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A Review on DMF Filing in EU, USA and Australia

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Abstract
Drug master file (DMF) is highly confidential information describing the aspect elements and error free information regarding API and finished dosage form. It consists of two parts. One is open part and another one is restricted part. Open part contains the information about the quality of drug product by the licence holder. Prohibited part which is Closed part which is protect the secret and unofficial information about manufacturing of product which is relived In front of respect regulatory authorities. When two or more persons involved in manufacturing of pharmaceutical. The drug master file contains overall information about product quality, maturing stability and purity of the medicaments. Drug master file gives the support to the IND (Investigational New Drug) application, ANDA (Abbreviated New Drug Application), NDA. Every country has its own drug filling format and content. The current observation is different countries drug master filing, content of drug master filing and format of the filing respect countries.

Keywords: API, IND, NDA, Investigational New Drug, Abbreviated New Drug Application, Drug Master File, DMF

1. Introduction

Drug master file filling is permitting the condense to secure the copy rights and patent rights from its partners while follow the specific regulatory needs for reporting of processing details. Drug master file contains the accurate information about resources, process or objectives used in manufacturing, processing, packing and keeping of human used drug product. Drug master file is a document prepared by pharmaceutical manufacturer and submitted to respect regulatory agency for in the considered drug market. Drug master file which is assist to an IND (Investigational New Drug application), NDA (New Drug Application), ANDA (Abbreviated New Drug Application), and another DMF. Drug master file is provided in 21CFR314.420. DMF contains the two sections:

Applicant's Part: Which has information regarding licence holder assessment of quality, licence applications and amendment applications.

Restricted Part: Which has secured information that is revealed to the respected regulatory authorities.

Drug master file filling allows a firm to protect its intellectual property from its partner. It doesn't come under the regulatory status and DMFs entered into database as per their types.

2. DMF Filing in USFDA

The submission of DMF in USFDA provides the secured information regarding facilities, processes or objectives used in manufacturing. The manufacturer can directly submit the product related confidential information to USFDA about information of drug, excipients, and packing material with revealing the information to their customers. But manufacturer should reveal the product specifications and general information of product to their customers.

US DMF Types

Type 1: Operation site, manufacturing resources, procedure of operation and man power.
Type 2: Drug substance information, drug substance intermediate, materials used in their preparation and drug product.
Type 3: Packing.
Type 4: Excipients, colorants, flavour, essence and material used in the preparation.
Type 5: FDA accepted reference information used for sterile manufacturing plants and contract facilities for biotech products.

2.1. DMF Filing FDA

DMF Filling: Two copies of drug master files send to the FDA by holder. DMF should reviewed by only central document room staff for administrative purpose holders entered into database, assigned then a specific number and acknowledgment letter sent to holder. ADMF neither approved or dis approved.

Filing Procedure in the US

Two copies of DMF with one original cover letter are submitted.
↓
Sent to FDA central drug evaluation and research (CDER).
↓
DMF staff should be evaluated all non-technical information to completeness of submission.
↓
If necessary, elements are missed then staff will inform to the holder to obtain those necessary documents to file the DMF.
↓
DMFs are determined and accepted.
↓
Assigns a DMF number by document room staff.
↓
Finally, letter is sent to the respect contact person.

Letter of Authorization

Holder must submit the two copies of LOA to DMF and a copy to the applicant. Drug master file will be review only when it is referenced in an application or another DMF. It is very mandatory at the review of DMF.

- The applicant defer a copy of Letter of authorisation along with their requisition.
- LOA is the only system trigger to DMF analysis by FDA.

DMF Review Procedure

DMF only reviews if it is referenced in an application or another DMF.

- If reviewer found any inadequacy in the DMF, the defects detailed in a letter to the holder.
- The applicant will be notifying the defect exist but not nature of inadequacy is not communicated to the applicant.

2.2. Format of DMF FDA

- DMF should be filled in electronically and in a common technical document. The appealable information should be transparent and unambiguous.
- Text and tables should be prepared by using margins that allows the documented to be printed on both A4 paper and 8.5 × 11 inch paper. The left-hand margin should be large and information should not be obscured by method of binding. Time New Roman, 12-point font should be endorsed for description text.

3. DMF Filing in Europe

In Europe, drug master file referred as active substance master file or European drug master file EDMF. It was established in 1989-91 and it was corrected in 2005 to became ASMF (Active Substance Master File). European drug master file describes the three types of active ingredients.

(1) New active ingredient
(2) Off patent ingredient
(3) Pharmacopoeia ingredient

DMF is only applicable to active ingredients. The design of drug master file in Europe to support regulatory needs of drug products to improve quality, efficacy and safety, it leads to claim market authorization.

EDMF Types

Applicant Section

Application section should be provided by the applicant with adequate information to enable the latter to take authority for analysis of the suitability of the active medicaments instructions to control the nature of the drug substance. This section generally composes with outline of the manufacturing methods such as information on potential debasements deriving from the manufacturing site, information on toxicity, particular impurities. This section of the EDMF will be integrated directly into the market authorisation which is redirected on to the suitable regulatory authority.

Restricted Section

The restriction section of the EDMF should include complete information of steps involved in manufacturing method, such as reaction conditions, temperature, validation and evaluation of certain crucial steps of manufacturing techniques and quality control such details should be passed to the suitable regulatory authority only.

EDMF Content

EDMF should include complete scientific information of drug product market authorisation in European union member states. EDMF is connect with veterinary medicinal products, it includes name,

description, nomenclature, site of action substance, outline of manufacturing process, quality control, batch analysis, stability studies and impurities.

