

# Registration process of API in U.S and Europe along with comparison of USDMF and EUDMF

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## ABSTRACT

APIs have been called bulk actives, bulk pharmaceutical chemicals, and even bulk chemicals. No matter what they are called, these materials are critical to the drug approval process in all regions of the world. Since APIs are the compounds that actually provide the activity and effectiveness of all drugs, they are subject to a significant amount of review during the filing and approval processes. In order to obtain a marketing authorisation for a drug product the applicant has to show evidence of efficacy, safety and quality of the drug product. To assure this, appropriate documentation on the active substance including the manufacturing of the active substance has to be submitted to the competent authority. Different regions have adopted different procedure for regulatory filing for API, in U.S it is done as per DMF procedure while in Europe it is done by CEP and ASMF procedure.

**Keywords:** API, DMF, Submission, Drug substance

## INTRODUCTION

**Active Pharmaceutical Ingredient (API) (or Drug Substance):** Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.<sup>[1]</sup>

API materials that are the active for new drugs are covered by NDA documentation. Innovator companies would use their IND or NDA filings to provide the expected details covering an API, while all others would establish and submit a DMF with the FDA or other appropriate country authority, such as EMA in Europe.<sup>[2]</sup>

**Drug Master File or DMF** is a document prepared by a pharmaceutical manufacturer and submitted solely at its discretion to the appropriate regulatory authority in the intended drug market. There is no regulatory requirement to file a DMF. However, the document provides the regulatory authority with confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.

It is known as “US-Drug Master file (US-DMF)” and “European Drug Master File (EDMF)” or “Active Substance Master File (ASMF)” in United States and Europe respectively.<sup>[3]</sup>

### Registration procedure for API in US:

DMFs have no legal or regulatory basis in the United States; however, they do provide companies a relatively easy and confidential way to provide confidential information about a process without making it available to other commercial companies. The DMF should contain all of the detailed information expected by the regulatory authorities so that a DMF reference in an NDA or ANDA can be used to complete an agency review process. In the United States there is no approval process for a DMF. In fact, DMFs are only examined when referenced in other regulatory filings, such as an NDA or ANDA; only then is the content of a DMF reviewed. If requested by FDA headquarters, an FDA inspection may take place at an API manufacturing site after a review of the DMF.<sup>[2]</sup>

In the United States, there are no regulations issued by the Food and Drug Administration that establish specific GMP requirements for APIs. The United States has adopted and agreed to the use of the **ICH Q7A** guidance as the GMP guide for API. <sup>[2]</sup>

#### **USDMF:** <sup>[3]</sup>

DMF is a submission to the 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. The submission of a DMF is not required by law or FDA regulation. A DMF is submitted solely at the discretion of the holder.

DMF can be submitted in support of:

- Investigational New Drug Application (IND)
- New Drug Application (NDA)
- Abbreviated New Drug Application (ANDA)
- Another DMF
- Export Application
- Supplements or Amendments to any of these.

A DMF is NOT a substitute for an IND, NDA, ANDA, or Export Application. It is not approved or disapproved. Technical contents of a DMF are reviewed only when referenced in other regulatory filings, such as an IND, NDA or ANDA or Export Application. If requested by FDA headquarters, an FDA inspection may take place at an API manufacturing site after a review of the DMF.

DMFs are used to permit the person holding the DMF (DMF holder) to authorize sponsors or applicants to rely on the information in the DMF to support a submission to FDA without the DMF holders having to disclose the information to them. When an applicant references its own material, the applicant should reference the information contained in its own IND, NDA, or ANDA directly rather than establishing a new DMF.

