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DRUG MASTER FILE (DMF) IN USA AND EUROPE

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ABSTRACT

DMF is known as the Drug Master File, which includes a proprietary document containing all detailed, reliable and accurate Active Pharmaceutical Ingredient (API) or dosage format information for the finished product. The Drug Master File consists of two parts, one being the part of the applicant and the other being a restricted part. The applicant's part covers all the details needed to be checked by the license holder on the quality of the product, and the restricted part covers all the sensitive production process information that can be submitted to the health authorities. The purpose of this article is to provide an overview of DMF filings and comparison of DMF in various countries, such as the USA and EUROPE. The drug master file is called DMF (Drug Master File) in the USA, but it is known as ASMF (active substance master file) in EUROPE.

Keywords: applicant part, API, ASMF, Drug Master File, restricted part

INTRODUCTION

Drug master file or DMF the drug master file or DMF is a document prepared by the manufacturer of drug products or excipients and introduced on the targeted market to the regulatory authority **[1]**. The purpose of the DMF is to provide confidential and comprehensive information on the facilities, processes or articles used to manufacture, package and store one or more drugs. There is no regulatory obligation for a DMF to be filled because it is not mandatory to be filed **[2]**. A DMF is not a replacement for an application for an IND, NDA, ANDA or export. It is not approved or disapproved; only in connection with the review of an IND,

NDA, ANDA or export application shall the technical content of the DMF be reviewed. If there is sensitive information that a producer does not want to share with the applicant, a DMF is mandatory **[3]**.

DMF are divide in two parts:

- **The Applicant's Part:** This provides all the details that the license holder needs to determine the standard and make an application for a license or amendment.
- **Restricted Part:** It includes classified information that has been made available to the authorities.

Role of DMF:

1. Supporting documentation relating to the registration/approval of medicines.
2. In the medication sections of Chemistry, Processing and Controls (CMC). The DMF records the identification, purity, intensity and efficiency of drugs.
3. Securing sensitive and proprietary information **[4]**.

DMF filling in US:

DMFs was sent to the Food and Drug Administration in the United States. The aim of the DMF filing is to support regulatory requirements and to provide for an IND (Investigational New Drug Application), NDA (New Drug Application and ANDA) to apply for the quality, safety, effectiveness, purity and potency of the medicinal product (Abbreviated New Drug Application). A DMF is neither approved nor disapproved and an IND, NDA, ANDA or export application is not replaced by a DMF **[1]**. In 21 CFR 314.420, drug master files are given. This guideline sets out all the procedures appropriate to the agency to prepare for the preparation and submission of a DMFF to the agency **[5]**.

Types of DMF in US:

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

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

Type III: Packaging Material

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

Type V: FDA Accepted Reference Information **[6]**.

Note: Form I DMFs were discontinued in 2000, but there was no improvement in the numbers of other forms of DMFs. Form II, III and IV DMF should include a firm's guarantee that all of its facilities are functioning in accordance with the laws in force.

DMF Submission in US:

In 2000, Type I DMFs were discontinued, but the number of other types of DMFs did not change.

The DMF Type II, III and IV should provide an assurance from the firm that all of its facilities operate in compliance with the laws in force.

Transmittal Letters:

It encompasses,

- The DMF form,
- Each supporter, applicant or holders name and address
- Signature of the holder or the representative approved
- The signer's typewritten name and title.

Administrative information:

a) It contains the following names and addresses:
   1) DMF owner
   2) Headquarters of companies
   3) Facility for production/processing
   4) Contact for FDA correspondence
   5) Agent(s)

b) Each person's obligations.

c) Declaration of engagement.

Format, Font, Font Size and Paper used for US-FDA submission:

- Only in electronic format should DMF be filled out.
- Each volume of a DMF should be no thicker than 2 inches.
- For narrative text, Times New Roman, a 12-point font is recommended.
- Each page should be numbered according to the document for granularity.
- The preferred standard US paper size is 8-1/2 by 11 inches.
- The length of paper should not be less than 10 or more than 12 inches.

The following should be submitted to DMF submissions and correspondence:

Drug master file food for staff; and drug management; 5901-B Ammendale Rd; Beltsville, MD 20705-1266.

Letter of authorisation to FDA:

The authorisation letter should contain the following:

- The date
- DMF holder's name
- Number of DMF
- Name of the person(s) approved by reference to include data in the DMF.
- Unique product(s) subject to the DMF.
- Date of submission
- To reference section numbers and/or page numbers.
- Declaration of agreement that the DMF is current and that the holder of the DMF will comply with the claims made therein.

- Signature of Official Authorization
- Type the name and title of the official references to the DMF authorization.

Filling, assessing and review of a DMF:

- The holder of the DMF should give the FDA two copies.
- The claimant, sponsor or other holder referring to a DMF is expected to include in the application a copy of the letter of authorisation from the DMF holder.
- If the application is incomplete, a letter of clarification from the Drug Master File Staff will be returned to the submitter and no DMF number will be assigned.
- A letter explaining the deficiencies is sent to the DMF holder if FDA reviewers find deficiencies in the details given in a DMF.

