Research Article

Available Online at: www.ijpir.com

International Journal of Pharmacy and Industrial Research

ISSN	Print	2231 – 3648
	Online	2231 – 3656

Drug master file of United States and europirean countries

Pedapaka Uday*, Ch.Madhava Reddy, Saddam Hussain

Department of Pharmaceutical Analysis, Holy Mary Institute of Technology and Science (College of Pharmacy), Bogaram, Keesara, Ranga Reddy District, Hyderabad, Telangana-501301

ABSTRACT

A Drug Master File is a confidential document used to provide detailed information about facilities, processes or articles used in the manufacturing process, packaging and storing of one or more human drug. The Drug Master File may be utilized either by the holder who establishes the file, or by one or more additional parties in support of their application.The Drug Master File filing allows a firm to protect its intellectual property from its partner while complying with regulatory requirements for disclosure of processing details. The review includes various types of Drug Master Files, the important aspects in filing and processing. In this presentation we did individually study about the rule & regulations which are followed for drug approval process in USA, Europe. This comparative study of dossier compilation given a brief idea about the difference in regulatory requirements for drug approval process among USA, EU. In this presentation we have also discussed about dossier. Process of reviewing and assessing the dossier of a pharmaceutical product containing its detailed data (administrative, chemistry, pre-clinical and clinical) and the permission granted by the Regulatory Agencies of a country with a view to support its marketing / approval in a country i.e., Product licensincing. We have provided few case studies of the Drug Master file for few drug products and binders and excipients collected from different companies.

Keywords: Drug Master File, Holder, Dossier, Intellectual property, Dossier, Regulatory requirements, Ecepients, Binders, Drug product.

INTRODUCTION

The pharmaceutical industry is one of the most regulated industries; no drug would be marketed without the teams of medical researchers and other specialists who worked to make sure it receives regulatory authority's approval. A regulatory authority is an agency of the government that is responsible for protecting public health in safety aspects. A Drug Master File is a confidential document used to provide detailed information about facilities, processes or articles used in the manufacturing process, packaging and storing of one or more human drug. A drug master file comprises two parts: the Applicant's Part, which contains all the information that the license-holder

Author for Correspondence:
Pedapaka Uday
Department of Pharmaceutical Analysis,
Holy Mary Institute of Technology and Science (College of Pharmacy).
Bogaram, Keesara, Ranga Reddy District, Hyderabad, Telangana-501301

needs to assess the quality and submit a license or amendment application; and the [1]

Restricted Part, which contains confidential information about the manufacturing procedure that only needs to be disclosed to the authorities. This review article provides information on regulatory requirements of Drug Master Files by Food and Drug Administration (USA), European Medicines Agency (Europe) and Health Canada (Canada) and their comparison [2].

The pharmaceutical industry is one of the most regulated industries; no drug would be marketed without the teams of medical researchers and other specialists who worked to make sure it receives regulatory authority's approval. Regulatory affairs professionals are key players in drug development for obtaining approvals and maintaining lifecycle management of both branded and generic drugs.

They are the primary communications link between the company and agencies such as SFDA, MHRA, CDSCO and TPD etc. A regulatory authority is an agency of the government that is Responsible for protecting public health in safety aspects. The present study focuses on API filing (DMF System) in United States, Canada and Europe

A regulatory process, by which a person/organization/sponsor/innovator gets authorization to launch a drug in the market, is known as drug approval process. In general, a drug approval process comprises of various stages: application to conduct clinical trials, conducting clinical trials, filing of Registration Dossier/ New Drug Application (NDA) and post-marketing studies. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs. The single regulatory approach for marketing authorization of a new drug product applicable to various countries (on the basis of single dossier) is utmost difficult. Therefore, the knowledge of exact and detailed regulatory requirements for Registration Dossier of each country should be known to establish a suitable regulatory strategy [5,6].

Drug registration implements one of the legal requirements for marketing of drugs in a country. Drug registration guidelines provide guidance to applicants who may wish to market their pharmaceutical products in the market. They intend to assist applicants in the preparation of acceptable application documents. It is therefore essential that every person who intends to market a medicinal product in country reads the whole of these guidelines carefully and follows strictly the instructions prescribed herein. Submission of applications, which do not comply with the prescribed requirements, may result in delays, queries or rejection of registration.

