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Review Article

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Similarities and differences in filing for Drug Master File in US, Canada and Europe

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Abstract

Drug Master File or DMF is a document prepared by a pharmaceutical manufacturer and submitted solely at its discretion to the applicable authority in the intended drug market. The document provides the non-supervisory authority with confidential, detailed information about installations, processes, or papers used in the manufacturing, processing, packaging, and storing of one or further mortal drugs. The DMF form allows an establishment to cover its intellectual property from its mate while complying with non-supervisory conditions for exposure of processing details. There is no non-supervisory demand to file a DMF. Drug Master Files (DMF) is a document containing complete information on an Active Pharmaceutical element (API) or finished drug capsule form. Though there are no non-supervisory conditions to file a DMF, the benefit of its use is inviting. A drug Master Files (DMF) is an voluntary non-supervisory submission and is submitted at the discretion of the DMF holder to help their guests. A DMF is NOT a cover for an IND, NDA, ANDA, or Export Application. It is not approved or disapproved. An Active Substance Master File (ASMF) is the presently honored term in Europe, formerly known as European drug Master file (eDMF) or a US- Drug Master File(US- DMF) in the United States.

Keywords: DMF, USFDA, ASMF, EDQM, Health Canada, IND, NDA, ANDA

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1. Introduction

DMF is a confidential set of proprietary documents detailing the design, process, data, testing procedures and other information about the ingredients, packaging and/or manufacture of pharmaceutical products used in its process or chemicals. The Drug Master File (DMF) is a sensitive document containing complete, accurate and precise information about active drug ingredients. DMF is a document prepared by the drug manufacturer or supplier and sent to the regulatory authority in preparation for the market. DMFs are sent 2-3 weeks after original documents are submitted.

1.1 Role of DMF

- DMF plays an important role for pharmaceutical companies by providing supporting information for drug registration/approval.
- The registration of APIs published on the web supports commercialization of APIs for all pharmaceutical companies.
- The CMC part of the delivery of pharmaceutical products is the identity, purity, potency and quality of the Pharmaceutical products.
- Protect private and confidential information.

1.2 DMFs Globally

- Highly Regulated Markets (Drug Master File used to support the approval process)
  - United States
  - Canada
  - Japan
  - Australia
  - Europe
  - China is developing its own DMF system
- Nearly Regulated Markets (Technical Package /Registration Dossier)
  - Russia
  - South Africa
  - Brazil

- Less Regulated Markets (No DMFs used in the registration process)
  - India and many others.

1.3 Mechanism of Drug Master File

- DMFs must pass two levels of evaluation before their content can be reviewed. Initially, the FDA evaluated the inclusion of all components of DMF in the correct order.
- DMF will be reviewed once it is determined to be acceptable.
- If the DMF cannot be received electronically, the owner is informed.
- To continue the administrative review of the DMF deficiency, the holder must respond to the deficiency in the DMF to be made by the DMF staff by the DMF staff in the Office of Pharmaceutical Quality (OPQ).
- Once the DMF has passed the review and is accepted, the OPQ sends a confirmation letter making it eligible for Content review.
- Otherwise, the OPQ sends an Administrative Filing Issues (AFI) that the responsible person must respond Adequately to monitor the content.