Holder obligations:

- Any alteration or extension, including a change of authorisation relating to individual customers, should be submitted in duplicate and cross-referenced format to the previous submission.
- The reference should include the affected date(s), volume(s), section(s), and/or page number(s).
- A DMF is expected to include a full list of individuals allowed by reference [21 CFR 314.420(d)] to integrate details into the DMF.
- In the annual update, the holder should update the list.
- By name, date, volume and page number, the revised list should be defined.
- Any person whose authorization was revoked in the preceding year should be listed under a suitable caption.
- If the list is unchanged on the anniversary date, a declaration that the list is current should be made by the DMF holder.

Transfer of ownership:

It should contain the following in the letter:

- Name of transferee
- Transferee's address
- Name of the official responsible for the move.
- Effective date of transition
- Signature of the official transfer officer
- Typewritten name and official transfer title.

Closure of drug master file:

- A holder who wants to close a DMF should send a request specifying the reason for the closure to the DMF workers and should include a declaration that the responsibilities of the holder have been fulfilled.

- If the holder does not update the references and the list of changes made since the previous annual report, the Agency can close the DMF **[7]**.

Reactivating a closed DMF:

Reactivation will be submitted by the holder. A full copy of the DMF containing any changes after the last submission should be included in it. Entry of a DARRTS reactivation switches the status to Active and the DMF is eligible for analysis **[8]**.

DMF Fee:

A DMF fee is payable to anyone who owns a type II active pharmaceutical ingredient DMF referred to in a generic drug application on or before October 1, 2012. This fee is due earlier than the date on which the first generic drug application relates to the associated DMF or the date on which the initial completeness assessment is requested by the drug master file holder. This is a one-time fee (for each DMF), and by dividing the total DMF goal revenue by the approximate number of fee-paying DMFs, the FY 2019 DMF fee has been determined. The DMF fee for FY 2019 is $55,013 **[9]**.

European DMF Filling System:

The European DMF was established between 1989 and 1991. After the introduction of the Common Technical Document (CTD) in the EU, it was revised in 2005 and became an ASMF (Active Substance Master File). DMF only refers to active substances. The material and format used in the United States for DMFs is distinct from that used in European countries to receive business authorisation (MA). The main purpose of the EDMF is to support regulatory requirements in order to show the consistency, protection and effectiveness of a medicinal product. This helps to secure a grant for marketing authorization.

For a single active substance, the ASMF holder can have an ASMF as well as a Certificate of Suitability (CEP) provided by EDQM. However, it is usually not appropriate for the applicant/MA holder to apply to both the ASMF and the CEP for a single active substance of a specific MAA. In cases where too little information (such as stability) is contained in the CEP, the National Competent Authorities/EMA can decide to include additional information in the dossier. In this case, reference to both the ASMF and the CEPF may be appropriate **[10]**.

Marketing Authorisation Application:

The applicant for the prior submission should inform the European Medicine Agency (EMA) of its intention to submit an application and include a fair estimation of the month of submission.

MAA can be filled in four ways:

1. **Centralized procedure:**
   A marketing authorisation issued under the centralized procedure is valid for the whole market of the Nation, which means that it is possible to position the medicinal product on the market of all Member States. Regulation (EC) 726/2004 lays down a centralized Community process for the authorisation of medicinal products for which a single application, a single assessment and a single authorisation enable a single application and a single authorisation allowing direct access to the community single market.
2. **Decentralised procedure:**
   For items that fall beyond the reach of the EMA with respect to centralized procedures, a decentralized procedure can be submitted by a sponsor. Using this method, for products that have not yet been approved in any EU country, a sponsor can apply for simultaneous authorization in more than one EU country.
3. **Mutual recognition procedure:**
   Companies that have a medicinal product approved in one EU Member State can apply to be recognized in other EU countries for this authorisation. It's a smoother way to hit the first market.
4. **National procedure:**
   An application must be sent to the competent authority of the Member State in order to receive the national marketing authorisation. The EU Member State, within its own jurisdiction, has its own authorisation procedures. MA applications should be completed within 210 days **[11]**.

Content of Active Substance Master File:

The overall content of ASMF should contain detailed scientific information for market authorizations for medicinal products in the member states of the European union.

ASMFs linked to human medicinal products should be presented in the format of Common Technical Document, and veterinary medicinal products should include:

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

It is important to physically divide the scientific knowledge in the ASMF into two separate parts:

Applicant's part: The AP includes details that the ASMF holder considers the applicant to be non-confidential. It is stressed that the AP is still a confidential document that, without the written permission of the holder of the ASMF, cannot be sent by anyone to third parties.