The word **"Dossier"** has its English meaning as - a collection or file of documents on the same subject, especially a file containing detailed information about a person or a topic. Any preparation for human use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient is called as "pharmaceutical product for human use". Process of reviewing and assessing the dossier of a pharmaceutical product containing its detailed data (administrative, chemistry, pre-clinical and clinical) and the permission granted by the Regulatory Agencies of a country with a view to support its marketing / approval in a country is called as the "Marketing Approval or the "Registration" "Marketing Authorization" or the "Product Licensing"

"Registration Dossier" of the pharmaceutical product is a document that contains all the technical data (administrative, quality, nonclinical and clinical) of a pharmaceutical product to be approved / registered / marketed in a country. It is more commonly called as the New Drug Application (NDA) in the USA or Marketing Authorization Application (MAA) in the European Union (EU) and other countries, or simply Registration Dossier. Basically, this consists of data proving that the drug has quality, efficacy and safety properties suitable for the intended use, additional administrative documents, samples of finished product or related substances and reagents necessary to perform analyzes of finished product. Therefore, they are the vehicle in a country through which drug sponsors formally propose that the Regulatory Agencies approve a new pharmaceutical for sale and marketing.

STER FILE (DMF) DEFINITION

Drug Master File or DMF is a document prepared by a pharmaceutical manufacturer and submitted solely at its discretion to the appropriate regulatory authority in the intended drug market. There is no regulatory requirement to file a DMF. However, the document provides the regulatory authority with confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs [7].

Generally DMF's have two parts

- **Applicant's Part**: This contains non confidential information that the license holder needs to assess for the marketing.
- **Restricted Part**: This contains confidential information about the manufacturing procedure that only needs to be disclosed to the authorities

The DMF can be referenced by drug manufacturers in support of their New Drug Submissions (NDSs), Abbreviated New Drug Submissions (ANDSs), Supplement to a New Drug Submission (SNDS) Supplement to an Abbreviated New Drug Submission (SANDS), DIN submissions, Notifiable Changes (NCs), New Product Number (NPN) applications and Clinical Trial Applications (CTAs). DMFs may be referenced by more than one drug manufacturer.

The guidance document has been updated to incorporate revisions resulting from the adoption of International Conference on Harmonization (ICH) guidelines. The terminology used in this guidance document is the same as used in the ICH guidelines. Where terminology is defined in the ICH guidance documents no definition is given and the reader is referred to these guidelines.

A DMF is **not** a substitute for an IND, NDA, ANDA, or Export Application. It is not approved or disapproved. Technical contents of a DMF are reviewed only in connection with the review of an IND, NDA, ANDA, or an Export Application.

This guideline does not impose mandatory requirements (21 CFR 10.90(b)). It does, however, offer guidance on acceptable approaches to meeting regulatory requirements. Different approaches may be followed, but the applicant is encouraged to discuss significant variations in advance with FDA reviewers to preclude spending time and effort in preparing a submission that FDA may later determine to be unacceptable.

Drug Master Files are provided for in 21 CFR 314.420. This guideline is intended to provide DMF holders with procedures acceptable to the agency for preparing and submitting a DMF. The guideline discusses types of DMF's, the information needed in each type, the format of submissions to a DMF, the administrative procedures governing review of DMF's, and the obligations of the DMF holder.

DMF's are generally created to allow a party other than the holder of the DMF to reference material without disclosing to that party the contents of the file. When an applicant references its own material, the applicant should reference the information contained in its own IND, NDA, or ANDA directly rather than establishing a new DMF [8].

WHAT ARE NEW DRUG SUBMISSIONS AND ABBREVATED DRUG SUBMISSIONS?

Food and Drug Administration (FDA) grants approval for marketing authorization for new as well as generic drugs against review of detailed scientific, clinical and non-clinical information included in the application called as NDA, ANDA and DMF

ANDA

An Abbreviated New Drug Application (ANDA) is an application for a U.S. generic drug approval for an existing licensed medication or approved drug.

