DMF FILING IN US, EUROPE AND CANADA

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REVIEW ARTICLE

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ABSTRACT

A Drug Master File or DMF is a reference source that provides drug evaluator's confidential information not available to drug product manufacturer about the specific process and components used in the manufacturing, processing and packaging of a drug meant for Human/Animal use. The submission of a DMF is not required by law or FDA regulation. A DMF is submitted solely at the discretion of the holder. The information contained in the 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, or amendments and supplements to any of these.

Keywords: DMF, ICH CTD, AP. RP, FDA, QOS, CMC.

INTRODUCTION

Drug Master File (DMF) 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. (1)

DMFs usually cover the Chemistry, Manufacturing and Controls (CMC) of a component of a drug product e.g. drug substance, excipient, packaging material. Drug product information or non-CMC information may be filed in a DMF. (2)

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.

Role of DMF

- To support the documents for the registration / approval of drug products.
- In the Chemistry, Manufacturing and Controls (CMC) sections of the drug submission, the DMF documents the drugs identity, purity, strength and quality.
- To protect Proprietary and Confidential Information. (3)

Table 1: Differences between Application and DMF

APPLICATION	DMF
1. Comes under regulatory status must be filed by applicant.	1. Does 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 into 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	5. DMFs are reviewed only when referenced by an

DMF.	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.

Table 2: Drug submissions: US, Canada, and EU

Country	Submission Types
USA	New Drug Application (NDA), for new drugs Accelerated New Drug Application (ANDA)-for generics Biologic License Application (BLA), for biologic.
Canada	New Drug Submission (NDS)—for both drugs and biologic products
EU	Marketing Authorization Application (MAA) - via the Centralized Procedure for eligible products. For other products, via the decentralized, mutual recognition or national authorization are applicable.

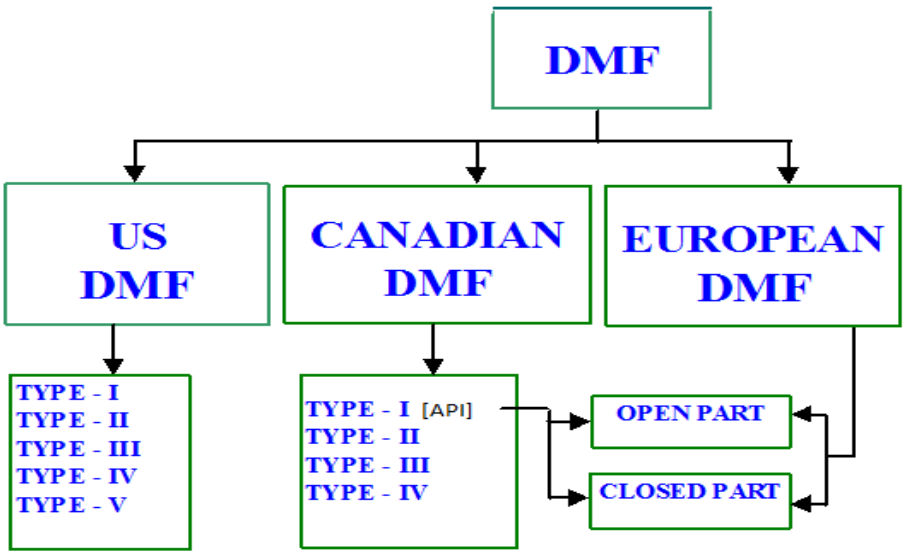

Figure 1: Types of DMF in US, Europe and Canada

US DMF – TYPES

Type I - Manufacturing Site, Facilities, Operating Procedures, and Personnel.
This is no longer accepted by the FDA.
Type II – Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product
Type III – Packaging
Type IV – Excipients, Colorant, Flavor, Essence, or Material Used in Their Preparation
Type V – FDA Accepted Reference Information
Used for sterile manufacturing plants and contract facilities for biotech products.

