's detailed manufacturer's label (DMF) [2,3]. A Drug Master File (DMF) is a private and secure document provided to regulatory agencies, detailing information about facilities,

processes, or materials used in the manufacturing, processing, packaging, and storage of human pharmaceuticals. The concept of DMFs was established to protect the intellectual property of manufacturers while ensuring regulatory compliance. In the United States, the Food and Drug Administration (FDA) introduced DMF guidelines in September 1989, providing a structured system for manufacturers to submit detailed information without disclosing proprietary data to their partners. In Europe, the European Drug Master File (EDMF) system was established between 1989 and 1991, later revised in 2005 to become the Active Substance Master File (ASMF). This system allows active substance manufacturers to submit confidential information directly to regulatory authorities, ensuring the protection of proprietary information while maintaining compliance with regulatory standards. Similarly, Health Canada released a draft guidance document on DMFs in

September 2008, revising the previous 1994 guidelines to align with contemporary regulatory requirements [4].

## 2.PURPOSE OF DMF

- a) Confidentiality: Enables API, excipient, or packaging manufacturers to submit proprietary data directly to regulators.
- b). Regulatory Compliance: Provides structured data aligning with GMP and regulatory standards
- c). Market Approval: Streamlines NDA/ANDA submissions by referencing DMFs, accelerating drug approval

## 3.NEED OF HAVING DMF

The role of protecting confidential information while allowing regulatory access is crucial in maintaining a balance between privacy, compliance, and oversight. Organizations, especially in sectors like finance, healthcare, and technology, implement security measures such as encryption, access controls, and data masking to safeguard sensitive data from unauthorized access. At the same time, regulatory frameworks like GDPR, HIPAA, and financial regulations mandate controlled disclosure to authorities when required.

## 4.STRUCTURE AND CONTENT OF DMF

A Drug Master File (DMF) is a confidential document submitted to regulatory authorities to provide detailed information about the manufacturing, processing, packaging, and storage of drug substances, excipients, or packaging materials. In the United States, DMFs are submitted to the U.S. Food and Drug Administration (FDA) under 21 CFR 314.420. A DMF typically includes administrative information, facility details, manufacturing process description, controls of materials, process validation data, specifications, analytical methods, stability data, and packaging information. DMFs are categorized into different types, such as Type II (drug substance), Type III (packaging materials), and Type IV (excipients). The purpose of a DMF is to protect proprietary information while allowing authorized parties to reference the file in regulatory submissions such as INDs, NDAs, or ANDAs [5].

## 5.CLASSIFICATION OF DMF

### THERE ARE FIVE TYPES

I. Type I: Type I Drug Master File (DMF) was previously submitted by manufacturers to provide the U.S. Food and Drug Administration (FDA) with detailed information about manufacturing facilities. Its primary purpose was to assist FDA personnel in conducting on-site inspections of manufacturing plants located outside the United States. According to the Federal Register (Volume 65, Number 8, dated January 12, 2000), the

Type I DMF category was discontinued and is no longer accepted by the FDA [6].

1. Type II Drug Substance, Drug Product, Intermediates And Materials Used In Their Manufacturing.

A Type II Drug Master File (DMF) is the most commonly submitted type of DMF. It is filed by a manufacturer to provide detailed and confidential information regarding the manufacturing, processing, packaging, and control of a drug substance (Active Pharmaceutical Ingredient, API), its intermediates, and, in some cases, the finished drug product.[7]

2. Type III Packaging Material

Type III DMF is submitted by manufacturer to provide detail information related to the packaging material. Private specific information on the facilities, practices, or equipment used in the production, application, an IND, an NDA, or an ANDA. It is neither accepted nor rejected. just. A DMF's main objective is to keep the holder's confidential information-like a manufacturing method-private. It also allows FDA reviewers to look at information to support applications that one or more applicants have provided. DMFs frequently address the Chemistry, Manufacturing, and Controls (CMC) of an ingredient used in a drug product, such as an excipient, a packing material, or the active pharmaceutical ingredient. Information on drug products or non-CMC information may be found in a DMF [8].