SUBMITTING ANDA: Information as per **5 MODULE ICH CTD** Guidelines

CTD Module 1: Administrative documents
CTD Module 2: Quality, non-clinical and Clinical Overviews and summaries
CTD Module 3: Detailed Quality information on API and Dosage Form
CTD Module 4: Non Clinical Study Reports (as available)

CTD Module 5: Clinical Study Reports (as Full text Papers) [9,10]

The entire set of information shall be submitted in triplicate as per below

Archival Copy

The archival copy is a complete copy of the application. It serves as the official archive of the application and may be used during the review of the application. It shall have blue color binder

Review copy

It includes the information needed by each review discipline for its evaluation. It shall have red color

Field copy

It contains only Quality section (Module 3)It shall have Green Color. The information provided in any format other than this may get ”Refuse to File ”letter from FDA.

Paper size-Standard U.S. letter size paper (8.5 x 11 inches) should be used for all submissions.

Font size-Narrative text is submitted in Times New Roman 12 point font. Font sizes9 to10 points are considered acceptable in tables.

Pagination-Page numbering should be at the document level and not at the volume or module level. (The entire submission should never be numbered consecutively by page.) In general, all documents should have page numbers. Since the page numbering is at the document level, there should only be one set of page numbers for each document [11].

Please Note that the following admin information (as to be included in CTD Module 1 is very critical

- Field copy certification
- Debarment certification
- Financial Certification
- Patent information on any patent that claims the drug, if applicable
- Patent certifications
- Letters of authorization for reference to other applications or drug master files (if applicable)
- US Agent Letter of Authorization
- Proprietary name request (if applicable)
- Basis of ANDA submission
- Comparison between Generic Drug and RLD - 505(j) (2) (A)
- Request for waiver
- Draft labeling
- Listed drug labeling
- Labeling requirements
- Financial disclosure Information
- Waiver requests
- Environmental assessment or request for categorical exclusion
- Statements of claimed exclusivity and associated certifications
- Prescribing information (Actual copies to be provided)
- Container and package labels
- Package inserts
- Draft labeling
- Patient leaflets
- Information sheets
- Medication Guides
- Labeling comparison with approved product.

Table .2 ANDA REVIEW PROCEDURE

Incomplete and Deficient applications are promptly issued "refuse to file letter" letter
Site verification and inspection concurrent with the application review. If the facility is deficient in GMP Compliance the approval is held up till the deficiencies are rectified.
Admin and technical info (CTD Documentation) is reviewed by OGD/CDER review team If Admin and Technical information (Labeling, Chemistry , Manufacturing, Control and Microbial Safety) info as provided in CTD submission is un-satisfactory “Not approvable “letter is issued to the applicant.
If BE study results are not satisfactory “bio deficiency “ letter is issued to the applicant
When there are no queries the applicant finally receives FDA approval letter

DIFFERENCE BETWEEN APPLICATIONS AND DRUG MASTER FILE

Table 3. Difference between applications and drug master file

Applications	DMFs
1. COMES UNDER REGULATORY STATUS.MUST BE FILED BY APPLICANT.	1.NOT COME UNDER REGULATORY STATUS.IT IS NOT MANDATORY TO FILE A DMF.
2. EACH APPLICATION AND ITS SUPPLEMENT ARE ENTERED INTO A COMMON DATABASE.	2. DMFs ARE ENTERED IN TO DATABASE AS PER THEIR TYPES. (SEPARATE DATABASE FOR EACH TYPE OF DMF)
3.SUBMITTED TO A PARTICULAR REVIEW DIVISION.	3.SUBMITTED TO CDR.
4. ASSIGNMENT TO A REVIEWER AND EACH SUBMISSION HAS A DUE DATE.	4.NO ASSIGNMENT TO A REVIEWER, NO DUE DATE.
5.REVIEW PROCEDURE QUITE DIFFERENT THAN DMF.	5.DMFs ARE REVIEWED ONLY WHEN REFERENCED BY APPLICATION OR ANOTHER DMF
6.IF THE ANNIVERSARY DATE FOR ANNUAL UPDATE IS MISSED FDA SENDS A REMINDER	6.IF THE ANNIVERSARY DATE FOR ANNUAL UPDATE IS MISSED FDA WILL NOT SEND A REMINDER

STATUS OF DMFs

- "A" = Active. This means that the DMF was found acceptable for filing, administratively, and has not been closed.
- "I" = Inactive. This means a DMF that has been closed, either by the holder or by the FDA. Numbers for DMFs that are Cancelled, Pre assigned and Pending or have been transferred to another center in the FDA are not included in the list. The status conveys no information about whether a DMF has been reviewed for technical content or whether it has undergone a Completeness Assessment.

