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Filing of DMF in US, Canada & Europe

Yamini SPK*, Jain N, Chandra A, Shukla VK, Bansal A and Kumar S

[1]Department of Drug Regulatory Affairs, Amity University, India

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***Corresponding author:** S P Yamini Kanti, Masters in Pharmacy, Department of Drug Regulatory Affairs, Amity Institute of Pharmacy, Amity University, Noida, Uttar Pradesh, India, Tel: 09205334134; Email: yaminikanti3@gmail.com

Abstract

DMF (Drug Master File) it is a kind of confidential document which contains complete, factual and correct information about active pharmaceutical ingredient or finished drug dosage form. 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 Drug master file consist of 2 parts: (a) the applicant's part – that contains all the information that the license holder needs to review about quality of drug product & (b) the restricted part – which contains all the confidential information about the manufacturing process that can only be presented in front of authorities. The purpose of this article is to present an overview of DMF filing in different countries which are USA, CANADA, and EUROPE. In USA, CANADA the drug master file is known as DMF only but in EUROPE it is known as ASMF (active substance master file).

Keywords: DMF; US; Europe; Canada

Introduction

Drug master file or DMF 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. There is no regulatory requirement for filing a DMF as it is not compulsory to file it. The document provides with all the important information about processes, facilities and articles used in manufacturing, processing, packaging & store of human drugs. DMFs are submitted to central drug registration office. DMFs are reviewed only when accompanied by an application [1,2].

DMF Submission Types

In USA

- NDA for new drugs
- ANDA for generic drugs
- BLA for biologics [3]

In Europe

- MAA via centralized procedure for eligible products
- For other products, via mutual recognition procedure, national procedure or decentralized procedure is applicable.

In Canada

- New drug submissions for both drugs and biologic products

DMF Filing in USA (US-DMF)

In United States, DMFs are submitted to the Food and drug administration [1]. The purpose of DMF filing is to assist regulatory requirements and to prove the quality, safety, efficacy, purity & potency of the medicinal product to apply for an IND (Investigational New Drug Application), NDA (New Drug Application), & an ANDA (Abbreviated New Drug Application). A DMF is neither approved nor disapproved & a DMF is not a replacement for an IND, NDA, ANDA or export application.

21 CFR 314.420 describes Drug master file. This guideline provides all the procedures 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.

In US there are 5 types of drug master files:

a) TYPE 1: Contain information about manufacturing sites, facilities, operating procedures and personnel (It is recommended for a person outside of US to assist FDA for conducting site inspection of their manufacturing facilities) [1].

b) TYPE 2: Contain information about drug substance, drug products, their intermediates & material used in their preparation.

- Manufacturing sections
- Quality control (Raw or packaging material inputs, intermediates, finished drug substance)
- Validation
- Stability data
- Impurities
- 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.

c) TYPE 3: 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.

d) TYPE 4:- 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.

e) TYPE 5:- The reference information used for sterile manufacturing plants and contract facilities for biotech products as accepted by FDA.

The TYPE 2, 3 & 4 DMF should contain surety by the firm that all of its facilities are operating in compliance with the applicable laws.

DMF Submission

Submission of each DMF should include a transmittal letter and a letter regarding administrative information about the submission [2].

The DMF must be provided in English language & if it is available in other language then an appropriate translation should be given. Each copy should be dated and numbered.

a) Transmittal Letters: It includes

- The type of DMF
- Identification of the application, that DMF is intended to support, name &address of each sponsor, applicant or holders [2].
- Signature of holder
- Typewritten name &title of signer

b) Administrative Information:

It includes, Name & address of - [2]

- DMF holder/correspondence
- DMF no.
- Corporate head quarter
- Manufacturing facility
- Agents
- Statement of commitment

Font, Format, Font Size & Paper Used For Submission to USFDA

- DMF should be filed in electronic format only.
- In CTD, the information should be transparent to facilitate the review of the basic data [1].
- 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 [4].

Letter of Authorization

DMF holder must submit a letter of authorization to FDA in support of an application permitting FDA to reference the DMF [1].

It should include:

- The date
- Name of DMF holder
- DMF no.
- Name of person authorized for incorporating information in the DMF.
- Specific product covered by DMF
- Section no. & page no. 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 authorizing official.

Filing, Assessing & Review of DMF

- DMF holder should sent two copies to FDA [2,5]

- Then DMF is entered into database system, a no. 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 [3].
- The reference should include the date, volume, section and or page no. 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 no. &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:-

- Name of transferee
- Address of transferee
- Name of responsible official of transferee
- Effective date of transferee
- Sign of transferring official

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 [3].

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 also state that all of 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 [3].

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 to **"ACTIVE"** [6].

DARRTS: Document archiving reporting and regulatory tracking, it is archival system of record for all new and subsequent INDs, NDAs, DMFs, BLAs, ANDAs [7].