Table 1: Types of Drug Master Files

Type I	Manufacturing Site, Facilities, Operating Procedures, and Personnel (no longer applicable)
Type II	Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product
Type III	Packaging Material
Type IV	Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation
Type V	FDA Accepted Reference Information

#### **Updating DMFs:**

DMF should be regularly updated so that it remains current. Updated DMF should be submitted when significant changes occur that may impact on products, such as the addition of a new product to a contract manufacturing facility. DMF updates should be submitted to the address as listed below:

FDA/CBER

Division of Manufacturing and Product Quality (HFM-670)

1401 Rockville Pike, Suite 200N

Rockville, MD 20852-1448

#### **Registration Requirements of DMF:** <sup>[3, 4]</sup>

##### **Submissions to Drug Master Files**

Each DMF submission should contain

- A. Transmittal letter
- B. Administrative information about the submission

##### **A. Transmittal Letters**

The following should be included:

##### **1. Original Submissions**

- a. Identification of submission: Original, the type of DMF as classified in Section III, and its subject.
- b. Identification of the applications, if known, that the 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. Typewritten name and title of the signer.

## 2. Amendments

- a. Identification of submission: Amendment, the DMF number, type of DMF, and the subject of the amendment.
- b. A description of the purpose of submission, e.g. updates, revised formula, or revised process.
- c. Signature of the holder or the authorized representative.
- d. Typewritten name and title of the signer.

## B. Administrative Information

Administrative information should include the following:

### 1. Original Submissions

- a. Names and addresses of the following:
  - i. DMF holder.
  - ii. Corporate headquarters.
  - iii. Manufacturing/processing facility.
  - iv. Contact for FDA correspondence.
  - v. Agent(s), if any.
- b. The specific responsibilities of each person listed in any of the categories in Section a.
- c. Statement of commitment.

A signed statement by the holder certifying that the DMF is current and that the DMF holder will comply with the statements made in it.

### 2. Amendments

- a. Name of DMF holder.
- b. DMF number.
- c. Name and address for correspondence.
- d. Affected section and/or page numbers of the DMF.
- e. The name and address of each person whose IND, NDA, ANDA, DMF, or Export Application relies on the subject of the amendment for support.
- f. The number of each IND, NDA, ANDA, DMF, and Export Application that relies on the subject of the amendment for support, if known.
- g. Particular items within the IND, NDA, ANDA, DMF, and Export Application that are affected, if known

## Drug Master File Format, Assembly, Delivery <sup>[3,4]</sup>

### Format:

- a. Type II DMF is filled in CTD-Q format.
- b. The DMF must meet the format requirements.
- c. Drug Master File holders and their agents/representatives should retain a complete reference copy that is identical to, and maintained in the same chronological order as, their submissions to FDA.
- d. The DMF is submitted as Original and Duplicate jackets, collated, assembled, paginated, and jacketed.
- e. Each volume of a DMF should, in general, be no more than 2 inches thick. For multivolume submissions, number each volume. For example, for a 3 volume submission, the volumes would be numbered 1 of 3, 2 of 3, and 3 of 3.
- f. The jacket covers are purchased from the government printing office and are specifically provided for the DMFs.
- g. Multiple volumes are numbered and paper must be standard U.S size paper. (8- 1/2 by 11 inches)
- h. The DMF must be submitted in two copies, one with **blue cover** and with a **red cover**.

### Overview of Type II DMF content as per CTD-Q format

In US, Type II DMF for API should be filled using CTD-Q format. FDA requires one continuous document embracing the CTD formats without the distinction of an "Applicant's Part" or "Restricted Part." This is because FDA considers the entire DMF document confidential and does not have the same marketing application

requirements that the EU requires for marketing approval. So, DMF is prepared by combining the "Applicant's Parts" and "Restricted Parts" of Modules 2 and 3. <sup>[5]</sup>

#### **Assembly:**

Paper length should not be less than 10 inches nor more than 12 inches. However, it may 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. <sup>[4]</sup>

#### **Delivery to FDA:** <sup>[4]</sup>

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
5901-B Amendable Road  
Beltsville MD 20705-1266

#### **Registration Procedure for API in EU:**

##### **Classification of Active Substances** <sup>[6]</sup>

API can be classified as below:

- 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. Pharmacopoeial active substances included in the Ph. Eur. or in the pharmacopoeia of an EU Member State.

In Europe, Drug Master File is known as Active Substance Master File (ASMF) or European Drug Master File (EDMF).