DMFS IN THE UNITED STATES

General introduction

In the United States, DMFs are submitted to the Food and Drug Administration (FDA). The Main Objective of the DMF is to support regulatory requirements and to prove the quality, safety and efficacy of the medicinal product for obtaining an Investigational New Drug Application (IND), a New Drug Application (NDA),As an Abbreviated New Drug Application (ANDA), another DMF, or an Export Application.

- There is no legal or regulatory requirement to file a DMF.
- A DMF may be filed to provide CMC information that the FDA reviews instead of including this information in the Application (IND, NDA, ANDA).
- A DMF is neither approved nor disapproved by the FDA.
- It is provided for in 21 CFR 314.420 (Code of Federal Regulations)
- DMFs are Confidential (Closed)

Generally US DMF's have two parts

(1) Applicant's Part: This contains non confidential information that the license holder needs to assess for the marketing.

(2) Restricted Part: This contains confidential information about the manufacturing procedure that only needs to be disclosed to the authorities

Information contained in a DMF may be used to

- Support an Investigational New Drug Application (IND))
- Support a New Drug Application (NDA)
- Support an Abbreviated New Drug Application (ANDA)
- Support another DMF
- Support an Export Application
- Support amendments and supplements to any of these.

DMF guidance recommendations, in general, still apply. However, the information below provides additional information or clarification in three categories:

- ✓ Category 1: Recommendations no longer applicable due to changes in regulations or guidance
- ✓ Category 2: Additional clarification of recommendations in the Guidance
- ✓ Category 3: New information for DMF filing aspects not in effect when the company wrote the Guidance.

IN UNITED STATES THERE ARE 5 TYPES OF DRUG MASTER FILE

- Type I Manufacturing Site, Facilities, Operating Procedures and Personnel
- Type II Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product
- Type III Packaging Material
- Type IV Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation
- Type V FDA Accepted Reference Information

TYPES OF DMFS WITH THEIR CONTENTS AND EXAMPLES

Type I DMFs (Category 1)

A Type I DMF is recommended for a person outside of the United States to assist FDA in conducting on site inspections of their manufacturing facilities. The DMF should describe the manufacturing site, equipment capabilities, and operational layout.

Type I DMF is normally not needed to describe domestic facilities, except in special cases, such as when a person is not registered and not routinely inspected.

Type II DMFs (Category 1)

For Type II DMFs filed in CTD-Q format, the FDA expects Module 2.Drug Substance Type II DMFs for drug substances may be submitted in the format for "Drug substance" in the "Guidance for Industry M4Q: The CTD - Quality".

MANUFACTURING SECTION:

QUALITY CONTROLS: To ensure quality at every stage of the process.

VALIDATIONS:

STABILITY DATA:

IMPURITIES:

PACKAGING AND LABELLING

Table 4. The following are examples of DMFs filed with the U.S. Food and drug Administration (U.S. FDA):

Companies	Drug product
Mallinckrodt Inc	ParzoneBitartrate (DihydrocodeineBitartrate)
FabbricaItalianaSintetici Spa	NitrofurantionNtrofurantoinMacrocrystals
CambrexProfarmaco Milano Srl	Hydrochlorothiazide
Siegfried UsaLlc	ButalbitalUsp
cinberg b l md	progesterone

Type III DMFs (Category 1)

The applicable Guidance for Type III DMFs is the "Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Documentation" and Questions and Answers. (Category 3)

Contents of a Type III DMF

- Description of intended use
- Components / composition
- Acceptance specifications
- Release specifications for finished material or component
- Provide the supplier / fabricator name & address
- Data supporting acceptability
- Toxicological data if appropriate

For Each Packaging Component

- Name, product code, manufacturer
- Materials of construction
- Description of any additional treatments

Protection: (by each component and/or the container closure system, as appropriate)

- Light exposure
- Moisture permeation
- Seal integrity or leak tests for unit-dose packaging

