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Review Article

DMF filing procedure in US, Europe and Canada: A Review

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Abstract

DMF widely known as Drug Master File, is a kind of confidential document which covers all comprehensive, accurate and precise information about Active Pharmaceutical Ingredient (API) or Finished Product Dosage Form (FP). The Drug master file consist of two parts, one the applicant's part which covers all the information that the license holder needs to review about quality of drug product & other one is the restricted part which covers all the confidential information about the manufacturing process that can only be presented in front of health authorities. A DMF can be used by holder who establishes the file or by one or more parties in support of their files or applications.

The present study is to brief an overview of DMF filing in different countries which are USA, Europe and Canada. In USA, Canada the drug master file is known as DMF and in EUROPE, known as ASMF (Active Substance Master File).

Keywords: Drug master file (DMF), ASMF, Master file (MF), API, IND, NDA, ANDA, FDA, eCTD, LOA

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1. Introduction

Drug master file is a document which is prepared by the manufacturer of the drug products or excipient and is submitted to the regulatory authority in the targeted market to provide confidential in detailed information about facilities, processes or articles used in the manufacturing process, packaging and storing of one or more drugs. There is no regulatory requirement for filing a DMF as it is not compulsory to file it.

A DMF is required to supply bulk materials to the United States but the FDA does not require all manufacturers to submit a DMF. However, the information contained in a DMF may be used to support an Investigational New Drug Application (IND), a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), another DMF, an Export Application or related documents. DMFs are reviewed only when accompanied by an application. (1-6)

2. DMF Filing procedure in US (US-DMF)

In United States, DMFs are submitted to the Food and Drug Administration (FDA). (1) The purpose of DMF filing is to support the regulatory necessities and to demonstrate the quality, safety, efficacy, purity & potency of the medicinal product to apply for an IND, NDA & ANDA. A DMF is neither approved nor disapproved & a DMF is not a replacement for an IND, NDA, ANDA or export application. (7,8)

21 CFR 314.420 describes about the Drug Master File. This guideline provides all the measures that the agency accepts for preparing and submitting a DMF. This guideline also includes types of DMF, information required in each type, format of submission of a DMF, review & assessment of DMF & DMF holder obligations.

DMF Submission in US

A Transmittal Letter should be attached with each submission along with a letter filled up with administrative information about the submission.

The DMF must be in English language & if it is in regional language then an appropriate translation should be provided additionally. Each copy should be marked with date and number. (9, 10)

Table 1 Difference between Application and DMF (1)

APPLICATION	DMF
Regulatory status must be filed by applicant.	Regulatory status it is not mandatory to file a DMF.
Each application and its supplement are entered into a common database.	DMFs are entered into database as per their types. (separate database for each type of DMF)
Submitted to a specific review division.	Submitted to CDR.
Assignment to a reviewer and each submission has a due date.	No assignment to a reviewer, no due date.
Review procedure quite different than DMF	DMFs are reviewed only when referenced by an application or another DMF.
If the anniversary date for annual update is missed FDA sends a reminder.	If the anniversary date for annual update is missed FDA will not send a reminder.

Table 2 DMF submissions in US, EU and Canada (1,2)

Country	Submission Types
USA	New Drug Application (NDA) for new drugs. Accelerated New Drug Application (ANDA) for generics. Biologic License Application (BLA) for biologic.
Europe	Marketing Authorization Application (MAA) via Centralized Procedure for appropriate products. Other products are via Decentralized, Mutual recognition or National authorization Procedures are applicable.
Canada	New Drug Submission (NDS) for both drugs and biologic products.

