Drug Master File: an Overview

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***Abstract*: The pharmaceutical industry is one of the most regulated industries and no drug would be marketed unless teams of medical researchers and other specialists tirelessly work toprove the safety and efficacy of the product so that it gets approved by regulatory authorities. When two or more companies collaborate to develop or manufacture a drug product, a drug master file (DMF) is created. A DMF is a confidential, detailed document containing accurate and complete information about a drug product's chemistry, manufacture, control, container closure system, excipient, packaging material, and cGMP status submitted by Active Pharmaceutical Ingredient (API) manufacturers to the US Food and Drug Administration (USFDA). The DMF filing enables a company to protect its intellectual property from its partner while meeting regulatory requirements for processing detail disclosure. Although DMF filing is not required by law or regulation, it helps in rapid processing of INDA, NDA, ANDA or export application. This review article provides in depth information about the contents and submission guidelines for DMF to USFDA.**

***IndexTerms:* Drug Master File (DMF), US Food and Drug Administration (USFDA), INDA, NDA, ANDA, Active Pharmaceutical Ingredient (API) manufacturers**

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1. INTRODUCTION:

US pharmaceutical market is highly regulated market and US pharmaceutical industry earned $550 billion in 2021. The US pharmaceutical market accounted for 48% of global pharmaceutical market as of 2020. On average the FDA approves about 38 drugs each year. Although the US pharmaceutical industry is often a controversial topic, but there is no denying that is a huge part of the US economy and has produced many lifesaving and life improving drugs.

The United States Food and Drug Administration (FDA or USFDA) is a federal agency of the Department of Health and Human Services, USA. The FDA is responsible for protecting and promoting public health through the control and supervision of food safety, tobacco products, dietary supplement, prescription and over-the-counter pharmaceutical drugs (medication), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), cosmetics, animal foods & feed and veterinary products.[1] [2]

1.1 USFDA and its Organization:

Food and Drug Act 1906 prompted formation of administration body that can prohibits interstate commerce of misbranded and adulterated foods, drinks and drugs. In 1930 the name of Food, Drug and Insecticide administration was shortened to Food and Drug Administration (FDA). The head office of USFDA is located in Montgomery County and Prince George's County, Maryland. FDA is an agency within the department of Health and Human Services and it consist of nine center-level organization and thirteen Headquarters offices.[3]