Safety: (for each material of construction, as appropriate)

- Chemical composition of all plastics, elastomers, adhesives, etc.
- For tablets, capsules, and powders, appropriate reference to the indirect food additive regulation may be submitted, but may not be appropriate for Powders for Reconstitution.
- For rayon and cotton fillers, data from USP monographs. For non-USP materials, data and acceptance criteria should be provided.
- For desiccants and other absorbent materials: the size and shape should differ from that of the dosage form
- For Each Packaging component received by the Applicant:
- Applicant's tests and acceptance criteria
- Dimensional (drawing) and performance criteria
- Method to monitor consistency in composition, as appropriate

For Each Packaging Component Provided by the Supplier

- Manufacturer's acceptance criteria for release, as appropriate
- Description of manufacturing process, as appropriate

Type IV DMFs (Category 3)

Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation

A Type IV Drug Master File (DMF) is a document prepared by the excipient's manufacturer (DMF holder) which contains information that the manufacturer wishes to remain confidential about the excipient's physicochemical nature, composition, quality and safety.

- CMC for a compendial excipient is usually not reviewed and therefore a DMF is not necessary.
- Exceptions: New route of administration or total dosing that may affect safety and efficacy, e.g. RESPITOSE, lactose for dry powder inhalation products.
- IPEC has prepared a draft guideline for comment NOT OFFICIAL FDA policy
- CMC requirements for a novel excipient (one not used in an approved drug product) are the same as those for a new drug substance.
- Safety testing (submitted in a Type V) is the subject of an FDA Guidance.

Typical content of Type IV DMF

The content of our Master Files conform to US FDA and IPEC recommendations. A typical DMF for a pharmaceutical excipient may include the following data:

- Product name and description
- Product identification and characterization
- A summary of all significant steps and controls in the manufacturing process
- Raw material control
- Product specifications and control methods
- Packaging specifications
- Stability data
- Safety data

TYPE V DMFs (Category 3)

FDA discourages the use of Type V DMF's for miscellaneous information, duplicate information, or information that should be included in one of the other types of DMF's.

If any holder wishes to submit information and supporting data in a DMF that is not covered by Types I through IV, a holder must first submit a letter of intent to the Drug Master File Staff. FDA will then contact the holder to discuss the proposed system.

To submit the data which is not covered in type I to IV DMF (clinical / toxicity data)

A holder must first submit a letter of intent to the drug master file staff

FDA will then contact the holder to discuss the proposed submission.

- May be filed without submission of letter of intent ◦ Sterile processing facilities ◦ Biotech manufacturing facilities}
- Information about these facilities can, like any other type of information, be submitted directly in an NDA or ANDA
- Prospective Type V DMF holders should send their request to dmfquestion@cder.fda.gov, including the following:

1. An explanation of the necessity for filing the information in a Type V DMF.
2. The proposed Subject (Title) of the DMF.
3. The rationale for not submitting the information in an IND, NDA, or ANDA.
4. The clinical division that will be reviewing the information, if applicable.

Exceptions to requirement for obtain clearance to file a Type V DMF

Information regarding manufacturing site, facilities, operating procedures, and personnel for sterile manufacturing plants.

- The Subject field should specify what the DMF covers i.e., Sterile Processing Facility.
- The Subject field should specify what the DMF covers i.e., Biotechnology Product Manufacturing Facility.

The FDA requires that DMFs be current at the time they're reviewed. The FDA regulations regarding DMFs states: "Any addition, change, or deletion of information in a drug master file is required to be submitted in two copies and to describe by name, reference number, volume, and page number the information affected in the drug master file."

The FDA ensures that DMFs are current. If a company has not submitted an annual report in for three years, the agency sends an "Overdue Notification Letters" to DMF holders. The holder has 90 days in which to respond and submit its annual report. If they fail to respond, their DMF may be closed.

S. No	Type	Type code	No. of DMFs
1	Manufacturing Site, Facilities, Operating Procedures, and Personnel (no longer applicable)	I	1826
2	Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product	II	16795
3	Packaging Material	III	4914
4	Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation	IV	1893
5	FDA Accepted Reference Information	V	377
6	Blanks	Blanks	2070
Grand Total			27876

FILING AND SUBMISSIONS OF DRUG MASTER FILES

Filing of DMF

There is no legal or regulatory requirement to file a DMF. A DMF may be filed to provide Chemistry, Manufacturing and Controls (CMC) information that the FDA reviews.