##### **Feasible Ways of API Registration:** <sup>[6]</sup>

Depending on the kind and classification of the active substance, the required data for API may generally be submitted in one of the following ways:

- A. Certificate of suitability to the monographs of the European pharmacopoeia (CEP)
- B. Active Substance Master File (ASMF) procedure
- C. Full details of manufacture
- D. Other supportive data in consideration of the qualification of impurities.

Table 2: Registration types for active substance

Type of Active substance	Registration Type
New active substance	(B) or (C)
Existing substances	(A) and (B) or (C)

#### **A. Certificate of suitability to the monographs of the European Pharmacopoeia (CEP)** <sup>[7]</sup>

CEP is applicable to Pharmacopoeial substances only (active substance or excipient). The manufacturer of a substance will be able to provide proof that the quality of the substance is suitably controlled by the relevant monographs of the European Pharmacopoeia by means of a certificate of suitability granted by the certification secretariat of the European Directorate for the Quality of Medicines (EDQM). To apply for a certificate a manufacturer will submit a detailed dossier which may contain confidential data.

The certificate of suitability certifies that by applying the relevant monographs of the European Pharmacopoeia, it is possible to check whether or not the quality of the substance is suitable for use in medicinal products. This procedure is intended to be used for substances for which a monograph (general monograph and/or specific monograph) has been adopted by the European

Pharmacopoeia Commission

### **CEP Procedure**<sup>[7]</sup>

The procedure for the certification of suitability will consist of the following steps:

- A. Submission of the Dossier
- B. Acknowledgement of Receipt
- C. Designation of Assessors
- D. Assessment
- E. Notification of the Decision
- F. Follow Up to Certification of Suitability

### **B. Active Substance Master File (ASMF) or European Drug Master File (EDMF)**<sup>[8]</sup>

Active substance Master File (ASMF) is only applicable to Active Substance (new or pharmacopoeial). Active Substance Master File is also known as "European Drug Master File (EDMF)".

Active Substance Master File (ASMF) is to allow valuable confidential intellectual property or know-how of the manufacturer of the Active Pharmaceutical Ingredient (API) 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.

#### **Content of the Active Substance Master File:**<sup>[8]</sup>

The information in the ASMF is divided into two separate parts:

- i. The Applicant's Part (AP) or Open Part and
- ii. The Restricted Part (RP) or Closed Part.

The AP contains the information that the ASMF holder regards as non-confidential to the Applicant/MA holder, whereas the RP contains the information that the ASMF holder regards as confidential. It is emphasized that the AP is still a confidential document that cannot be submitted by anyone to third parties without the written consent of the ASMF holder. The RP may contain the remaining information, such as detailed information on the individual steps of the manufacturing method (reaction conditions, temperature validation and evaluation data of critical steps) and the quality control during the manufacture of the active substance.

The applicant's ("open") part of the ASMF should be included in section 3.2.S of the Quality documentation presented in the CTD-format. The active substance manufacturer's restricted ("closed") part of the ASMF should follow the structure of Module 3.2.S of the CTD. A separate Quality Overall Summary for the information included in the active substance manufacturer's restricted ("closed") part should also be provided, as part of the ASMF.

When an ASMF is provided as part of a new application for which the Quality data are submitted in the EU-CTD format, the complete ASMF (open and closed part and the Quality Overall Summary on the ASMF) must also be presented in the EU-CTD format.

### **C. Full details of Manufacture**<sup>[6]</sup>

Full details of Manufacture are applicable for new active substance and for existing pharmacopoeial active substance:

#### **In the case of new active substances:**

- a. The applicant may submit as part of the MA application full details of chemistry, manufacturing process, quality controls during manufacture and process validation for the active substances as outlined in the note for the guidance chemistry of active substances.
- b. Proof of structure may not be necessary where this can be shown by specific Identification tests in relation to reference substances sufficiently described in the Dossier, where necessary.