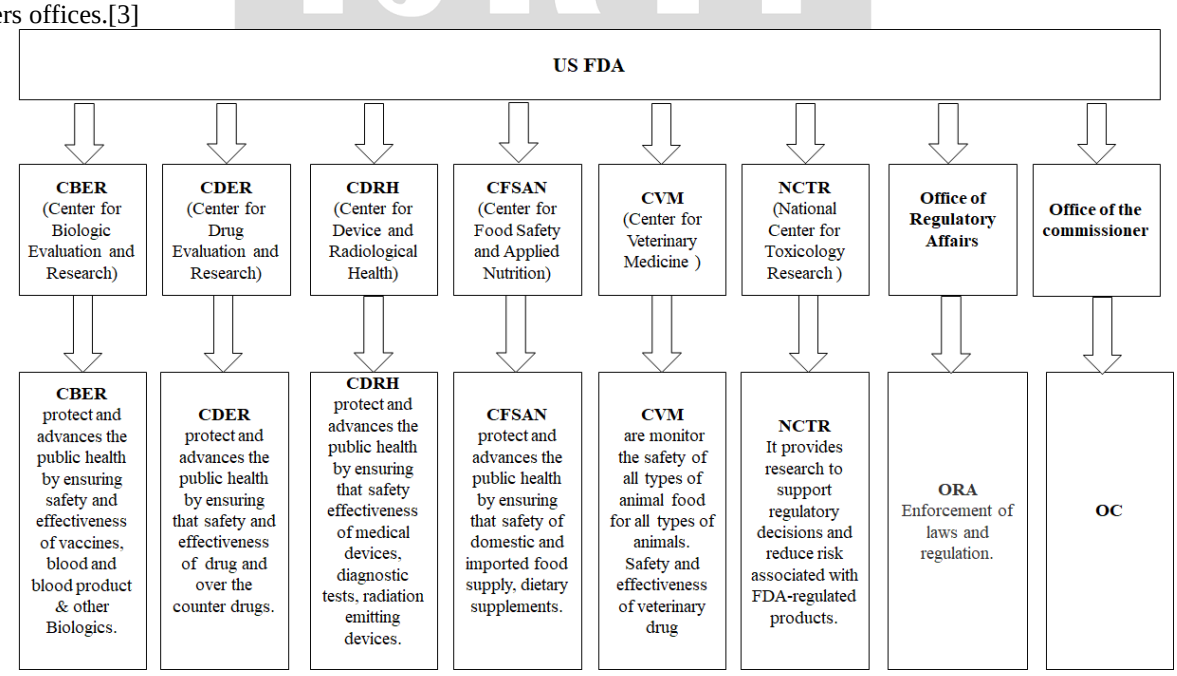

Fig. 1: Organizational Structure of USFDA.[3]

1.2 DMF:

A drug master file (DMF) is a collection of documents submitted to the FDA by a pharmaceutical manufacturer. 21 CFR 314.20 specifies the contents of DMF that the company may be required to provide to regulatory authorities for a complete understanding of their product, facility, and the processes, systems, equipment, and articles used for various processes of manufacturing and quality assurance, or storage and distribution.

The departments of USFDA namely CBER receives biologics master files, while the CDER receives drug master files.

Although DMF submission is not required by law or FDA regulations, however, it may help in speedy evaluation or approval of different types of drug applications and hence it is submitted solely at the holder's discretion. The submission of drug master file by a pharmaceutical manufacturer is done to support various applications like a new DMF, as well as amendments and supplements to any of these applications, New drug application (NDA),Investigational new drug application (INDA), Abbreviated new drug application (ANDA) and Export application. The DMF does not replace an INDA, NDA, ANDA, or export application but it provides information in support of approval of these applications. DMF is not a Patent Certificate.[4-6]

1.3 Merits of DMF Submission:

- Support the documentation required for the registration or approval of pharmaceutical product
- Provides information about the identity, purity, strength, and quality of the drug in the chemistry, manufacturing, and control (CMC) part of the drug submission.
- To secure private and proprietary information.[7]