Reasons/Need for Filing

To maintain confidentiality of proprietary information (e.g., Manufacturing procedure) of the holder. To permit review of information by reviewers in the Center for Drug Evaluation and Research (CDER) to support applications submitted by one or more applicants.

Submissions Required For Filing A DMF

a. Transmittal letter
   1) Original Submissions, 2) Amendments
b. Administrative information
   1) Original Submissions 2) Amendments
c. Drug Master File contents
   1) Transmittal letters: The following should be included

Original Submissions

- Identification of Submission: Original, the type of DMF and its subject.
- Identification of the applications, if known that the DMF is intended to support, including the name and address of each sponsor, applicant or the holder and all relevant document holders.
- Signature of the holder or authorized representative.
- Type written name and title of the signer.

Amendments

- Identification of submission:
- Amendment, the DMF number, type of DMF and the subject of amendment.
- A description of the purpose of the submission, e.g., update, revised formula or revised process.
- Signature of the holder or the authorized representative.
- Type written name and title of the signer.

Administrative Information: Should include the following

Original Submission

- Name and addresses of the following DMF holder.
- Corporate headquarters.
- Manufacturing/Processing facilities.
- Contact for FDA correspondence.
- Agent(s) if any.
- The specific responsibilities of each person listed in any of the categories mentioned just above.
- Statement of commitment.
- A signed statement by the holder certifying that the DMF is current and that the DMF holder will comply with the statements made in it.

Amendments

- Name of DMF holder.
- DMF number.
- Name and address for correspondence.
- Affected section and/or page numbers of the DMF.
- The name and address of each person whose IND, NDA,ANDA, DMF, or Export
- Application relies on the subject of the amendment for support.

Drug Master File Contents

It includes Types of DMF's and General Information and Suggestions (Environmental assessment, Stability, Format, Assembly and Delivery).

DMF FILING PROCESS

Two copies of the Drug Master File with one signed original of the covering letter and other necessary documents are sent to the FDA's Central Drug Evaluation and Research (CDRL).

The Drug Master File staff will audit the nontechnical information for completeness and adequacy for submission. If the key elements are missing, the staff will contact the proposed holder to try to obtain the necessary documents in order to file the DMF.

Once the DMFs are determined to be acceptable for filing, the document room staffs assigns a DMF number and a letter is sent to the contact person listed in the DMF.

Steps for Filing A DMF

1. Set the document margins at 3/4 inch for the left (atleast) and 1/2 inch for the right.
2. Print the transmittal page, administrative information and DMF information on standard letter-size paper. If a larger sheet of paper is required for a diagram or schematic, fold the sheet and attach it to a letter-sized page in a manner that will allow for the page to be opened and refolded. At a maximum, each volume of a DMF should be no more than 2 inches thick.
3. Number multiple volumes for one submission according to the total number of volumes (if more than one). (For example, 1 of 3, 2 of 3, etc.)
4. Sign all documents requiring signature (only if you are the DMF holder or authorized representative).
5. Copy and collate the document; FDA requires you submit both.
6. Punch documents with a standard hole-punch.
7. Cover each original and copy of each volume with a document jacket. Prepare the submission for shipping and mail to:

   Drug Master File Staff
   Food and Drug Administration
   5901-B Ammendale Rd.
   Beltsville, MD 20705-1266

   Delivery charges to the above address must be prepaid.

DMF File Format

The DMF must meet the format requirements. The DMF is submitted as Original and Duplicate jackets, collated, assembled, paginated, and jacketed, using covers obtained from the government printing office and are specifically provided for the DMFs.