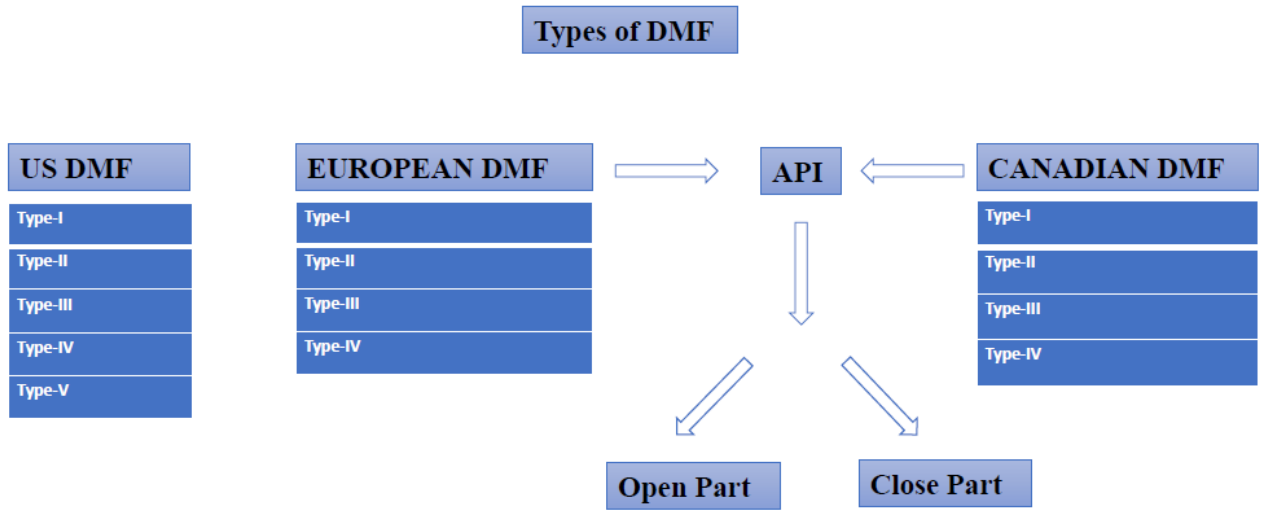

Figure 1. Types of DMF in US, Europe and Canada (7)

Table 3 Types of DMF in US

Type(s)	Contain Information(s)	Remark(s)
TYPE I	Manufacturing Sites Facilities Operating Procedures	It is recommended for a person outside of US to assist FDA for conducting site inspection of their manufacturing facilities [1].
TYPE II	Drug Substance Drug Products Intermediates & Material used for preparation of DS and DP.	All the manufacturing processes and quality controls for finished dosage forms should be submitted in an IND, ANDA or NDA & if the information is not submitted in these applications then it should be submitted in DMF.
TYPE III	Packaging Material	All packaging materials should be identified by its use, composition & controls. Name of the manufacturer and acceptance criteria should also be submitted in DMF.

TYPE IV	Excipient	All excipient, colorants, flavors or materials used in their preparations. All excipient, colorants, flavors should be identified and characterized by its manufacturing method. Toxicological data should also be included in the DMF.
TYPE V	Reference Information	Used for sterile manufacturing plants and contract facilities for biotech products as accepted by FDA.

Note: TYPE II, III & IV DMF should contain indemnity by the firm that all its facilities are operating in compliance with the appropriate regulations.

Transmittal Letters: It includes,

- Type of DMF
- Identification of the application, that DMF is intended to support, name &address of each sponsor, applicant or holders
- Signature of DMF holder
- Typewritten name & title of signer

Administrative Information: It includes, Name & address of below,

- DMF holder/correspondence
- DMF number
- Corporate head quarter
- Manufacturing facility
- Agents
- Statement of commitment

Font, Font Size, Format & Paper used for Submission to US-FDA

- DMF should be filled in electronic format only
- In CTD, the information should be transparent to facilitate the review of the basic data
- Text and tables should be prepared using margins so that document can be printed on A4 sheet
- Times new roman, 12 point font is recommended for narrative text.
- Every page should be numbered
- US standard paper size (8.5 by 11 inches) is preferred
- Paper length should not be less than 10 inches nor more than 12 inches

DMF Submission & Correspondence should be addressed as follows

Drug master file staff; Food and drug administration; 5901-B Ammendale road; Beltsville, MD 20705-1266. (11)

Letter of Authorization:

DMF holder must submit a letter of authorization to FDA in support of an application permitting FDA to reference the DMF.

It should include;

- Date
- Name of DMF holder
- DMF number
- Name of person authorized for incorporating information in the DMF
- Specific product covered by DMF
- Section number & page number to be referenced
- Statement of commitment that the DMF is current & that the DMF holder will comply with the statements made in it.
- Signature of the Authorized person

Filing, Assessing & Review of a DMF

- DMF holder should sent two copies to FDA
- Then DMF is entered into database system, a number is assigned, and an acknowledgement letter is sent to holder.
- DMF will only be reviewed when it is referenced with an application, so the applicant should submit a copy of letter of authorization in their application because letter of authorization is the only mechanism to trigger the review of the DMF by the FDA.
- If the reviewer finds any deficiency the reviewer will issue a letter to the holder stating the deficiencies but will not describe the nature of deficiencies.

Holder Obligations

- Any change or addition in DMF or in authorization related to specific customers should be submitted in duplicate copy and with reference to previous submission.
- The reference should include the date, volume, section and / page number affected.
- A DMF should contain a list of persons authorized to incorporate information in the DMF by reference (21 CFR 314.420).
- The DMF holder should update the list in the annual update. It should contain the holder's name, DMF number and date of the update.
- If any person's authorization is withdrawn during previous year, it should be identified under a suitable & different caption.