2. Types of DMF:

There are five types of DMF are as follows

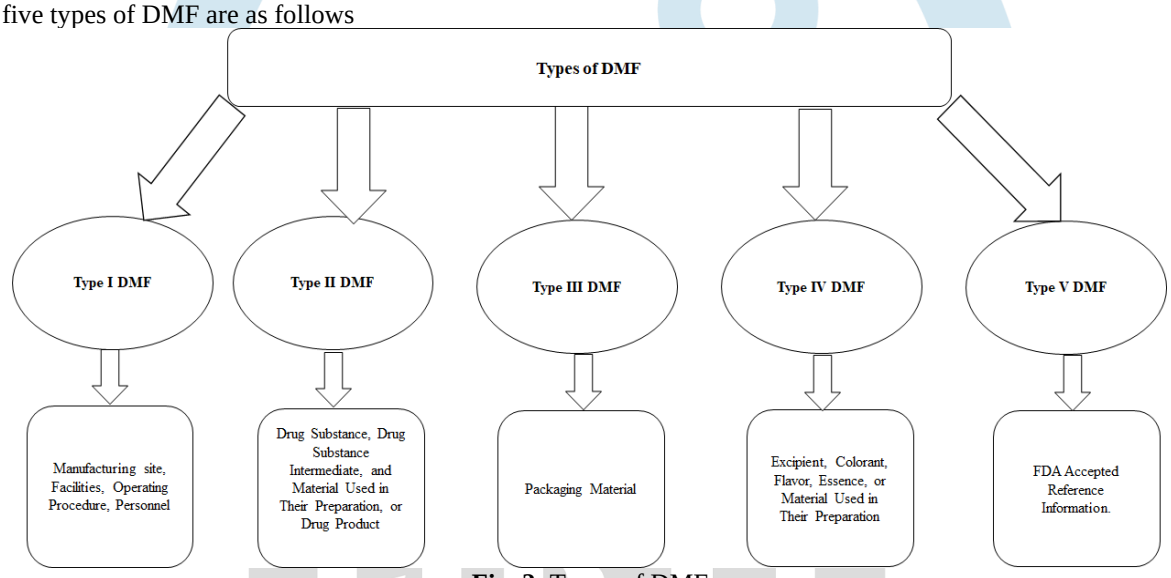

Fig. 2: Types of DMF

2.1 Type I DMF: Manufacturing facility or site, technical personnel employed by the company, and operating procedures.

A Type I DMF is submitted by manufacturer to assist the FDA personnel to perform on-site inspections of manufacturing plants outside of the US. The DMF should provide details about the manufacturing facility, the equipment it uses, and its operating design. A map indicating the property's location in connection to the nearest city, its actual address, and its acreage should all be included in the description of the site. A map of the location and an aerial shot may be useful.

Understanding the operational layout is made easier with the aid of a diagram showing the main production and processing areas. Major pieces of equipment need to be explained in terms of their capabilities, use, and placement.

A schematic of important corporate organisational aspects, with key manufacturing, quality control, and quality assurance personnel indicated, at both the manufacturing site and corporate headquarters, is also helpful. Domestic facilities generally do not require a submission of Type I DMF. According to the federal register, volume 65, number 8, dated January 12, 2000, type I DMF is no longer in use. [6, 8-10]

2.2 Type II DMF: Drug Substance, Drug Substance intermediate, and preparation material or drug product

Type II DMF is submitted by manufacturer to provide detail information related to the manufacturing of the drug and drug product including any drug substance intermediate. The detailed information to be given for drug substance and drug product is given below.

An active pharmaceutical ingredient (API), its intermediates, the materials used in their preparation, or a drug product.

The most typical type of DMF, Type II, can also cover dosage form medications created
under contract for a different business that will submit an ANDA.[6, 8-10]

2.3 Type III DMF: packaging Material

Type III DMF is submitted by manufacturer to provide detail information related to the packaging material. The detail information to be given for the packaging material is given below.
The intended application, components, composition, and release controls for each packing material should be noted. The acceptance specifications and the names of the suppliers or manufacturers of the parts used in creating the packing material should also be provided.
In accordance with the "Guideline for Submitting Documentation for Packaging for Human Drugs and Biologics," data demonstrating the suitability of the packaging material for its intended application should also be submitted.
If not already available by cross-referencing another document, toxicological information on this material would be included under this sort of DMF.[6, 8-10]

2.4 Type IV DMF: Excipient, Colourant, Flavours, Essence, or Material Use in their preparation

Type IV DMF is submitted by manufacturer to provide detail information related to excipient, colorant, flavours, essence, or material. The detail information to be given for the excipient, colorant, flavours, essence, or material
Each additive should be recognised and prescribed according to its manufacturing process, release equipment and testing procedures.
If not already available by cross-referencing another document, toxicological information on this material would be included under this sort of DMF.
The preparation of a type IV DMF should follow the guideline provided for the type II DMF's and the DMF should include any additional supporting data and information that cannot be found through cross referencing with another document. [6, 8-10]

2.5 Type V DMF: FDA Accepted Reference Information.

Type V DMF is submitted by manufacturer to provide detail information related to the FDA accepted reference information. The detail information to be given for the FDA accepted reference information is given below.
This is essentially FDA-accepted reference data that is not included in the other types of DFMFs.
It should be noted that the manufacturer of any material (e.g., API, DP, container/closure components, etc.) has the option of submitting the necessary information for review directly to their customers for inclusion in the IND, NDA, ANDA, and BLA, as well as supplements or amendments to these applications. This can be done entirely or partially. If only a portion is submitted, it is considered the "open part" of a shared DMF, whereas the proprietary portion is the "closed part" of the DMF. [6, 8-10]