US DMF Filing System

1. **Filing the DMF**

- Holder sends two copies of the DMF to FDA
- DMF is reviewed for administrative purposes only by Central Document Room staff.
- DMF entered into database, assigned a number and acknowledgment letter sent to holder
- A DMF is neither approved or disapproved

2. **Accessing the DMF: Letter of Authorization (LOA)**

- The DMF will be reviewed only when it is referenced in an Application or another DMF
- The Holder must submit a two copies of the LOA to the DMF, plus a copy to the Applicant.
- The Applicant submits a copy of the LOA in their Application.
- The LOA is the only mechanism to trigger a review of the DMF by the FDA.

3. **DMF Review Procedure**

- The DMF is reviewed only if referenced by an Applicant or another DMF
- If the reviewer finds deficiencies in the DMF, the deficiencies are detailed in a letter to the Holder.
- The Applicant will be notified that deficiencies exist, but the nature of the deficiencies is not communicated to the Applicant. (4)

Format, Font, Font Size and Paper used for submission to USFDA, whether DMF gets approved or rejected by USFDA

- Electronic DMF should be filed. In Common Technical Document, the display of information should be unambiguous and transparent, in order to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents.

- Text and tables should be prepared using margins that allow the document to be printed on both A4 paper (E.U. and Japan) and 8.5 x 11" paper (U.S.). The left-hand margin should be sufficiently large that information is not obscured by the method of binding. Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying.

- Times New Roman, 12-point font is recommended for narrative text. Every page should be numbered, according to the granularity document. Acronyms and abbreviations should be defined the first time they are used in each module.

- DMF neither approved nor disapproved by USFDA.

- U.S. standard paper size (8.5 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.

Referral letters required for FDA submission:

In CTD, in Module 1 – Administrative Information, 1.4 Sub-section deals with References.

- **1.4.1 - Letter of Authorization (LOA)** Submission by the owner of information, giving authorization for the information to be used by another. An Agent Appointment Letter is NOT an LOA and should not be called "Letter of Authorization" and should not be submitted in Section 1.4.1.

- **1.4.2 - Statement of Right of Reference** Submission by recipient of a Letter of Authorization with a copy of the LOA and statement of right of reference. Submitted in a DMF only when another DMF is referenced. If a DMF holder references other DMFs a list of those DMFs can be provided in this section. This is not the same as the list of authorized parties to be provided in 1.4.3.

- **1.4.3 - List of authorized persons to incorporate by reference**: This list should be submitted in DMF annual reports.

EUROPEAN DMF - TYPES

European DMF was established in 1989-1991. It was revised in 2005 and became ASMF (Active Substance Master File) after implementation of Common Technical Document (CTD) in EU. DMF is applicable only to active substances.

The content and the format for DMF used in United States differs from that used in European Countries to obtain market authorization (MA). The Main Objective of the EDMF is to support regulatory requirements of a medicinal product to prove its quality, safety and efficacy. This helps to obtain a Marketing Authorisation grant.

The ASMF holder may have an ASMF as well as a Certificate of Suitability (CEP) issued by EDQM for a single active substance. Generally, it is however not acceptable that the Applicant/MA holder refers to an ASMF as well as to a CEP for a single active substance of a particular MAA/MAV. In cases where the CEP contains too little information (e.g. stability) the National Competent Authorities/EMA may decide that additional information should be provided in the dossier. In such case it may be acceptable to refer both to an ASMF and a CEP.

European DMF has been divided into 2 parts

- Applicant Part (Open): Contains all the required information including an outline of the manufacturing method.
- ASM Restricted Part (Closed / Confidential): Confidential information of on the manufacturing of Active Pharmaceutical Ingredient. (5)

European DMF Filing System

The applicant's part of a DMF is provided by the ASM (Active Substance Manufacturer) to the applicant directly and becomes part of the application for marketing authorization. Both the applicant's part and the ASM Restricted Part of the DMF are submitted to the authorities.