Transfer of Ownership

If the DMF holder wants to grant the ownership of DMF to any other person, the holder should inform FDA and authorized person about granting ownership in writing. The letter should include;

a. Name and Address of transferee
b. Name of responsible official of transferee
c. Effective date of transferee
d. Sign of transferring official

Note, the new holder should submit a letter of acceptance of DMF ownership & update all the information of the DMF and any changes relating to new ownership.

Closure of a DMF

Any holder, who wants to close a DMF, should submit a request to the DMF staff stating the reason for the closure and state that all the holder's obligations have been fulfilled.

The agency may close a DMF if the holder regularly does not update the references and the list of changes in annual update report from the previous updated report.

Reactivating a Closed DMF

The holder must submit a reactivation request and a complete copy of the DMF, including any revisions since the last submissions. Once the reactivation request enters into DARRTS, the status of DMF changes into **"ACTIVE"**.

DARRTS: Document archiving reporting and regulatory tracking, it is archival system of record for all new and subsequent INDs, NDAs, DMFs, BLAs, ANDAs.

3. European DMF Filing System

European DMF was established in 1989-1991 & was revised in 2005 & then it became ASMF (Active substance master file), after CTD was implemented in EU. The ASMF in Europe is covered under Directive 2001/83/EC. There is difference in the content & format in US & EU. The main purpose of the ASMF {commonly known as European Drug Master File (EDMF)} is to protect the confidential intellectual property and at the same time allowing applicant to take full responsibility for the medicinal product and quality control of the active substance. (12)

EMEA or the competent authorities have permission to the whole information which is important for the evaluation of suitability of the active substance in the medicinal product. Since July 1, 2016, the eCTD format is compulsory for human ASMFs submission by centralized procedure and EU Directive 2003/63/EC defines the list of active substance for which ASMF can be submitted and include information on (13, 14);

a. Full description of manufacturing process
b. Quality control procedure during manufacture
c. Process validation

Market Authorization Application (MAA)

Before submission of MAA, the applicant should notify the EMEA (European medicine agency) of their intention to submit an application & should submit an estimate of month of submission.

Marketing Authorization Application is an application to the relevant authority to market a drug or medicine in Europe market. {Typically, the UK's MHRA or the EMA's Committee for Medicinal Products for Human Use (CHMP)}.

Manufacturers can enter into EU market by using following authorized ways for application of MAA. European Economic Area (EEA) unites the 28 EU member states & EEA European Free Trade Association (EFTA) states (Iceland, Liechtenstein, Switzerland & Norway).

Austria	Belgium	Bulgaria
Croatia	Cyprus	Czech Republic
Denmark	Estonia	Finland
France	Germany	Great Britain
Greece	Holland	Hungary
Iceland	Ireland	Italy
Latvia	Liechtenstein	Lithuania
Luxembourg	Malta	Netherlands
Norway	Poland	Portugal
Romania	Slovakia	Slovenia
Spain	Sweden	Switzerland

Table 4 Filing procedure of MAA (5)

MAA Procedure(s)	Contain Information(s)
National Procedure	If an applicator wishes to market their product only in single EU country, then national procedure is preferred. The organization need to inform the relevant authority before filing for MA. The organization must apply to the competent authority of the member states for obtaining national MA. Market authorization applications should be completed within 210 days.
Centralized Procedure	A marketing authorization is granted for the entire community market which is valid in market of the all member states. The regulation (EC) 726/2004 lays down a centralized procedure for authorization of medicinal products &for this, there is a single application, a single procedure for evaluation & a single authorization allowing direct entry to the single market of the community.
Decentralized Procedure	For products which do not come under the scope of EMA in centralize procedure, a sponsor can submit under the decentralized procedure. In this procedure, sponsor can apply for simultaneous authorization in more than one EU country for products that have not been yet authorized in any EU country.

Mutual Recognition Procedure	If a company have market authorization in one EU member states and wishes to have authorization in several countries simultaneously can apply for this authorization to be recognized in other EU countries. It's a quicker way to reach first market.

