World Inventia Publishers

Journal of Pharma Research

http://www.jprinfo.com/

Vol. 6, Issue 5, 2017 ISSN: 2319-5622 USA CODEN: JPROK3

Review Article

# PROCESSING AND SUBMISSION OF DRUG MASTER FILE

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**Received on: 24-04-2017; Revised and Accepted on: 16-05-2017**

## *ABSTRACT*

*A Drug Master File is a confidential document used to provide detailed information about facilities, processes or articles used in the manufacturing process, packaging and storing of one or more human drug. The Drug Master File may be utilized either by the holder who establishes the file, or by one or more additional parties in support of their application. The Drug Master File filing allows a firm to protect its intellectual property from its partner while complying with regulatory requirements for disclosure of processing details. The review includes various types of Drug Master Files, the important aspects in filing and processing.*

***KEYWORDS:*** *Drug Master File, Holder, Intellectual property, Regulatory requirements.*

## INTRODUCTION

Drug Master File or DMF is a document prepared by a pharmaceutical manufacturer and solely at its discretion to the appropriate regulatory authority in the intended drug market. Typically, a DMF is filed when two or more firms work in partnership on developing or manufacturing a drug product. The DMF filing allows a firm to protect its intellectual property from its partner while complying with regulatory requirements for disclosure of processing details [1].

**Description:**

Drug Master File (DMF) is a document containing complete information on an Active Pharmaceutical Ingredient (API) or finished drug dosage form. It is known as European Drug Master File (EDMF) or Active Substance Master File (ASMF) and US-Drug Master File (US-DMF) in Europe and United States respectively. 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.

**Definition:**

DMF 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. Drug product information or other non-CMC information may be filed in a DMF. (Or) 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 drug [1].

Generally DMF's have two parts:

(1) Applicant's Part: This contains non confidential information that the license holder needs to assess for the marketing.

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(2) Restricted Part: This contains confidential information about the manufacturing procedure that only needs to be disclosed to the authorities.

**Types of DMF's:**

Originally there are five types, they are: [2]

I. Manufacturing Plant Information
II. Drug Substance, Drug Product, Intermediates and material used in their manufacture
III. Packaging
IV. Excipients, Colorant, Flavour, Essence or Materials Used in the preparation
V. Other Sterile Manufacturing Plants, Biotech Contract facilities, clinical, to x

**Current types of DMF's:**

Now four types are present, they are: [2]

I. Drug Substance, Drug Product, Intermediates and material used in their manufacture
II. Packaging Material
III. Excipients, Colorant, Flavour, Essence, or Material Used in Their
IV. Preparation
V. Other Sterile Manufacturing Plants, Biotech Contract facilities, clinical.

**Types of drug Master file:** [3, 4]

***Type I:*** Manufacturing Site, Facilities, Operating Procedures, and Personnel Recommended for a person outside of the United States to assist FDA in conducting on site inspections of their manufacturing facilities.

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

1. Quality controls
   i. Inputs (raw/packaging Materials)
   ii. Intermediates and in-process
   iii. Finished drug substance

2. Validations
3. Stability data
4. Impurities
5. Packaging and labelling

In general, be limited to a single drug intermediate, drug substance, drug product or type of material used in their preparation. Detailed guidance on what should be included in a Type II DMF for Drug Substances and intermediates may be found in the following guidelines:

i. Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances.
ii. Guideline for the Format and Content of Chemistry, Manufacturing and Controls selection of an Application.

***Type II*** DMF is submitted for a Drug Product the applicant/sponsor should follow the guidance provided in the following guidelines:

i. Guideline for the Format and Content of the Chemistry, Manufacturing and Controls Selection of an Application.
ii. Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products.
iii. Guidelines for Submitting Samples and Analytical Data for Method Validation.

***Type III:*** Packaging Material should be identified by the intended use, components, composition and controls for its release. The name of the suppliers or fabricators of the components used in preparing the packing material and the acceptance specifications should also be given. Data supporting the acceptability of the packing material for its intended use should also be submitted as outlined in the "Guideline for Submitting Documentation for Packing for Human Drugs and Biologics."

***Type IV:*** Excipient, Colorant, Flavour, Essence, or Material Used in Their Preparation Each additive should be identified and characterized by its method of manufacture, release specifications, and testing methods. Usually the official compendia and FDA regulations for color additives (21 CFR parts 70 through 82), direct food additives (21 CFR parts 170 through 173), indirect food additives (21 CFR parts 174 through 178) and food substances (21 CFR parts 181 through 186) may be used as sources for release tests, specifications and safety. Guidelines suggested for Type II DMF may be helpful for preparing a Type IV DMF.

***Type V:*** Other Sterile Manufacturing Plants, Biotech Contract facilities, clinical, tox.

**DMF's in various countries:** [4, 5]

***United States DMF's:*** In the United States, DMFs are submitted to the [Food and Drug Administration] (FDA).

The Main Objective of the DMF is to support regulatory requirements and to prove the quality, safety and efficacy of the medicinal product for obtaining an [Investigational New Drug] Application (IND), a [New Drug Application] (NDA), as an [Abbreviated New Drug Application] (ANDA), another DMF, or an Export Application.