The main objective of the Active Substance Master File (ASMF) procedure, formerly known as the European Drug Master File (EDMF) procedure, 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 Authorisation (MA) holder to take full responsibility for the medicinal product and the quality and quality control of the active substance. National Competent Authorities/EMA thus have access to the complete information that is necessary for an evaluation of the suitability of the use of the active substance in the medicinal product.

The ASMF procedure can be used for the following active substances, including herbal active substances/preparations. i.e.:

A. New active substances;

B. Existing active substances not included in the European Pharmacopoeia (Ph. Eur.) or the pharmacopoeia of an EU Member State;

C. Pharmacopeial active substances included in the Ph. Eur. or in the pharmacopoeia of an EU Member State.

- **Applicant's part of a DMF – Open part**

  The applicant must be supplied by the ASM with sufficient information to be able to take responsibility for an evaluation of the suitability of the active substance specification to control the quality of the substance. This normally includes a brief outline of the manufacturing method, information on potential impurities originating from the manufacturing method, from the isolation procedure (natural products) or from degradation and, where applicable, information on the toxicity of specific impurities. (6)

- **ASM Restricted Part of DMF – Closed part**

  Detailed information on the individual steps of the manufacturing method such as reaction conditions, temperature, validation and evaluation data for certain critical steps of the manufacturing method, etc. and on quality control during manufacture may contain valuable know-how. Such information may therefore be supplied to the authorities only. (7)

CANADA DMF – TYPES

Canada has 4 Types of DMFs
Type I - Drug Substance, Drug Intermediates and materials used in their preparations
Type II - Packaging material
Type III - Colorants, Flavours and Other Additives
Type IV - Dosage form

Type I & IV have two sections:

- Sponsor's (Open)
- Restricted (Closed)

Table 3: Timelines for filing a DMF

PHASE	ACTIVITY	TIMELINES (APPROX.)
Pre-Phase 1	Patent Search	30 Days
Phase - 1	Feasibility Report	60 Days
	Optimization Report	130 Days
	Lab Validation	50 Days
Phase - 2	Pilot Scale, Validation	70 Days
Phase – 3	Commercial, Validation, DMF Filing	50 Days
Phase - 4	Stability Studies	90 Days

Timelines (approx.) to complete a product filing is 480 days.

Fees for USDMF Filling (8)

Under GDUFA (Generic Drug User Fee Amendments), the DMF fee is owed by each person that owns a type II Active pharmaceutical ingredient DMF that is referenced, on or after October 1, 2012, in a generic drug submission by an initial letter of authorization. This is a one-time fee for each individual DMF. This fee is due no later than the date on which the first generic drug submission is submitted that references the associated DMF.

Under section 744 B (a) (2)(D)(iii) of the FD & C Act, if a DMF has successfully undergone an initial completeness assessment and the fee is paid, the DMF will be placed on a publicly available list documenting DMFs available for reference. Thus, some DMF holders may choose to pay the fee prior to the date that it would otherwise be due in order to have the DMF placed on that list. In order to calculate the DMF fee, FDA assessed the volume of DMF submissions overtime.

The statistical forecasting methodology of power regression analysis was selected because these models how very good fit to the distribution of DMF submissions overtime. Based on the 8 months of available data representing the total paid DMFs from FY2013 and projecting a 5-year timeline (October 2013 to October 2017), FDA is estimating 583 fee-paying DMFs for FY 2014. Fee is determined by dividing the DMF revenue by the estimated number of fee-paying DMFs in FY 2014.

Section 744B (b) (2) (A) specifies that the DMF fees will make up 6 percent of the $305,659,000, which is $18,340,000 (rounded to the nearest thousand dollars). Dividing the DMF revenue amount ($18,340,000) by the estimated fee-paying DMFs (583), and rounding to the nearest $10, yields a DMF fee of $31,460 for FY 2014.