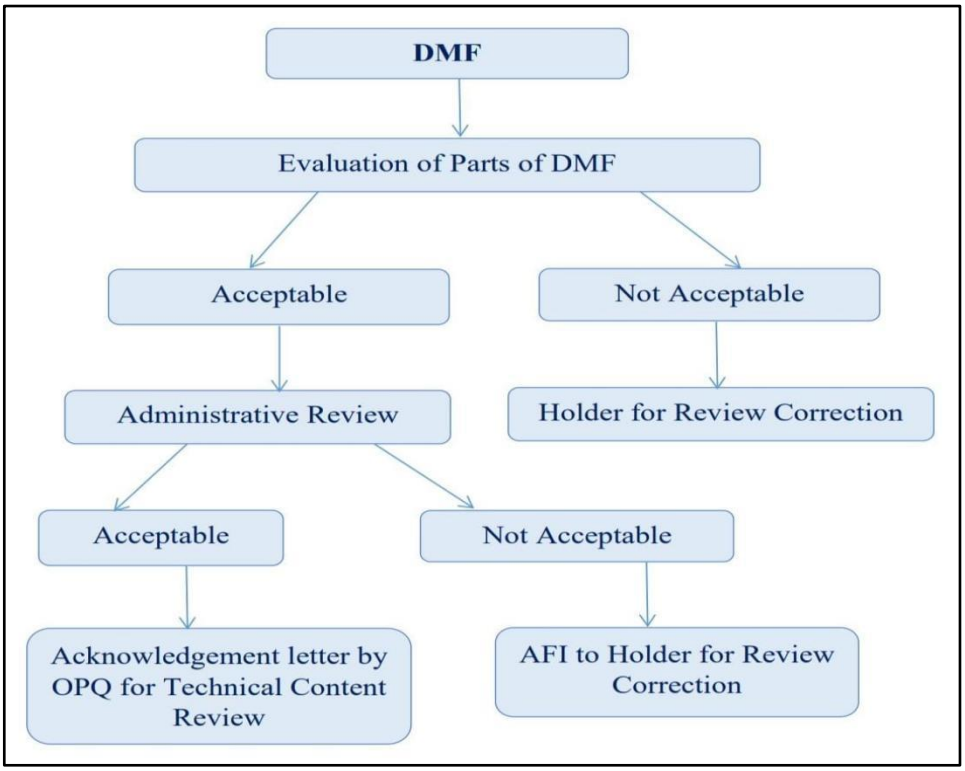

Figure 1. Flowchart of mechanism of Drug master file

2. USFDA – DMF

- A Drug Master File (DMF) is a document submitted to the Food and Drug Administration (FDA) to provide confidential information about facilities, processes, or products used in the manufacture, processing, packaging, and storage of one or more drugs human medicine. Information contained in the DMF may be used to support changes and additions to an Investigational New Drug (IND), New Drug Application (NDA), an Abbreviated New Drug
- Application (ANDA), another DMF, export application, or any application. Drug Master File is provided in 21 CFR 314.420. This guide aims to provide institutional recognition to DMF holders or preparing and presenting DMF.

2.1. Types of Drug Master File in USA

There are five types of DMFs:

Type I: Manufacturing Site, Facilities, Operating Procedures, and Personnel

The DMF should describe the manufacturing location, equipment capacities, and operating procedures.

Type II: Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product

A Type II DMF should, in general, be limited to a single drug intermediate, drug substance, drug product, or type of material used in their preparation.

A. Drug Substance Intermediates, Drug Substances, and Material Used in Their Preparation

B. Drug Product

Type III: Packaging Material

Each packaging material should be identified by the intended use, components , composition, and controls for its release.

Type IV: Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation

Each additive should be identified and characterized by its method of manufacture, release specifications, and testing methods.

Type V: FDA Accepted Reference Information

The FDA prohibits the use of Type V DMFs for other information, resumes, or information that needs to be included in any of the other types of DMFs. (1-6)

3. Canada - DMF

A Master File (MF) is a document that provides information about specific processes or materials used in the manufacture, processing or packaging of a drug.

Health Canada is bound by law to protect confidential business information. This guide provides basic information on MFs,information on the application, processing and evaluation procedures for Class I to V MFs and registration for new

MFs as well as other MF transactions including the management of transfers, renewals, cancellations and closures outlines its requirements.

Master File is a voluntary registration form submitted to Health Canada for applicants seeking marketing authorization for drugs or authorization for clinical trials involving drugs and Biologics. (7, 8)

3.1. Types of Drug Master File in Canada

There are five types of DMFs:

Type I: Active Substance Master Files (ASMFs)

Active Pharmaceutical Ingredients (API) (drug substances), starting materials or intermediates used in the manufacture of a drug substance.