**In United States there are 5 types of Drug Master File:**

***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

**European DMF's:** [6-12]

Established in 1989-1991Revised in 2005 and became ASMF (Active Substance Master File) after implementation of CTD in EU Applicable only to active substances Has been divided into 2 parts.

An applicant's part and an ASM Restricted Part. 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 theapplicant's part and the ASM Restricted Part of the DMF are submitted to the authorities. Applicant's part of a DMF – opening part Established in 1989-1991.

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 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.

ASM Restricted Part of DMF – closing 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.

Canadian DMF's: Since 1994 (1st guide), new revision published and under comment • Canadian DMF: division of format into Sponsor's (Open) and Restricted (Closed) part for DMFs type I and IV

**Canadian DMFs:** 4 types

***Type I:*** Drug substance or intermediate in the manufacture of DS

***Type II:*** Container-closure systems or components

***Type III:*** Excipients, colorants, flavours and other additives Type IV-Dosage forms and drug product intermediates (e.g. blend of drug substance and excipients

**Filing of DMF:** There is no legal or regulatory requirement to file a DMF. A DMF may be filed to provide Chemistry, Manufacturing and Controls (CMC) information that the FDA reviews.

**Reasons/Need for Filing:**

To maintain confidentiality of proprietary information (e.g., Manufacturing procedure) of the holder. To permit review of information byreviewers in the Center for Drug Evaluation and Research (CDER) to support applications submitted by one or more applicants. Submissions Required For Filing A DMF:

A. Transmittal letter
1) Original Submissions
2) Amendments

B. Administrative information
1) Original Submissions
2) Amendments

C. Drug Master File contents

**A) Transmittal letters:**

The following should be included

***1)Original Submissions:***

• Identification of Submission: Original, the type of DMF and its subject.
• Identification of the applications, if known that the DMF is intended to support, including the name and address of each sponsor, applicant or the holder and all relevant document holders.
• Signature of the holder or authorized representative.
• Type written name and title of the signer.

***2)Amendments:***

• Identification of submission:
• Amendment, the DMF number, type of DMF and the subject of amendment.
• A description of the purpose of the submission, e.g., update, revised formula or revised process.
• Signature of the holder or the authorized representative.
• Type written name and title of the signer.

**B) Administrative Information:**

Should include the following;

***1) Original Submission:***

a) Name and addresses of the following DMF holder.
b) Corporate headquarters.
c) Manufacturing/Processing facilities.
d) Contact for FDA correspondence.
e) Agent(s) if any.

• The specific responsibilities of each person listed in any of the categories mentioned just above.
• 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:***
Name of DMF holder.
DMF number.

Name and address for correspondence.

Affected section and/or page numbers of the DMF.

The name and address of each person whose IND, NDA, ANDA, DMF, or Export Application relies on the subject of the amendment for support.

**Drug Master File Contents:** [10-12]

It includes Types of DMF's and General Information and Suggestions (Environmental Assessment, Stability, Format, Assembly and Delivery).

***General Information and Suggestions:*** Type II, III and IV DMF's should contain a commitment by the firm that its facilities will be operated in compliance with applicable environmental laws. If a completed environmental assessment is needed see, 21 CFR part 25. Stability study design, data, interpretation and other information should be submitted, when applicable as outlined in the "Guideline for Submitting the Documentation for the Stability of Human Drugs and Biologics." An original and duplicate copy is to be submitted for all DMF submissions. The original and duplicate copy must be collated, fully assembled and individually jacketed. Standard paper size is preferred (e.g., 8-1/2 by 11 inches for US DMF).

DMF submissions and Correspondence should be addressed as follows: Drug Master File Staff Food and Drug Administration 5901-B Amendable Rd. Beltsville, MD 20705-1266 Delivery charges for the above address must be prepaid.

**DMF Filing Process:** [12, 13]
• Two copies of the Drug Master File with one signed original of the covering letter and other necessary documents are send to the FDA's Central Drug Evaluation and Research (CDRL).
• The Drug Master File staff will audit the nontechnical information for completeness and adequacy for submission. If the key elements are missing, the staff will contact the proposed holder to try to obtain the necessary documents in order to file the DMF.
• Once the DMFs are determined to be acceptable for filing, the document room staffs assigns a DMF number and a letter is sent to the contact person listed in the DMF.