3. Submission of DMF:

DMF submission must include the transmittal letters, administrative information about the submission, and the precise data as described in the following sections.
The DMF must be written in English. A precise certified English translation must be submitted whenever a submission includes in another language.
Each page of every copy of the DMF needs to be dated and numerically sequenced. Each submission should come with a new table of contents.[6] [9] [11]

3.1 Transmittal Letter: Transmittal Letter should have

Original Submission	Amendments
a. Identification of submission: Original, the type of DMF as classified in Section III, and its subject.	a. Identification of submission: Amendment, the DMF number, type of DMF, and the subject of the amendment.
b. Identification of the applications, if known, that the DMF is intended to support, including the name and address of each sponsor, applicant, or holder, and all relevant document numbers.	b. A description of the purpose of submission, e.g., update, revised formula, or revised process.
c. Signature of the holder or the authorized representative.	c. Signature of the holder or the authorized representative.
d. Typewritten name and title of the signer.	d. Typewritten name and title of the signer.

3.2 Administration information: Administration information should include

Original Submission	Amendments
a. Names and address of the following	a. Name of DMF holder
(1) DMF Holder name	b. DMF number
(2) Corporate headquarter	c. Name and address for correspondence
(3) Manufacturing/processing facility	d. Affected section and/or page numbers of the DMF
(4) Contact for FDA correspondence	e. The name and address of each person whose IND, NDA, ANDA, DMF, or Export Application relies on the subject of the amendment for support
(5) Agent (if any)	f. The number of each IND, NDA, ANDA, DMF, and Export Application that relies on the subject of the amendment for support, if known
b. The specific responsibility of each person listed in any of the categories in section 1	g. Particular items within the IND, NDA, ANDA, DMF, and Export Application that are affected, if known

c. Statement of commitment	
A sign statement by the holder certifying that the DMF is current and that the DMF holder will comply with the statement made it	

4. Letter of Authorization to FDA:

Before FDA can review DMF data supporting an application, the DMF holder must send a letter authorizing FDA to make use of the DMF in duplicate to the DMF. The letter of authorization does not require a transmittal letter. The letter of authorization should include the following

- The Date
- Name of DMF holder:
- DMF Number
- Name of person (s) authorized to incorporate information in the DMF by reference:
- Specific products (s) covered by the DMF:
- Section numbers and /or page number to be referenced:
- Statement of commitment that the DMF is current and that the DMF holder will comply with the statement made in it:
- Signature of authorized official:
- Typed name and title of official authorized reference to the DMF.[9]

5. Copy to Applicant, Sponsor, or other Holder:

The holder should also send a copy of the letter of authorization to the affected applicant, sponsor, or other holder who is authorized to incorporate by reference the specific information contained in the DMF. The applicant, sponsor, or other holder referencing a DMF is required to include a copy of the DMF holder's letter of authorization in the application.[9]

6. Examining the DMF:

A DMF is NEVER APPROVED OR DISAPPROVED. The agency will review information in a DMF only when an IND sponsor, an applicant for an NDA, ANDA, or Export Application, or another DMF holder incorporates material in the DMF by reference. As noted, the incorporation by accompanied by a copy of the DMF holder's letter of authorization.[9]