Fees

Fee Category	Fee Rate
Applications	
Drug master file	$57,140
Facilities	
API- Domestic (US)	$44,234
API Foreign	$59,234

Table 1: Fees for the application and facilities in USA should be paid in accordance with the Table 1 [8].

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 [1].

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 also include information on -

- Full description of manufacturing process
- Quality control procedure during manufacture, &
- 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 a estimate of month of submission [8].

MAA can be filled in 4 ways:

a) **National Procedure:** If an organization wishes to market their product only in one EU country, then national procedure is preferred. The organization need to inform the relevant authority before filing for MA. The organization must submit an application to the competent authority of the member states for obtaining national MA. Market authorization applications should be completed within 210 days.

b) **Centralized Procedure:** In this 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.

c) **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.

d) **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.

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 [9,10].

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

The scientific information of ASMF includes two parts:

a) **Applicant's Part**: It is open and contains the information that is said to be non-confidential to the applicant. It should contain sufficient 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.

b) **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 [1].

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 applicants part
- A copy of the quality overall summary on the latest version of the applicants 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 [10].

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 (European medicines agency) and applicant should be informed.

All the changes should be mentioned in a covering letter. The covering 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 applicants part / restricted part with each a new version no.

Fees

Item	Fee
Simple chemical certificate	5,000 €
Double certificate	8,000 €
Certificate for chemical purity and sterility	8,000 €
Renewal	1,500 €
Notification	1,000 €
Minor revision	1,500 €
Grouped revision	2,000 €
Major revision	2,000 €
Transfer of holdership	1,500 €

Table 2: For different procedures as given in Table 2 [8].

DMF Filing in Canada

In 1994, a new revision was published in the name of CANADIAN DMF which contains 2 parts – a) applicant's part & (b) restricted part, and it is of 4 types [5,11]:

a) Type 1- Active Substance Master File (ASMF)

- For pharmaceuticals, it includes API in the manufacturing of a drug substance.
- For biologics, it includes process intermediates, vaccines antigens, excipient of biological origin.

b) Type 2- Container Closure System Master File (CCSMF)

c) Type 3- Excipient Master File (EMF)

- Includes information related to excipient, coating ingredients, colorants, flavors and other additives.

d) Type 4- Dosage Form Master File (DFMF)

- Includes information related to dosage form & their intermediates.

From January 1, 2016, health Canada will not accept paper copies of DMF. Any paper received after the date will be cancelled & returned back at the owner's cost.

From March 31, 2016, all DMFs 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 will result in the suspension of the DMF [12].

Need For Filing DMF

- To maintain confidentiality of information of the holder [11].
- To allow review of all the information by reviewers of Centre for Drug Evaluation & Research (CDER) to support applications.

Canadian DMF Filing Procedure

a) Filing of DMF

• Type 1 & 4 DMF are divided into 2 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 [1].

• 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.

b) Registration Requirements

For new MF (Master File) registration, following documents are required [1]:

- 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 1 & type 4 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 2 and type 3 excipient master files multiple components can be included in a single MF (multiple flavors, a complete closure system etc.). A limit of 50components can be included in a single MF, for more than 50; a new MF is to be filed.

Naming a Master File

For type1 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 4 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 [1,11].

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 [1,11].

Letter of authorization includes:-

- MF no. , 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 [1].

- 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 no. affected [1].

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

Fees

Cheques, money orders or bank drafts are to be made payable at "receiver general for Canada" [8].

Types of Submission	Fees in CDN
DMF New Registration	$433CDN
DMF Biannual Update	$196CDN
No. of Letter of Access	$196CDN

Table 3: Once the fee is paid, the DMF will be reviewed by the regulatory authority. Fees should be paid in accordance with Table 3.

Withdrawal of Letter of Authorization

Any MF holder, wish to withdraw a LOA for a particular applicant should inform MF administration unit in writing of the reasons responsible for withdrawal and should also provides 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 [11].

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.

Master File Closuure

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 [11]. 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.

Then the same MF no. can be retained and new MF registration fee will be applied.

Critical Abbreviations

- NDA- New Drug Application
- ANDA- Abbreviated New Drug Application
- BLA- Biologics License Application
- MAA- Marketing Authorization Application
- CFR- Code of Federal Regulations
- DARRTS- Document Archiving, Reporting & Regulatory Tracking
- EMEA- European Medicine Agency
- ASMF- Active Substance Master File
- CCSMF- Container Closure System Master File
- EMF- Excipient Master File
- CDER- Centre for Drug Evaluation and Research

Critical Definition

- DARRTS- DARRTS is an archival system of record for all new & subsequent INDs, NDAs, ANDAs, DMFs, and BLAs.

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 from 2016, most of the countries will use the eCTD format for DMF submission.

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