#### **In the case of existing pharmacopoeial active substances:**

- a. Stability data may not be necessary where adequate literature evidence can be Cited and summarized and where the monograph covers the degradation products for which suitable limits have been set as indicated in the Note for Guidance Stability testing on existing active substances and related finished products. In this Situation the applicant should demonstrate that the substance complies with the Monograph immediately before use.
- b. Special emphasis should be given to demonstrating that those potential impurities, most likely to arise during synthesis, from the actual manufacturing process can be controlled by the manufacturer, particularly where these differ from any included in the monograph. In case that not all potential impurity is mentioned in an impurity section of the monograph, the Applicant should demonstrate whether the tests of the monograph can control these additional impurities. If the manufacturer uses different methods to control specified impurities, equivalence to the pharmacopoeial method should be

demonstrated. The toxicological implications of impurities not included by the monograph should be addressed.

**D. Other Evidence of Suitability of the Pharmacopoeial Monograph** [6]

With respect to the ASMF procedure or full information as part of the MA Application, the applicant may supply other supportive data obtained from the active ingredient manufacturer in order to consider impurities as qualified.

This may include the following:

- a. Information as to the length of time that the active substances from the particular named source has been on sale in the European Union and elsewhere, include the copy of dosage forms (and the target species) involved.
- b. A statement that, in the above period, there had been no significant change in the method of manufacturing leading to a change in the impurity profile of the active substance.
- c. If possible, evidence that samples of the active substance from the named source had been supplied to the Ph. Eur. Commission or a national pharmacopoeia commission and has been taken into account in the development of the monograph.

Table 3: COMPARISON OF U.S. DMF AND E.U. DMF

U.S DMF	E.U DMF
<p><b>Definition:</b>                      “A Drug Master File 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.”                      Or                      “It is a submission to the FDA of information, usually concerning the Chemistry, Manufacturing and Controls (CMC) of a component of a drug product, to permit the FDA to review this information in support of a third party’s submission.”</p>	<p><b>Definition:</b>                      “European Drug Master File 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 authorization (MA) holder to take full responsibility for the medicinal product and the quality and quality control of the active substance. It is also called as “Active Substance Master File (ASMF)”.”</p>
<p><b>Types:</b>                      Five types:                      1) Type I - Manufacturing Site, Facilities, Operating Procedures, and Personnel (no longer applicable)                      2) Type II - Drug Substance, Drug Substance Intermediate, and Material Used in their Preparation, or Drug Product                      3) Type III - Packaging Material                      4) Type IV - Excipient, Colorant, Flavor, Essence, or Material Used in their Preparation                      5) Type V - FDA Accepted Reference Information                      Only Type II deals with the Drug substances (API).</p>	<p><b>Types:</b>                      Mainly two types:                      1) Certification of suitability to the monographs of the European Pharmacopoeia (CEP).                      2) Active substance master file (ASMF).</p>
<p><b>Regulatory authority:</b>                      FDA- Food and Drug Administration</p>	<p>Both deals with Drug substances (API).                      CEP - Pharmacopoeial substances only (active substance or excipient).                      ASMF - Applicable to active substances only (new or pharmacopoeial).</p>
<p><b>Regulatory authority:</b>                      FDA- Food and Drug Administration</p>	<p><b>Regulatory authority:</b>                      EU DMF handled by two agencies:                      1) European Medicines Agency (EMA) – ASMF                      2) European Directorate for the Quality of Medicines and HealthCare (EDQM) – CEP</p>
<p><b>Division/Office Handling DMFs:</b></p>	<p><b>Division/Office Handling DMFs:</b></p>

**DMF review for Administrative purposes** by Office of Business Informatics (OBI) staff within Center for Drug Evaluation & Research

**Completeness Assessment** is performed by Office of Generic Drug (OGD)/DMF Review Staff

**Content:**

FDA requires one continuous document embracing the CTD formats without the distinction of an "Applicant's Part" or "Restricted Part."

Only one part contains all significant steps in the manufacturing and controls of the drug intermediate or substance.

Whenever DMF is filed by person or firm is checked by FDA and if it is containing all necessary documents, FDA accepts DMF file and give a DMF number. It is the identification of DMF for applicant who wants to review that DMF

**Format and Assembly:**

- Requirement to file DMF s in electronic format. Paper DMF will continue to be accepted.
- Filed in CTD- Q format
- The DMF must be submitted in two copies, one with a blue cover and one with a red cover.
- U.S standard paper size (8-1/2 by 11 inches) is preferred.