3.1. EDMF Filing Procedure

Applicant's part of DMF is submitted to the applicant which is provided by API manufacturer, it includes both applicant part and restricted part then it will change as marketing authorisation application then it will be submitted to authorities. It allows the applicant to take responsibilities of medicinal products such as quality, safety, and efficacy. It cannot be used in biological products. A copy of latest version of applicant's part, a copy of quality summary of product, a copy of letter of authorisation to marketing authorization holder by applicant's holder.

DMF Filling Procedure in EU

API manufacture → Create a applicants DMF

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Provides the applicant part DMF to applicant which is contains both applicant and restricted part.

↓

Then it will be a part of marketing authorisation application.

↓

Then it will be submitted to the authority.

4. DMF Filing in Australia

Main Content

- The purpose of DMF is to submission to the Food and Drug Administration (FDA) that may be used to provide perfect detailed information about facilities, processes or articles used in the manufacturing, processing, packaging and storage of one or more human drugs.
- The submission of a DMF is not required by law or FDA regulation; it is submitted at the discretion of the DMF holder.
- The DMF contains fact and complete information on drug products chemistry, manufacture, stability, purity, impurity, profile packaging and the cGMP status of any human drug product.
- The present work gives the detailed information on how file drug master file in Australia.
- DMF filing was done through NDS (New Drug Submission) for both drugs and biologic products, whereas in Australia different application processes and regulatory requirement apply depends on the type of therapeutic goods that is applied.

Types of Drug Master Files (DMFs)

Type 2: Drug substance and substance intermediate.
Type 3: Packaging material.
Type 4: Inactive substance, colorant, flavour, essence or material used in their preparation.
Type 5: FDA accepted correct reference information.

Type 2: Drug Substance, Drug Substance Intermediate

The Generic Drug User Fee Amendments (GDUFA) include provisions for DMF fees, a complete assessment, and communications with DMF holders for Type 2 DMFs for drug substances (API) used to

support ANDs. These provisions do not apply to others types of DMFs or to Type 2 DMFs used to exclusively support NDAs or INDs.

Type 3: Packaging Material

- FDA does not require that packaging information be submitted in a DMF.
- NDA, ANDA OR BLA applicants or IND sponsors who receive information from the manufacturer of a packaging component or material of construction may include that information directly in the application.
- If, however, the manufacturer does not wish to share information with the applicant or sponsor. They may be placed in a Type 3 DMF and incorporated into the application by a manufacturers letter authorizing reference the DMF.

Type 4: Inactive Substance, Colorant, Flavour, Essence or Material used in their Preparation

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

Additional Sources

Non-clinical studies for the safety evolution of pharmaceutical inactive substance:

- This document provides guidance regarding development of safety profiles to support use of new excipients as components of drug or biological products.
- It is intended for use by reviews within both the Centre of Drug Evaluation and Research (CDER) and the centre for biologics.

Type 5: FDA Accepted Reference Information

- This MAPP will assist the product quality microbiology reviewer in the centre for drug evaluation of research (CDER) by providing the expected location in applications submitted in the CTD-Q format.

4.1. Submitting a Drug Master File (DMF)

- TGAs prefer to submit the DMF in electronic common technical document (eCTD) or non-eCTD electronic submission format. the electronic submissions web page provides information and describes the requirements on how to submit these files to the TGA. visit submitting data in the eCTD format and submitting data in the eCTD format and submitting data in the needed format for further information.
- Once the DMF is submitted in eCTD format, subsequent submissions should be in the eCTD format in order to maintain a lifecycle. If not submitting in eCTD or NeeS, a DMF administrative details form must be filled out.

4.2. Submission of DMF Administrative Details Form

- This form is for stakeholders that are not submitting in eCTD or the drug master file (DMF). Administrative details form is to be competed electronically. Complete this form when submitting a new DMF to TGA (Therapeutic Goods Administration), or when updating an existing DMF already held by the TGA. Complete all questions and press the ‘submit’ button at the end of the form.
- Once the DMF is received by the TGA, an acknowledgment email that includes the TGA reference number will be sent to the DMF holder within 6 weeks.

Australia DMF Filing System

(1) Pre-submission
(2) Submission
(3) First round of assessment
(4) Consolidated section 32 request
(5) Second round assessment
(6) Expert advisory review
(7) Decision
(8) Post decision

(1) Pre-submission

The pre-submission phase applies into Category 1 and Category 2 applications, excluding requests for additional trade names. Pre-submission form provides the TGA (Therapeutic Goods Administration) with the necessary information on the scope and scale of an application to arrange appropriate resourcing for the processing and evaluation of the application.

(2) Submission

The TGA sends a letter to the applicant identifying whether the application has been considered effective and accepted for evaluation or considered.

(3) First Round of Assessment

In this phase, applicants send 3 letters which includes:

- A consolidated section 31 request for information or documents if required.
- Copies of the first-round assessment reports prepared by the quality, nonclinical, clinical and risk management plan (RMP) evaluators.

(4) Consolidated Section 31 Request Response

- Applicants should send TGA(Therapeutic goods administration) for response.
- Any consolidated section 31 request for information or documents.

(5) Second Round Assessment

- All second-round assessment reports should be completed.

(6) Expert Advisory Review

- The TGA should notify the applicant of the advice received from the adversary committee.

(7) Decision

- The decision is made for approval or rejection of the application for a new registration or for a variation to a registration and the decision letter is send to the applicant.

(8) Post Decision

- Administrative and regulatory activities should be completed.
- Payments are finalised by the ARTG (Australian Register of Therapeutic Goods) entry is finalised.

Conclusion

Content, format and filling procedure for drug master file is used to obtain market authorization. Drug master file contains complete and detailed information about active pharmaceutical ingredient, stability, purity, chemistry, packing of drugs or excipients. The main objective of DMF is to support regulatory aspects of drug product for quality, safety and efficacy for market authorization approval.

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