Content of the ASMF

The EDMF should contain all the details related to scientific information for market authorizations for medicinal products in the member states of the European Union. (15)

EDMF, linked to human medicinal products should be present in CTD format, and EDMF linked to veterinary medicinal product should include;

- Name and site of active substance manufacturer
- Nomenclature
- Description
- Outline of manufacturing route
- Detailed description of manufacturing method
- Quality control during manufacture
- Development chemistry
- Analytical validation
- Impurities
- Batch analysis
- Stability studies

ASMF includes two parts:

Applicant's Part: It is open and contains the information that is said to be non-confidential to the applicant. It should contain adequate information so that the applicant can take full responsibility for the evaluation of suitability for the active substance which is used in manufacturing of a specified medicinal product. Applicant part still can be considered as confidential because it cannot be submitted by anyone to the third parties without a written consent of the EDMF holder.

Restricted Part: It is closed, contains all the information which is considered as confidential, and all the information such as detail information about individual steps of manufacturing methods like reaction conditions, temperature, validation data of critical steps, where the EDMF is provided in CTD format, both summaries should be provided in Quality overall summary type. Both applicants and restricted part should have version no. and the structure of version no. should be unique and follow a logical order.

European DMF Filing Procedure

The active substance manufacturer provides applicant's part DMF to the applicant which contains both the applicant & restricted part & then it becomes the part of the market authorization application which is then submitted to the authorities. (16, 17)

The main objective of the ASMF is to maintain confidentiality & to protect the information about the active substance, while at the same front allowing applicant to take full responsibility about the quality, safety & efficacy of the medicinal product. Then National competent authorities assess the complete information which is necessary to check suitability of active substance in medicinal products.

The ASMF procedure can be used for the following active substance;

- New active substance
- Existing active substance that are not included in European pharmacopoeia
- Pharmacopoeia active substance that is included in European pharmacopoeia

The EDMF holder should submit to the applicant;

- A copy of latest version of the applicant's part
- A copy of the quality overall summary on the latest version of the applicant's part
- The letter of access, if it is not submitted before for the product.
- For each MAA (market authorization application) or each MAV (market authorization variation), the EDMF holder should submit the EDMF to the competent authorities.

Changes & Updates to the ASMF

For all medicinal products, the EDMF holders should keep the content of their EDMFs updated according to actual synthesis or manufacturing process.

The contents of the EDMF should not be changed by EDMF holders without the written consent of applicant and competent authority. Before making any change in EDMF, EMEA and applicant should be informed.

All the changes should be mentioned in a cover letter. The cover letter to the EMEA should contain the following info;

- A summary of all the changes carried out since 1st submission of the EDMF
- A comparison between old and new contents of EDMF
- Information regarding, whether the change has been accepted, rejected, or withdrawn by another member states.
- An updated quality overall summary
- The new applicant's part / restricted part with each a new version number

4. DMF Filing in Canada

Canadian DMF contains two parts, one is an applicant's part and other one is restricted part.

Requirements for Filing of Canadian DMF

- To maintain confidentiality of information of the holder
- To allow review of all the information by reviewers of Centre for Drug Evaluation & Research (CDER) to support applications.

Note: From January 1, 2016, health Canada is not accepting paper copies of DMF. Any paper received are either cancelled or returned. From March 31, 2016, all

DMFs which are existing in paper format must be replaced by a DMF in "non e-CTD electronic only" format. If applicant fails to provide the electronic copy of the DMF, then it results in the suspension of the DMF. (18)

Table 5 Types of DMF in Canada

Type(s)	Contain Information(s)	Remark(s)
TYPE I	Active Substance Master File (ASMF)	For solid dosage forms, it includes API in the manufacturing of a drug substance. For biologics, it includes process intermediates, vaccines antigens, excipient of biological origin.
TYPE II	Container Closure System Master File (CCSMF)	
TYPE III	Excipient Master File (EMF)	Includes information related to excipient, coating ingredients, colorants, flavors and other additives.
TYPE IV	Dosage Form Master File (DFMF)	Includes information related to dosage form & their intermediates.

Canadian DMF Filing Procedure

Filing of DMF

- Type I & IV DMFs are divided into two parts, the restricted and the applicant part, both the parts are provided by manufacturer to the applicant and then is used in the support of applicant's drug submission or clinical trial application with a letter of authorization.
- The applicant part contains outline information about the drug product & it is considered as non-confidential and the restricted part contains all the information about drug product, and it is considered as confidential part.
- DMF should be filed in electronic format and if it is originally submitted in paper than it is to be resubmitted in electronic DMF. (19)

Registration Requirements

For new Master File registration, required

- MF application form
- One signed cover letter, including MF names
- MF fee form
- MF agent authorization letter from MF holder
- LOA (Letter of Authorization)
- Certificate of suitability

For Type I & Type IV dosage form master file following documents are required;

- Both applicant and restricted part must be included.
- A quality overall summary copy
- The document of information on certified product, if applicable, in word format.