4. Type IV Excipients

A Type IV Drug Master File (DMF) is submitted to provide comprehensive and confidential information on excipients, colorants, flavouring agents, essences, and other materials used in the formulation and preparation of pharmaceutical products. Although these substances are not active pharmaceutical ingredients, they play a critical role in product stability, performance, and patient acceptability [9].

5. Type V FDA Accepted Reference Information

Information that is not covered by Type II and Type IV DMF can be transmitted via Type V DMF, including data from clinical and non-clinical investigations, shared system REMS, contract manufacturing facilities, sterilising procedures, and medical devices. Device master files may contain in-depth information regarding specific manufacturing methods, procedures, or components used in the production, processing, or packaging of medical devices. They may also contain information on completed medical devices [10].

## 6.MECHANISM OF DRUG MASTER FILE

compliance during drug approval. Drug Master File operates through submission of confidential technical data, referenced by applicants, facilitating regulatory evaluation and ensuring quality A Drug Master File works through confidential submission of manufacturing data to regulatory authorities, allowing applicants to reference it

via authorization letters, ensuring data protection, quality evaluation, and regulatory standards

## 7.DRUG MASTER FILE FILLING PROCEDURE IN US FDA

The USFDA places a strong emphasis on the safety, efficacy, and quality of drugs that it accomplishes through DMF filing. Guidelines for the preparation and submission of a DMF to the USFDA are mentioned in 21 CFR 314.420 (Code of Federal Regulations Title 21). All DMFs are submitted through an electronic submission gateway in eCTD format with a transmittal letter, administrative information, and specifications as per USFDA guidelines. DMF is only reviewed if it is referred to in any other application or DMF. To trigger the reviewing process, the holder should submit one copy of the letter of authorization to the USFDA and the other to the applicant. After reviewing the process, copies of DMFs go to the USFDA's Central Drug Evaluation and Research (CDRL). The USFDA contacts the DMF holder to obtain proposed information in case of any discrepancies. Once all aspects of DMF are reviewed and verified, a DMF number is assigned, and the specified contact person mentioned in the DMF is notified. DMF holders are liable to submit any changes or additions as amendments, including a change in the holder's name or address. Transfer of ownership, closure, and reactivation of a DMF is also allowed as per the guideline [11].

## 8.DRUG MASTER FILE IN INDIA: CURRENT TRENDS

The CDSCO, India has provided regulatory guidelines on the submission process of DMFs through its "Guidance Document on Common Submission Format for Import and Registration of Bulk Drugs and Finished Formulations in India. These guidelines are for the import of bulk drugs or formulations and require detailed information on the manufacturer processes and facilities, similar to DMF. The stability studies of API are required to be mentioned in the DMF as per "Appendix IX of Schedule Y of the Drug and Cosmetic Act." The DMF provides comprehensive information about the drug and thereby serves as a supporting document for the MAA in India. CDSCO does not levy any charges for assessing the DMF document. Unlike the USFDA, a DMF number is not assigned after submitting the DMF in India. CDSCO has individual documentation and regulatory guidelines for the manufacturing process of the drug called a "plant master file" that carries the details of facilities equipment and procedures [12].

## 9.NEED FOR OF A DRUG MASTER FILE: INDIAN PERSPECTIVES

DMF is a common application in many countries with highly regulated markets. India being categorized as having a less regulated market currently does not have its

own DMF guidelines [13]. Consequently, DMF is not mandated under Indian law and is not a quality norm for products in India. This absence warrants the need and urgency of establishing a DMF system in India to promote a better quality of pharmaceutical products benefitting the pharmaceutical companies as well as the patients [14]. Given the advantages of DMF filing in better patient care, Mankind Pharma is currently heavily engaged in building awareness around it, among all stakeholders. As of date, Mankind Pharma has filed several DMFs for various products, spread across therapy areas such as ophthalmology, dermatology, endocrinology, pulmonology, and cardiology with a strong resolve to continue its efforts to include many more products in this category [15]. This situation highlights the need to establish a structured DMF system in India to strengthen regulatory standards and enhance the overall quality of medicines. Implementing a formal DMF framework would benefit pharmaceutical companies by improving documentation practices and regulatory compliance, while also ensuring better safety and efficacy for patients. In conclusion, establishing a robust DMF system in India would improve pharmaceutical quality standards, encourage regulatory discipline, protect intellectual property, and ultimately enhance patient care [16].