Type II: Container Closure System Master Files (CCS MFs)

Container closure systems (CCS) or CCS components.

Type III: Excipient Master Files

All excipients including excipients of biological origin (e.g., albumin), capsule shells, coating ingredients, colourants, flavors, and other additives (e.g., gelatin, alum and growth media).

Type IV: Dosage Form Master Files (Dosage Form MFs)

Dosage forms and drug product intermediates.

Type V: Facilities and Equipment Master Files (FMFs) Information on all properties being built or approved to be built or operated on the same site as the applicant's properties. Information on facility procedures (e.g. maintenance and production) and design (such as area classifications) to prevent contamination or contamination of areas, and equipment preparation and commercial production for the Cell bank. (7, 8)

4. Europe – DMF

The European DMF was established in 1989-1991. After the EU Common Technical Document (CTD) was completed, it was updated in 2005 and became ASMF (Active Substance Master File). DMF is for active ingredients only. The main purpose of the Active Substance Master File (ASMF) program (formerly the European Medicines Master File (EDMF) program) is to allow companies to market active ingredients that are classified or "known-how" active ingredients (ASM) for protection purposes at the same time, allow the applicant or Marketing Authorization (MA) holder to take full responsibility for the management of quality products and pharmaceutical products.

The content and format of DMF used in the United States differs from that used in Europe to obtain a Marketing Authorization (MA). The main purpose of the EDMF is to promote the regulation of drugs to demonstrate their quality, safety and efficacy. This helps with business authorization. ASMF holders can hold a Certificate of Suitability (CEP) issued by ASMF and EDQM for an active substance. However, in general, the applicant/MA secretary does not need to apply to ASMF and CEP for a specific MAA/MAV active ingredient. If the CEP contains very little information (eg. G. stability) National Security Agency / EMA may decide to provide additional information in the document. In such cases, ASMF and CEP will be applied.

4.1. Types of Drug Master File in Europe

European DMF has been divided into 2 parts:

a) Applicant Part (Open): Contains all the required information including an outline of the manufacturing method.

This usually includes a brief summary of the manufacturing process, information on the adverse effects of the manufacturing process, the isolation process (natural products) or degradation process and, if necessary, the toxicity of the particular impurity.

b) ASM Restricted Part (Closed / Confidential): Confidential information of on the manufacturing of Active Pharmaceutical Ingredient.

Reaction conditions, temperature, usability and evaluation data etc. for some important steps of the manufacturing process detailed knowledge of the individual steps of the production process, such as good management during production will have important skills. (9-10)

Table 1. Comparison of Drug Master File (DMF) in USA, Canada and Europe (11-15)

Sr. No.	DMF Requirements	USA	Canada	Europe
1.	Authority	U.S Food and Drug Administration	Health Canada	European Medicines Agency