For Type II and Type III excipient master files multiple components can be included in a single MF (multiple flavors, a complete closure system etc.). A limit of 50 components can be included in a single MF, for more than 50; a new MF is to be filed.

Naming a Master File

For Type I ASMF, MF name should be written as the generic name for an API followed by API brand name or codes to identify the particular product. For Type IV dosage form master file, it must include more than one MF for a single and similar product, and the cover letter should state it clearly and provide all the information to differentiate the products.

Assessment of DMF

Letter of Authorization

The applicant files all the confidential information regarding drug in Health Canada in support of drug submission or clinical trial application. The information will only be accessed by Health Canada if the MF holder provides a signed and original copy of letter of authorization to Health Canada.

Letter of authorization includes;

- MF number, if assigned by Health Canada and if not assigned state "to be assigned"
- MF name
- Manufacturer's internal code
- Applicant's name
- MF fee form & fees

DMF Processing

Master files are processed according to the date of receipt. As soon as MF registration package is received the following procedure starts.

- First assign an MF no. and a dossier ID to the master file.
- Check that the correct and complete information, documents are provided, and the forms have been filled.

Once the MF registration is complete – a filing date is assigned, and an acknowledgement letter is sent to the MF applicant as listed on the MF.

If any information, forms or fees are incomplete, then MF is to be placed on administrative hold and it will remain on hold until the required information is submitted.

All the information is to provide in the PDF or Microsoft word format and in Canada's official language.

Holder Obligations

Any change or addition in the master file related to customers should be submitted in duplicate and proper

cross referenced to previous submission. It should include date, volume, section and page number affected.

A holder must inform each sponsor who has stated of any changes in its DMF. Notice should be provided before making any change.

Master File Closure

If Master file holder wish to close a MF, then they should notify the administrative unit in writing of the reasons for closure. On closure, the MF holders should provide a list of all the applicants using the master file.

When a MF is closed, the product related to MF will no longer be manufactured for use in Canadian marketed drug products.

Health Canada will deeply go through all the reasons for closure that are related to safety, the applicant should be informed and should contact Health Canada regarding health risk assessment and any recall actions to be taken.

If in some case, if the MF holder wishes to reactivate the MF with Health Canada, the MF should be filed in non-eCTD or eCTD format and a cover letter stating the MF holder wish to reactivate the MF along with the updates and applicable data should be provided. (20, 21)

Then the same MF number can be retained, and new MF registration fee will be applied.

Withdrawal of Letter of Authorization

Any MF holder wish to withdraw a LOA for a specific applicant should inform MF administration unit in writing of the reasons responsible for withdrawal and should also provide a list of applicants who have access to their MF. Any applicant whose LOA is being withdrawn from the Master file should be informed of the withdrawal of the LOA be the MF holder.

The letter should state the date after which the MF will no longer be active.

Health Canada will continue the withdrawn LOA in accordance with the process followed for record retention and disposal in accordance with library and archives of Canada act, and it is assumed that when a LOA is withdrawn, the previously manufactured drug will no longer be supplied to the applicant.

Table 6 Format Comparison Table (22)

Issue	Paper Format (CTD) along with Electronic Data	Non-eCTD Electronic-only Format	eCTD Electronic-only Format
Portion of regulatory activity provided electronically	Complete regulatory activity provided in paper format, along with partial/complete electronic data.	Complete regulatory activity provided in "non-eCTD electronic only" format.	Complete regulatory activity provided in eCTD electronic - only format.
Legal record	The regulatory activity in paper format remains the legal document.	The regulatory activity in "non - eCTD electronic-only" format is the legal document.	The regulatory activity in "non - eCTD electronic-only" format is the legal document.
Signature	Scanned copy of signed document (or a digital signature where applicable) is Required		
Letter of Attestation	Letter of Attestation stating that material in the regulatory activity or additional information provided electronically is exactly matching the material in paper format.	Not applicable	Not applicable
Plan for format requirement	Health Canada is phasing out this format.	This format is an interim option for filing regulatory activities.	Health Canada is considering a date for mandatory filing of this format for regulatory activities in scope of the eCTD guidance document.

5. Conclusion

The Drug Master File contains complete & correct information about active pharmaceutical ingredient or finished drug dosage form and CMC data i.e., chemistry, manufacture, stability, purity, impurity profile, packaging of any drug product or excipient. 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 grant.

Now onwards, most of the countries will use the eCTD format for DMF submission.

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Conflict of Interest

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