- ✓ Each volume of a DMF should, in general, be no more than 2 inches thick. For multivolume submissions, number each volume. For example, for a 3 volume submission, the volumes would be numbered 1 of 3, 2 of 3, and 3 of 3.
- ✓ The DMF must be submitted in two copies, one with a blue cover and one with a red cover.
- ✓ The jacket covers are purchased from the government printing office.
- ✓ U.S. standard paper size (8-1/2 by 11 inches) is preferred. Paper length should not be less than 10 inches nor more than 12 inches. However, it may occasionally be necessary to use individual pages larger than standard paper size to present a floor plan, synthesis diagram, batch formula, or manufacturing instructions.
- ✓ Those pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved.
- ✓ The agency's system for filing DMF's provides for assembly on the left side of the page. The left margin should be at least three fourths of an inch to assure that text is not obscured in the fastened area. The right margin should be at least one half of an inch.
- ✓ The submitter should punch holes 8 1/2 inches apart in each page. See the page measurements shown in the following figure (PTO) (figure 12) [11]

Processing and Reviewing Policies

Policies Related to Processing Drug Master Files

- An original DMF submission will be examined on receipt to determine whether it meets minimum requirements for format and content. If the submission is administratively acceptable, FDA will acknowledge its receipt and assign it a DMF number.
- If the submission is administratively incomplete or inadequate, it will be returned to the submitter with a letter of explanation from the Drug Master File Staff, and it will not be assigned a DMF number.
- Drug Master File Review
- A DMF is never Approved or Disapproved.
- A DMF is reviewed for Administrative content when it is received. This may take 2-3 weeks.
- If the DMF is acceptable from an administrative point of view an

Acknowledgement Letter will be issued, notifying the holder of the DMF number.

- If FDA reviewers find deficiencies in the information provided in a DMF, a letter describing the deficiencies is sent to the DMF holder. At the same time, FDA will notify the person who relies on the information in the deficient DMF that additional information is needed in the supporting DMF.
- The general subject of the deficiency is identified, but details of the deficiency are disclosed only to the DMF holder. When the holder submits the requested information to the DMF in response to the agency's deficiency letter, the holder should also send a copy of the accompanying transmittal letter to the affected persons relying on the DMF and to the FDA reviewing division that identified the deficiencies. The transmittal letter will provide notice that the deficiencies have been addressed.

To facilitate processing of documents that are submitted to an existing DMF, list the Submission Type and the Category/Subcategory of the Amendment (Supporting Document) in bold type in the header on the Cover Letter (transmittal letter).

Example: If updated stability data is submitted at the same time as an Annual Report, the heading of the Cover Letter should state:

Annual Report

Original: Quality/Stability

FDA's database is structured as follows

- ✓ Application, Submission
- ✓ Amendment (called "Supporting Document") in the database. Amendments (Supporting Documents) are named by a Category and Subcategory

For the Application Type "Drug Master File" the Submission Types are

- Original: Amendments containing changes to technical information are filed in the "Original" submission and the Category/Subcategory should be specified in the header of the Cover Letter. A new DMF does not need a "Category/Subcategory" designation by the holder. See Categories and Subcategories below.
- Annual Report: There is only one Category with two Subcategories:
  - ✓ Annual Report
  - ✓ Amendment
- Letter of Authorization: There is only one Category with two Subcategories:
  - ✓ Letter of Authorization
  - ✓ Withdrawal of Authorization

Table 21. Difference between UNITED STATES DMF and EUROPEAN DMF

U.S DMF	E.U DMF
DEFINITION A Drug Master File is a submission to the Food and Drug Administration (FDA) that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.	**DEFINITION** European Drug Master File is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the Applicant or marketing authorization (MA) holder to take full responsibility for the medicinal product and the quality and quality control of the active substance. It is also called as "Active Substance Master File (ASMF)"
Types : Five types: • Type I - Manufacturing Site, Facilities, Operating Procedures, and Personnel (no longer applicable)	**Types :** Mainly two types: • Certification of suitability to the monographs of the European Pharmacopoeia (CEP). • Active substance master file (ASMF). Both deals with Drug substances (API). CEP - Pharmacopoeial substances only (active

- Type II - Drug Substance, Drug Substance
- Intermediate, and Material Used in their Preparation, or Drug Product
- Type III - Packaging Material
- Type IV - Excipient, Colorant, Flavor, Essence, or Material Used in their Preparation
- Type V - FDA Accepted Reference Information

Only Type II deals with the Drug substances (API)

substance or excipient).

ASMF - Applicable to active substances only (new or pharmacopoeial).