**Steps for Filing a DMF:** [8, 9]
1. Set the document margins at 3/4 inch for the left (at least) and 1/2 inch for the right.
2. Print the transmittal page, administrative information and DMF information on standard letter-size paper. If a larger sheet of paper is required for a diagram or schematic, fold the sheet and attach it to a letter-sized page in a manner that will allow for the page to be opened and refolded. At a maximum, each volume of a DMF should be no more than 2 inches thick.
3. Number multiple volumes for one submission according to the total number of volumes (if more than one). (For example, 1 of 3, 2 of 3, etc.)
4. Sign all documents requiring signature (only if you are the DMF holder or authorized representative).
5. Copy and collate the document; FDA requires you submit both.
6. Punch documents with a standard hole-punch.
7. Cover each original and copy of each volume with a document jacket. Prepare the submission for shipping and mail to:

Drug Master File Staff
Food and Drug Administration
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

DMF File Format: The DMF must meet the format requirements. The DMF is submitted as Original and Duplicate jackets, collated, assembled, paginated, and jacketed, using covers obtained from the government printing office and are specifically provided for the DMFs. Multiple volumes are numbered, and the paper must be standard paper size. The DMF must be submitted in two copies, one with a blue cover and one with a red cover. The jacket covers are purchased from the government printing office.

Processing and Reviewing Policies: Policies Related to Processing Drug Master Files

• An original DMF submission willbeexamined on receipt to determine whether it meets minimum requirements for format and content. If the submission is administratively acceptable, FDA will acknowledge its receipt and assign it a DMF number.
• If the submission is administratively incomplete or inadequate, it will be returned to the submitter with a letter of explanation from the Drug Master File Staff, and it will not be assigned a DMF number.
• Drug Master File Review
• A DMF is never Approved or Disapproved.
• A DMF is reviewed for Administrative content when it is received. This may take 2-3 weeks.
• If the DMF is acceptable from an administrative point of view an Acknowledgement Letter will be issued, notifying the holder of the DMF number.
• If FDA reviewers find deficiencies in the information provided in a DMF, a letter describing the deficiencies is sent to the DMF holder. At the same time, FDA will notify the person who relies on the information in the deficient DMF that additional information is needed in the supporting DMF.
• The general subject of the deficiency is identified, but details of the deficiency are disclosed only to the DMF holder. When the holder submits the requested information to the DMF in response to the agency's deficiency letter, the holder should also send a copy of the accompanying transmittal letter to the affected persons relying on the DMF and to the FDA reviewing division that identified the deficiencies. The transmittal letter will provide notice that the deficiencies have been addressed.

**• The DMF will be reviewed for technicalinformation only when all of the following events occur:** [10-16]

1. The DMF holder submits a Letter of Authorization (LOA) in two copies to the FDA. This LOA must contain the DMF number.
2. The holder sends a copy of the LOA to the authorized party (customer).
3. The customer submits an application to the FDA that contains a copy of the LOA.

Public availability of the information and data in a DMF is determined under 21 CFR Part 20, 21 CFR 314.420(e) and 21 CFR 314.430.

Holder Obligations: Any change or addition, including a change in authorization related to specific customers Should be submitted in duplicate and adequate cross referenced to previous submission(s). The reference should include date(s), volume(s), section(s) and/or page number(s) affected.

Notice Required for Changes to a DMF: A holder must notify each affected applicant/sponsor who has referenced its DMF of any pertinent change in the DMF (21 CFR 314. 420 (c)). Notice should be provided well before making the change in order to permit the sponsor/applicant to supplement or amend any affected application(s) as needed.

**Annual Update:** The holder should provide an annual report on the anniversary date of the original submission. All changes and additional information incorporated into the DMF since the previous annual report on the subject matter of the DMF should be provided. If the subjectmatter of the DMF is unchanged, the DMF holderprovide a statement that the subject matter of the DMF is current.

Electronic Filing of DMF's and CTD:
• Companies are encouraged to submit their DMF's in electronic form, including updating current paper DMF's.
• All applications to CDER, including DMF's that are submitted in electronic format MUST be in ECTD format, unless a waiver is granted. Waivers are granted for DMF's. • CTD (Common Technical Document) format not required for paper DMFs, although acceptable. Required for electronic DMFs
• DMFs originally submitted in paper can be resubmitted as electronic DMFs. Entire DMF must be resubmitted.
• Once a DMF has been submitted in electronic form NO paper documents (including LOAs) to be submitted.

• Module 1 is required for all eCTD submissions, as it contains the necessary administrative information to identify the DMF.
• Module 1 should contain the following information Section 1.2: Cover Letter and Statement of Commitment Section 1.3: Administrative Information.
• Electronic signatures are accepted for electronic DMF's.

## CONCLUSION

A Drug Master File is a confidential document used to provide detailed information about facilities, processes or articles used in the manufacturing process, packaging and storing of one or more human drug. The Drug Master File may be utilized either by the holder who establishes the file, or by one or more additional parties in support of their application. The Drug Master File filing allows a firm to protect its intellectual property from its partner while complying with regulatory requirements for disclosure of processing details. The review includes various types of Drug Master Files, the important aspects in filing and processing.

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**How to cite this article:**

B. Priyanka Reddy et al. PROCESSING AND SUBMISSION OF DRUG MASTER FILE. J Pharm Res 2017;6(5):64-67.

**Conflict of interest:** The authors have declared that no conflict of interest exists.

**Source of support: Nil**