## 10.CHALLENGES

Complexity Of Regulatory Requirments In Drug Master Files (DMFs)

- Regional Variability: Different regions have unique standards. The US FDA (21 CFR 314.420) uses five DMF types with strict eCTD formatting. The EU (EMA) employs an ASMF system with Open/Closed parts. Japan (PMDA), China (NMPA), and India (CDSCO) also have distinct rules and often require local agents.

Data Accuracy and Consistency

- Accurate and consistent data across manufacturing, analytical methods, and specifications are crucial. Any mismatch between the DMF and the applicant's dossier may lead to regulatory queries or rejection

Technical Documentation and Scientific Justification

- DMFs require detailed documentation, including process validation, impurity profiles, and stability studies. Scientific justification for changes in process, raw materials, or suppliers can be complex and data-intensive.

Ntellectual Property And Confidentiality

- Protecting proprietary information while providing sufficient detail for regulatory review is challenging. Secure handling of confidential data and proper Letters of Access are essential for third-party submissions

Common Issues in DMF Preparation

## Electronic Submission (e CTD COMPLAINT)

- Agencies now mandate eCTD submissions, requiring investment in software, training, and adherence to technical validation standards [14].

## 11.OPPORTUNITES

A Drug Master File (DMF) is a private and comprehensive document voluntarily submitted to regulatory bodies like the U.S. Food and Drug Administration (FDA). It includes critical details regarding the facilities, manufacturing procedures, packaging, and storage methods used in producing human pharmaceuticals [17].

Opportunities and benefits of submitting a DMF:

- Maintaining Confidentiality of Proprietary Information in a drug
- Facilitating Regulatory Approvals
- Enhancing Business Opportunities

Opportunities for global market access through DMFs

- Regulatory Compliance Across Multiple Markets.
- Facilitating Partnerships and Outsourcing.
- Streamlining Regulatory Submissions

## 12. FUTURE PERSPECTIVES

Ensuring compliance with the regulatory authority's guidelines and measuring up to the quality of the global market is pertinent for Indian pharmaceutical manufacturers to facilitate the growth of the Indian pharmaceutical industry with quality products. DMF can prove to be a key element in bringing about significant improvements, to the same.

- Better transparency: DMF filing will allow regulators to take more informed decisions about the safety and efficacy of the drug which in turn will increase the transparency and public trust in the regulatory process
- Improved quality of drugs: DMF filing requires detailed information about the quality, safety, and efficacy of the drugs which can help to improve the quality of drug manufacturing in India
- Increased regulatory compliances: Mandatory DMF filing may encourage the manufacturer to comply with Indian regulatory requirements and to remain adherent to GMP [18].

## 13.CONCLUSION

The Drug Master File (DMF) is a crucial regulatory document that contains complete, accurate, and confidential information about active pharmaceutical ingredients (APIs), excipients, packaging materials, and finished dosage forms, including detailed CMC data such as manufacturing process, stability, purity, and impurity profiles. It plays a significant role in supporting regulatory submissions while protecting proprietary information of manufacturers.

DMFs act as a bridge between pharmaceutical companies and regulatory authorities like the US FDA, EMA, and other global agencies. They facilitate streamlined review processes, support market authorization, and ensure compliance with international regulatory standards. Properly maintained DMFs enhance transparency, regulatory efficiency, and global market access.

However, challenges such as regulatory inconsistencies, documentation updates, harmonization issues, and administrative requirements must be effectively managed. Regular updates, digitalization, and strategic regulatory planning can improve the efficiency of DMF management.

## 14. AUTHOR CONTRIBUTIONS

All authors are contributed equally.

## 15. FINANCIAL SUPPORT

None

## 16. DECLARATION COMPETING INTEREST

The authors have no conflicts of interest to declare.

## 17. ACKNOWLEDGEMENTS

None

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