DMF Fees in Europe (9)

Table 4: DMF fees for Registration of Active Substance manufacturers & Importer/Distributor

Fees for Registration of Active substance manufacturers		Fees	Notes
New Application	New application for registration as a manufacture of Active substances	**£5006**	£3143 application fees plus £1863 assessment fees £2655 inspection fees less £1863 assessment fees
	Additional fees if the risk assessment of the initial application triggers an inspection	**£792**	
	Inspection fees (per site if required)	**£2655**	Charged for Inspections conducted post registration
Variations	Notification of changes (Variation)	**£257**	--
	Inspection fees (per site if required)	**£2655**	--

DMF Fees in Canada (10)

Table 5: Drug Master File (DMF) Fee Form

Drug Master file name:		
DMF Number (if used):	**Customer/Client Account Number (if issued):**	
DMF Company Name:		
Calculation of Payment		
DMF for New Registration:	**X $408 Cdn=**	**$**
DMF Biannual Update:		
Number of Letters of Access Enclosed:		
Total Fees (Sum of the above):		
Fees Paid by: ☐Owner ☐Agent ☐Other –For Letter of Access Only (Specify):		
Method of Payment Cheques, Money orders, International bank Drafts or wires		

Table 6: Electronic DMF deadline for different countries

US FDA	CANADA	EUROPE	AUSTRALIA
The deadline for having a DMF in electronic format is May 5, 2017	As of Jan 1, 2016, Health Canada will no longer accept paper copies of DMF transactions. Any paper received after this date will be shredded or returned at the owner's expense. Canada mandates DMF in eCTD format.	From July 1, 2015, new marketing authorization applications for decentralized procedures must be submitted (eCTD) format	From Jan 1, 2016, all eCTD applications must be submitted to the TGA in version 3.0

SOUTH AFRICA	THAILAND	SWITZERLAND
South Africa (ZA-MCC) has a plan to start accepting dossier in eCTD format, from Jun 1, 2015, eCTD is open for entire Industry	From Jan 1, 2016, onwards, eCTD will be the mandatory format in Thailand for new chemical entity (NCE) and New molecular entity (NME)	The new version (v1.3) are accepted from Oct 1, 2015, however the transition period applies until March 31, 2016.

Table 7: Comparison of DMF's of USA, Europe and Canada

DRUG MASTER FILE REQUIRE-MENTS	USA	EUROPE	CANADA
HEALTH AUTHORITY	U.S. Food And Drug Administration	EUROPEAN MEDICINES AGENCY SCIENCE · MEDICINES · HEALTH	Health Canada Santé Canada
FOR API	US DMF	EDMF/ASMF	DMF
DEFINITION OF DMF	A drug master file (DMF) is a submission to the FDA. The main objective is to support regulatory requirements and to prove the quality, safety, and efficacy of the medicinal	In Europe, Drug Master File is known as Active Substance Master File (ASMF) or European Drug Master File (EDMF).	A DMF is a reference that provides information about specific processes or components

	products for obtaining an IND, NDA, ANDA or an export application		used in the manufacturing, processing, and packing of a drug.
TYPES OF DMF	Five Types of DMF: I. Manufacturing Site, Facilities, Operating Procedures, and Personnel. II. Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product III. Packaging IV. Excipients, Colorant, Flavor, Essence, or Material Used in Their Preparation V. FDA Accepted Reference Information.	No Types of DMF	Four Types of DMFs: I. Drug Substance, Drug Intermediates and Materials Used In Their Preparations II. Packaging Material III. Colorants, Flavours and Other Additives IV. Dosage Form
FORMAT	The USFDA require two copies of each type DMF in the CTD format, but not in CTD Module form. FDA requires one continuous document in the CTD format. QOS is also required. Electronic submission and paper submission.	ICH CTD Module 3-Quality and QOS. ASMF divided into two: Applicant's Part (AP) and Restricted Part (RP). The UK and the Netherlands will only accept Electronic copies each in their own separate electronic format, while France requires both a paper copy and an electronic copy. France also requires special application forms to accompany the DMF as well as a letter certifying that the electronic version is identical to the paper copy. Several other countries process are in the process of converting to the non-ICH (Xml), Non-eCTD electronic filing format. These include Belgium, Denmark, Germany, and France.	ICH CTD Module 3-Quality and QOS. DMF divided into two separate parts, namely the Applicant's Part (AP) and the Restricted Part (RP) Electronic submission and paper submission.
SUBMISSIONS ALONG WITH DMF	**A. Transmittal Letters** a. Identification of Submission: Original, The type of DMF as classified in Section III, and it's Subject. b. Identification of the Application, if known, that the	Letter of Access to the NCA/EMA. A Copy of the Letter Of Access to the MA Holder for inclusion in the annexes To their MA/MAV Application. A Submission details form to the NCA/EMA subsequent	The DMF Should include the following information: • The Name and Address of the agent if applicable.