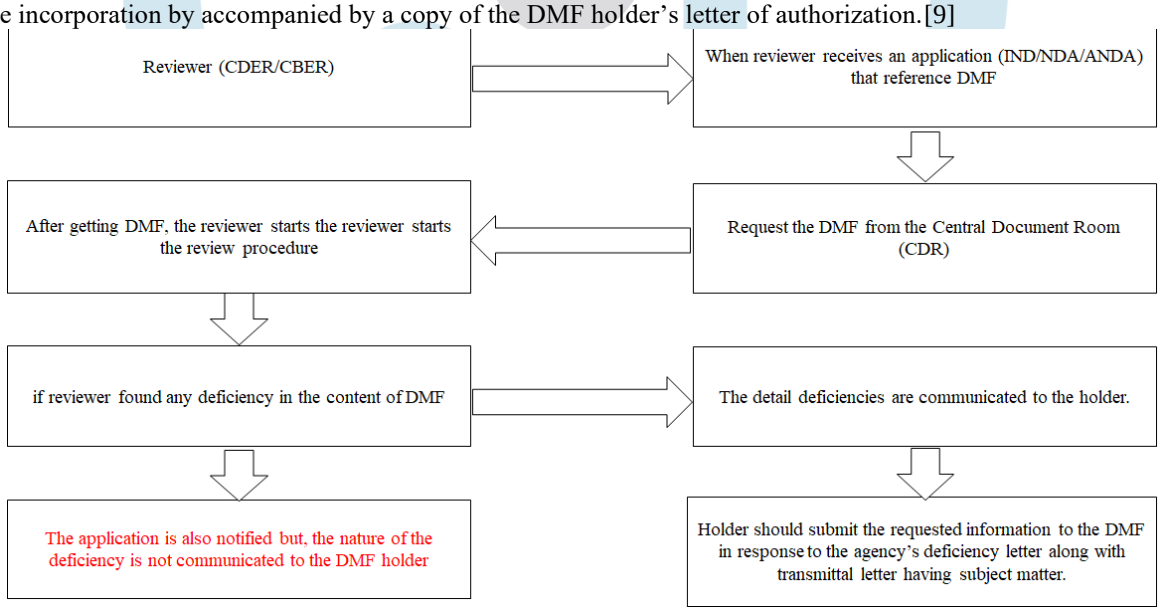

Fig. 3: Examination process of DMF [9]

7. DMF Submission Fee:

FDA fees must be paid for a Type II DMF Submission from an API Manufacturer for a generic drug application. The FDA DMF Fees for 2020 are USD 57,795. Other types of DMF submissions do not incur FDA fees.

The FDA discusses the requirements for filing a DMF under 21 CFR 314.420, or Applications for FDA Approval to Market a New Drug, in the Code of Federal Regulations.[8]

8. Annual Report:

On the anniversary date of the original submission, the holder should provide an annual report. all changes and additional information incorporated into the DMF since this previous annual report on the DMF's subject matter. If the DMF's subject matter remains unchanged, the DMF holder must provide a statement stating that the DMF's subject matter is current.

FDA review of a pending IND, NDA, ANDA, export application or any amendment or supplement to such an application may be delayed if previously submitted materials and lists in the DMF are not updated annually or FDA is not assured that they remain current. Additionally, FDA may begin procedures for DMF closure.[9]

9. Transfer of Ownership:

The holder must give written notice to the FDA and other authorized parties whenever they transfer ownership of a DMF to another party the following should be in the letter.

1. Name of transferee
2. Address of transferee
3. Name of responsible official of transferee
4. Effective date of transfer
5. Signature of the transferring official
6. Typewritten name and title of the transferring official.

A letter of acceptance of the transfer and, if required, an update to the data in the DMF must be given by the new holder The location and operation procedures of the factory, for example, should be updated to reflect the new ownership.[9]

10. Closure of DMF:

A holder who wishes to close a DMF should submit a request to the Drug Master File Staff, explaining why the closure is necessary. The Agency may close a DMF if it lacks an annual update of persons authorized to incorporate the information in the DMF by reference, as well as a list of changes made since the previous annual report. The holder will be notified if the FDA decides to close the DMF.[9]

11. Contact Information:

Mail ID: dmfquestion@fda.hhs.gov

Physical Media Submission:[12]

CDER	CBER
Food and Drug Administration Centre for Drug Evaluation and Research Central Document Room 5901-B Ammendale Road Drug Master File Staff Beltsville, MD 20705-1266	Document Control Centre 10903 New Hampshire Avenue Building 71, Room G112 Silver Spring, MD 20993-0002

Conclusion:

The DMF contains complete and confidential information about active pharmaceutical ingredient, packaging material, excipient, CMC, packaging material, etc. and the main purpose of DMF is to support regulatory requirements of a medicinal product to prove its quality, safety and efficacy and this helps in obtaining a market authorization with in minimum period of time. All relevant scientific information for the market authorization of medicines in US market starting May 5, 2018, any new submissions to the existing DMF must be assembled and submitted in eCTD format.

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Conflict of Interest:

There is no conflict of interest regarding the publication of this article.

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