Regulatory authority:

FDA- Food and Drug Administration

Regulatory authority:

EU DMF handled by two agencies:

1. European Medicines Agency (EMA) – ASMF
2. European Directorate for the Quality of Medicines and HealthCare (EDQM) – CEP

Content:

FDA requires one continuous document embracing the CTD formats without the distinction of an "Applicant's Part" or "Restricted Part." Only one part contains all significant steps in the manufacturing and controls of the drug intermediate or substance.

Whenever DMF is filed by person or firm is checked by FDA and if it is containing all necessary documents, FDA accepts DMF file and give a DMF number. It is the identification of DMF for applicant who wants to review that DMF

Content:

Contains two parts:

a. Applicant part (Open part): contains the information that the ASMF holder regards as non-confidential to the applicant/ MA holder.

b. Restricted part (Closed part): contains the information that the ASMF holder regards as confidential.

EU Authority (EMEA) does not give DMF number. If the API is in EU. Pharmacopoeia, EMEA can accept EDMF filing and issue a “Certificate of Suitability” for it.

Format and Assembly:

- Requirement to file DMFs in electronic format. Paper DMF will continue to be accepted.
- Filed in CTD- Q format
- The DMF must be submitted in two copies, one with a blue cover and one with a red cover.
- U.S standard paper size (8-1/2 by 11 inches) is preferred.

Format and Assembly:

- Paper and electronic format are accepted.
- Electronic format is preferred.
- Filed in EU - CTD format.

Fee:

The holder of a Type II API DMF must pay a onetime DMF fee as described under Generic Drug User Fee Amendments of 2012 (GDUFA).

Fee

CEP

- For New application - 3000 €
  For revision of existing CEP –500 € (Simple notification). **ASMF**
- For New application - £5006
- Notification of Changes (Variation) - £257

DMF fee only applies for Type II DMFs for drug substances (APIs) used to support ANDAs. There are no fees for any other type of DMF or for Type II DMFs used to support NDA or INDs.

Letter of authorization (LOA)

A written statement by the holder or designated agent or representative permitting FDA to refer to information in the DMF in support of another person's submission.

Language: English

Validity:

Not Applicable.

Delivery:

Food and drug administration
Centre for drug evaluation and research
Central document room
5901-B Ammendale road
Beltsville MD 20705-1266

Letter of access (LOA)

The ASMF holder should give permission to the competent authorities/EMA to assess the data in the ASMF in relation to a specific MAA/MAV, in the form of a Letter of Access.

Language:

One of the two official languages of the Council of Europe: English or French (preferably in English)

Validity:

CEP: Valid for 5 years from the date of first issue and valid indefinitely following the 5-year renewal.

Delivery :

CEP:

European Directorate for the Quality of Medicines and Healthcare Council of Europe
Division certification of substances
7, allee kastner, CS 30026, F-67081,
Strasbourg, France.

ASMF:

European Medicines Agency
CPMP, 7 westferry circus, Canary wharf,
London, E 14, 4 HB, U.K.

SUMMARY

The DMF system presents challenges for both the industry and the FDA

- Some of the changes have made the system smoother (hopefully for both industry and FDA)
- Problems can be minimized:

✓ With full understanding of their responsibilities and adherence to Guidances on the part of holders and applicants
✓ With adherence to policies and procedures on the part of reviewers.

REFERENCES

[1]. https://www.google.co.in/?gfe_rd=cr&ei=W9hZVsytBYHI8AfQ_K2ABw&gws_rd=ssl#q=intellectual+property+rights
[2]. https://en.wikipedia.org/wiki/Intellectual_property
[3]. http://www.bits-pilani.ac.in/uploads/Patent_ManualOct_25th_07.pdf
[4]. http://www.dmflegal.com.tr/EN/DMF/Service-Detail/Services/Intellectual-Property-Rights/
[5]. http://m.esa.int/About_Us/Law_at_ESA/Intellectual_Property_Rights/What_is_intellectual_property
[6]. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122886.htm

[7]. http://impactfactor.org/IJPQA/4/IJPQA,Vol4,Issue3,Article4.pdf
[8]. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/chem/draft_ebauche_dmf_fmm_guide_ld-eng.php
[9]. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073280.pdf
[10]. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm321884.pdf
[11]. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070551.pdf