Restricted part: The RP includes information that the holder of the ASMF considers the applicant to be confidential. The RP may provide detailed information on the individual stages of the production methods, such as reaction conditions, temperature, critical phase validation data.

European DMF Filing Procedure:

For the following active substances, like herbal active substances / preparations, the ASMF technique may be used. Thus, i.e.:

- New active ingredients;
- Existing active substances which are not included in the European Pharmacopoeia (Ph.Eur.) or the EU Member State Pharmacopoeia;
- Pharmaceutical active ingredients used in the Ph.Eur.. Or in an EU Member State's pharmacopoeia.

The holder of the EDMF should provide the applicant with:

- A copy of the most recent edition of the applicant section
- A copy of the overall quality review of the current version of the applicant section
- Letter of entry, if it has not been submitted to the product before.
- The EDMF holder should apply the EDMF to the competent authorities for each MAA (market authorisation application) or each MAV (market authorisation variation).

Changes & Updates to the ASMF:

ASMF holders should keep the content of their ASMFs updated for medicinal products with regard to the actual synthesis/manufacturing process.

The contents of their ASMF shall not be altered by the ASMF holders, i.e.

- Manufacturing process
- Specifications

Each MA holder should report any changes to the ASMF to the appropriate National Competent Authority/EMA by means of the appropriate variation procedure.

On the occasion of the 5-year renewal of a medicinal product, MA holders are expected to announce that the preparation and control methods are in compliance with the standard of the product. All amendments should be mentioned in a covering letter. The cover letter addressed to EMEA should contain the following information:

A list of all the improvements made since the EDMF's 1st submission.

Comparison of old and current EDMFF material Details as to whether or not the amendment was approved, rejected or withdrawn by other Member States **[12]**.

Table 1: Comparision of DMF's of USA and Europe:

DMF REGULATORY REQUIREMENTS	USA	EUROPE
Regulatory authority	U.S. Food and Drug Administration	European medicines agency
For API	US DMF	EDMF/ASMF
Definition of DMF	A drug master file 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 products for obtaining an IND, NDA, ANDA or an export application	In Europe, drug master file is known as Active Substance Master File (ASMF) or European drug master file (EDMF)
Types of DMF	Five types of DMF	No types of DMF
Review authority	USFDA	CEP: European directorate for quality of medicines and healthcare ASMF: European Medical Agencies
Scope	No legislation or FDA policy requires the submission of DMF. A DMF shall be submitted exclusively at the holder's discretion. An Investigational New Drug (IND), a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), another DMF, an export application, or modifications or supplements can be used to support the details contained in the DMF.	This Guideline is intended to assist applicants/MA holders in compiling their Marketing Authorization Application (MAA) or Marketing Authorization Variant (MAV) dossiers for the active substance portion of a medicinal product. It is also intended to assist holders of ASMFs in compiling their ASMFs.
Format	Two copies of each DMF sort are required by the USFDA in the CTD format, but not in the CTD module format. In the CTD format, the FDA needs one continuous text. There is also a need for Consistency Overall Submission (QOS). Electronic submission and submission on paper.	Module 3 of ICH CTD-Quality and QOS. The United Kingdom and the Netherlands will only allow electronic copies, each in its own separate electronic format, while both paper copies and electronic copies are required by France. France also allows the DMF to be accompanied by special application forms and a letter certifying that the electronic edition is similar to the paper copy.
Letter of Authorization	Letter of access is required	Letter of access is required
Mandatory	Not mandatory	Not mandatory
Forwarding address	Drug Master File Staff, 5901-B Amendable Rd. Beltsville, Md 20705-1266.	DMF submitting address: • 7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom Telephone+44(0)2074188400 Facsimile+44 (0) 2074188416 E-mail info@ema.europa.eu Website www.ema.europa.eu
Closure of DMF	A holder who wishes to close a DMF should send a letter, specifying the reason for the closure, to the drug master file workers. The request should contain a declaration that the holder's responsibility has been fulfilled.	The active material is no longer administered to the holder of the MA or a Ph.Eur is substituted for the corresponding ASMF. Certificate of Adequacy (CEP). A withdrawal of the access letter to the NCA/EMA should be issued by the ASMF holder.
DMF fees	According to GUDFA fees will be taken only for type II DMF is $31,460.	New applications- £5006

CONCLUSION

The DMF has been filed in support of different applications. The DMF provides details on a drug that is complete and factual. CMC (Chemistry Development and Control), durability, impurity profile, any

substance or excipient packaging. The contents of the DMF are used to receive marketing permits that help to obtain a grant for a marketing authorization. The main aim of the DMF is to endorse, in order to prove its consistency, protection and effectiveness, the regulatory standards for a medicinal product and this helps to gain a marketing authorisation grant. DMF to be submitted in a timely manner and that the criteria used to challenge it are of the same nature as the drug submission, and there is also a need for potential harmonization of the worldwide filling of DMF.

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