2.	Definition of Drug Master File	A Drug Master File (DMF) is a submission to the U.S. Food and Drug Administration (US FDA) that may provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.	A Master File (MF) is a reference that provides information about specific processes or components used in the manufacturing, processing, or packaging of a drug.	The "know-how" of API manufacturing procedures is protected in a master file by pharmaceutical marketing authorization applicants (MAAs) and holder (MAHs).
3.	Types of Drug Master File	There are 5 types of DMFs.	There are 5 types of DMFs.	The DMF does not have a types.
4.	Format	USFDA requires two copies of each kind of DMF in CTD format, but not in CTD Module format. The CTD format is required by the FDA for all continuous documents.	All MF Transactions must be filed via the Common Submission Electronic Submission Gateway (CESG) in the non-eCTD or eCTD format as appropriate.	ASMFs linked to human medicinal products should be presented in the format of the Common Technical Document (CTD).
5.	Submission name	Drug Master File (DMF)	Master File (MF)	European Drug Master File (EDMF)
6.	Use of DMF support of application	IND, NDA, ANDA	NDS	MAA
7.	Language	English	English or French	English or French
8.	Is it mandatory	No	No	No
9.	Submission Type	eCTD	eCTD	eCTD
10.	Forms of DMF Filling	Not Applicable Except Type I DMF, Form FDA 3794	Not Applicable	Not Applicable
11.	DMF number Assigned by reviewers	Yes	Yes	Yes
12.	Approved/ Disapproved by Regulatory Authority	Only Accepted	Only Accepted	Only Accepted
13.	Review Time	Assessment must be completed within 60 days of payment. 6 to 8 months for the scientific evuation process.	no more than one year but no less than 2 months	10 to 11 month required
14.	CTD- modules	Modules 1, 2 and 3 are submitted.	Only Module 2,3	Modules 1, 2 and 3 are submitted.
15.	Applicant Part (AP)/ Restricted Part (RP)	AP & RP are not separated Consolidated DMF is submitted to the authority. Only AP is given to the customer. Upon request, RP is provided to the customer.	The Restricted Part contains the information that the MF Holder regards as confidential and is filed by the MF Holder to Health Canada directly. The Applicant's Part contains the information that the MF Holder regards as non-confidential.	Applicant Part Contains all the required information including an outline of the Manufacturing method. ASM Restricted Part Confidential information of on the manufacturing of Active Pharmaceutical Ingredient.
16.	Agent Requirements (Mandatory to be a citizen of that country)	Mediates between the manufacturer and agency.	Yes	Yes
17.	Audit Timeline	The audit is carried out every 3 years.	The audit is carried out every 3 years.	-

18.	Validity	No validity The DMF is said to be active based on the annual updates submitted by the manufacturer.	-	Valid for 5 years from the date of first issue and valid indefinitely following the 5- year renewal.
19.	Organization of eCTD	Module 1 : Administrative Information Cover Letter Annual Reports Letters of Authorization Statement of Right of Reference List of Authorized Person Module 2: Quality Module 3: Drug Substance	Module 1 : Correspondence Administrative Information Compliance and Site Information Module 2 : Quality Overall Summary Module 3 : Quality	Module 1 : Complete Application Form with signed certificates Cover Letter Expert CV. Module 2 : Quality Overall Summary Module 3 : Drug Substance
20.	Fee	$51,140	$1,324	£5006
21.	Fees Type	One time including life cycle management	Fees for bi-annual update and LOA reference	Depends on EU countries requirements
22.	Updation	Annually	Bi-annually	5 years once or based on customer feed back
23.	Deficiency Letter	Applicable	Applicable	Applicable
24.	Changes and approved	Applicable	Applicable	Applicable
25.	Letter of Authorization	Applicable	Applicable	Applicable
26.	Closure of DMF	A holder who wishes to close a DMF should submit a request to the DMF Staff stating the reason for the closures.The agency may close a DMF that does not contain an annual update of persons authorized to incorporate information in the DMF by reference and a list of changes made since the privous annual report.	Where the active substance is no longer supplied to the MA Holder or the corresponding ASMF is replaced by Ph. Eur. Certificate of Suitability (CEP), The ASMF Holder should provide a withdrawal of access letter to the NCA/EMA.	A DMF be withdrawn by the Owner, The Owner should advise Health Canada in writing and provide a list of the Canadian Customers using their DMF. Health Canada will close a DMF that has not been update within a 5 years period.
27.	Closure or Withdrawal	Applicable	Applicable	Applicable
28.	Reactivation	Applicable	Applicable	Applicable

5. Conclusion

There is no regulatory requirement to filling a Drug Master File in any country. Each country has different rules and regulations to file the Drug Master Files (DMF). From 2016, most of regulated countries use to eCTD Format for their Drug Master File (DMF) submissions.

Drug Master File (DMF) is to support the regulatory requirements of Drug Substance and Drug Product to prove its efficacy, quality and safety.