**Fee:**

The holder of a Type II API DMF must pay a onetime

CEP: Certification of Substances Division (DCEP) within EDQM

ASMF: Working Group of EMA, CHMP, CVMP, CMDh, CMDv, EDQM

**Content:**

Contains two parts:

a. Applicant part (Open part): contains the information that the ASMF holder regards as non-confidential to the applicant/ MA holder.

b. Restricted part (Closed part): contains the information that the ASMF holder regards as confidential.

EU Authority (EMEA) does not give DMF number. If the API is in EU. Pharmacopoeia, EMEA can accept EDMF filing and issue a "Certificate of Suitability" for it.

**Format and Assembly:**

- Paper and electronic format are accepted. Electronic format is preferred.
- Filed in EU - CTD format.

**CEP:**

**Paper format:**

Module 1

- a. EDQM application form including signed declarations.
- b. Cover letter.

Module 2

- a. QOS, in word format, prepared using the EDQM template.
- b. CV of the expert.

Module 3

Technical documentation in accordance with the CTD format.

**Electronic format:**

3 possible formats are accepted for electronic submissions:

eCTD, or NEES, or A simple PDF file.

**ASMF:** CTD format is applicable.

- a. Submission letter and administrative details form, Letter of access, Applicant s part, Restricted part
- b. Separate or combined QOS for the applicant s and restricted parts
- c. Copy of the expert s CV
- d. Copy of the proposed ASMF holder s drug substance specification (3.2.S.4.1)

**Fee:**

**CEP**

DMF fee as described under Generic Drug User Fee Amendments of 2012 (GDUFA).

DMF fee only applies for Type II DMFs for drug substances (APIs) used to support ANDAs. There are no fees for any other type of DMF or for Type II DMFs used to support NDA or INDs.

**Type II DMF fee for fiscal year (FY) 2013: \$21,340**

**Letter of authorization (LOA):**

A written statement by the holder or designated agent or representative permitting FDA to refer to information in the DMF in support of another person's submission.

**Language:**

English

**Validity:**

Not Applicable.

**Delivery:**

Food and drug administration  
Centre for drug evaluation and research  
Central document room  
5901-B Ammendale road  
Beltsville MD 20705-1266

- For New application - **3000 €**
- For revision of existing CEP -**500 €** (Simple notification).

**ASMF**

- For New application - **£5006**
- Notification of Changes (Variation) - **£257**

**Letter of access (LOA):**

The ASMF holder should give permission to the competent authorities/EMA to assess the data in the ASMF in relation to a specific MAA/MAV, in the form of a Letter of Access.

**Language:**

One of the two official languages of the Council of Europe: English or French (preferably in English)

**Validity:**

CEP: Valid for 5 years from the date of first issue and valid indefinitely following the 5-year renewal.

**Delivery :**

CEP:  
European Directorate for the Quality of Medicines and Healthcare Council of Europe  
Division certification of substances  
7, allée Kastner, CS 30026, F-67081,  
Strasbourg, France.

**ASMF:**

European Medicines Agency  
CPMP, 7 Westferry Circus, Canary Wharf,  
London, E 14, 4 HB, U.K.

**CONCLUSION:**

Active Pharmaceutical Ingredients are not only the heart and brain of drug products, but are also crucial to the regulatory filing success of drug applications. From the current scenario of the regulatory requirements, it is important to keep in mind that FDA is scrutinizing DMFs more closely than ever before. With the considerable increase in the number of DMF submissions and FDA's interest in keeping track of such filings electronically and FDA more stringently insists on uniformity in DMF submissions in accordance with its current administrative guidelines. Thus, more than ever before, it is important to consult FDA's current DMF guidance when preparing DMF submissions and to adhere to FDA's requirements for various types of DMF filings. Moreover, to maintain the active status of a DMF and ensure that it is not retired by FDA making it unavailable for review, it is important to regularly comply with FDA's Annual Report requirement. At the end, the Drug Master File is a critical document used to support a drug application. Deficiencies in the Drug Master File can result in the delay of approval of drug applications. It is important that the DMF be filed in a timely manner and that the standards used to compete it are of the same quality as the actual drug application.

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