	DMF is intended to support, including the Name and Address of each Sponsor, Applicant, or Holder, and all relevant document numbers. c. Signature of the Holder or the Authorized Representative. d. Type written Name and Title of the Signer. **B. Administrative Information** a. Names and Address of the following: 1) DMF Holder 2) Corporate Headquarters 3) Manufacturing Processing Facility 4) Contact for FDA Correspondence. 5) Agent(S), If any b. The Specific responsibilities of each person listed in any of the categories in Section A. Statement of Commitment.	updates to an ASMF where the information in the form is the same for all. Application: • Applicant's Part • Restricted Part • Separate or Combined Quality Overall Summary (QOS) for the Applicant's and Restricted Parts Copy of the Expert's Curriculum Vitae.	• The Name and Address of the Corporate Headquarters (DMF Owner); and The Name and Address of the Manufacturing Processing, and Packaging Facilities.
FORWARDING ADDRESS	Drug Master File Staff FDA, 5901-B Amendable Rd. Beitsville, Md 20705-1266	In Europe according to Marketing Authorization Procedures, DMF submitting address will be change. **EMA Address:** 7 Westferry Circus • Canary Wharf • London E14 4hb • United Kingdom **Telephone** +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416 **E-Mail** Info@Ema.Europa.Eu **Website** www.ema.europa.eu	Drug Master File Administration Unit, Therapeutic Products Directorate, Finance Building, Al: 0201d, 101 Promenade Tunney's Pasture Driveway, Tunney's Pasture Ottawa, Ontario K1a 0k9 Canada Email:DMF_Enquiries@Hc-Sc.Gc.Ca Fax Number: 613-957-3989
LETTER OF AUTHORI-ZATION	Letter of Access is required	Letter of Access is required	Letter of Access is required
CLOSURE OF DMF	A Holder who wishes to close a DMF should submit a request to the DMF Staff stating the reason for the closure. The agency may close a DMF that does not contain an annual update of persons	Where the active substance is no longer supplied to the MA Holder or the corresponding ASMF is replaced by a Ph. Eur. Certificate Of Suitability (CEP), The ASMF Holder should provide a withdrawal	A DMF be withdrawn by the Owner, The Owner should advise Health Canada in writing and provide a list of the

	authorized to incorporate information in the DMF by reference and a list of changes made since the previous annual report.	of access letter to the NCA/EMA.	Canadian Customers using their DMF. Health Canada will close a DMF that has not been update within a 5 years period.
DMF FEES	Only for Type 2 DMF fees will be taken according to GDUFA- $31,460	New Applications- £5006	DMF For New Registration- $408Cdn

CONCLUSION

The DMF contains factual and complete information on a drug product's chemistry, manufacture, stability, purity, impurity profile, packaging, and the cGMP status of any human drug product. The content and the format for Drug Master File are used to obtain market authorization. The main objective of the DMF is to support regulatory requirements of a medicinal product to prove its quality, safety and efficacy. This helps to obtain a marketing authorization grant. Now from 2016 onwards most of the regulated countries will use eCTD or their electronic format for their DMF submission.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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