Based on this study, Europe and Canada is do not have harmonized guidelines and are not transparent enough as compare the USA. So there is a need of harmonization on filling of DMF in the world in future.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

References

1. Drug Master Files (DMFs). U.S. Food and Drug Administration [Internet]. US FDA; 2022 Oct 24 [cited 2023 Apr 6]. Available from: https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs
2. Drug Master Files: Guidelines. U.S. Food and Drug Administration [Internet]. US FDA; 2017 Nov 16 [cited 2023 Apr 6]. Available from: https://www.fda.gov/drugs/guidances-drugs/drug-master-files-guidelines
3. Types of DMFs. U.S. Food and Drug Administration [Internet]. US FDA; 2021 Jan 27 [cited 2023 Apr 6]. Available from:

https://www.fda.gov/drugs/drug-master-files-dmfs/types-drug-master-files-dmfs
4. DMF Submission Resources. U.S. Food and Drug Administration [Internet]. US FDA; 2023 Mar 27 [cited 2023 Apr 6]. Available from: https://www.fda.gov/drugs/drug-master-files-dmfs/drug-master-file-dmf-submission-resources
5. Drug Master File Fee. U.S. Food and Drug Administration [Internet]. US FDA; 2017 Jan 19 [cited 2023 Apr 22]. Available from: https://www.fda.gov/industry/generic-drug-user-fee-amendments/drug-master-file-fee
6. Drug Master File – Food and Drug Administration. U.S. Food and Drug Administration [Internet]. US FDA; 2019 Oct [cited 2023 Apr 6]. Available from: https://www.fda.gov/media/131861/download
7. Guidance Document: Master Files. Health Canada/ Government of Canada [Internet]. canada.ca; 2022 Jun [cited 2023 Jun 30]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/guidance-document-master-files-procedures-administrative-requirements.html
8. Fees for Master Files. Health Canada/ Government of Canada [Internet]. canada.ca; 2022 Dec 16 [cited 2023 Apr 23]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/funding-fees/fees-respect-human-drugs-medical-devices/fees-master-files-human-drugs.html
9. Active Substance Master File Procedure – Scientific Guideline. European Medicines Agency. [Internet]. EMA; 2019 Jun 17 [cited 2023 May 13]. Available from: https://www.ema.europa.eu/en/active-substance-master-file-procedure-scientific-guideline
10. Guideline on Active Substance Master File Procedure. European Medicines Agency. [Internet]. EMA; 2018 Nov 8 [cited 2023 May 13]. Available from: https://www.ema.europa.eu/en/documents/report/final-guideline-active-substance-master-file-procedure-revision-4_en.pdf
11. Sravanti VKL, Bandla R, Reddy Juturi RK. Filing of DMF in the US, EU, and India, and its comparative review. Int J Drug Reg Affairs [Internet]. 2021 Mar. 16 [cited 2023 Jun. 17];9(1):22-. Available from: https://ijdra.com/index.php/journal/article/view/453.
12. Danej M, Dedania R, Gandhi S, Randeria J, Gaurav K. Regulatory requirements for Drug master file in context to Canada and Australia. Int J Drug Reg Affairs [Internet]. 2018 Jun. 15 [cited 2023 Jun. 17]; 6(2):41-7. Available from: https://ijdra.com/index.php/journal/article/view/236
13. Suraj Kause, Raut P. Drug Master File- A Review. Int J Drug Reg Affairs [Internet]. 2023 Jun. 15 [cited 2023 Jun. 17]; 11(2):50-3. Available from: https://ijdra.com/index.php/journal/article/view/592
14. Kanti SPY, Jain N, Chandra A, Shukla VK. Filing of DMF in US, Canada & Europe. Int J Drug Reg Affairs [Internet]. 2019 Mar. 16 [cited 2023 Jun. 17];7(1):6-12. Available from: https://ijdra.com/index.php/journal/article/view/295
15. Patel R, Girase KR, Rao VT, Patel AA, Patel RJ. Assessment of Regulatory requirements and filing procedure of Drug Master File for Brazil, Europe and South Africa. Int J Drug Reg Affairs [Internet]. 2022 Jun. 19 [cited 2023 Jun. 17];10(2):14-7. Available from: https://ijdra.com/index.php/journal/article/view/517