International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2079-2084 www.ijprajournal.com ISSN: 2249-7781

# Compressive Review of Drug Master File(Dmf) in Regulatory Affair

Ms.Amruta Dipak Pawara*, Mr. Atish B. Velhal, Prof. (Dr) V.K.Redasani. Ms.Komal Ramesh Lohar Ms. Divya Ravindra Pawar
*Yashoda Shikshan Prasarak Mandal,Yashoda Technical Campus, Faculty of Pharmacy (B.Pharmacy),Wadhe, Satara – 415001*

Submitted: 25-05-2023 Accepted: 05-06-2023

**ABSTRACT**
A Drug Master File (DMF) is highly confidential information that describes secondary elements and error-free information about the final API and dosage forms. It consists of two parts. One is the open side and the other is the restricted side. The open part contains information about the quality of the drug for the holder of the registration certificate. The restricted section, a closed section that protects confidential and unofficial product manufacturing information, is repeated before respected regulatory authorities. When several people are involved in the production of a drug. The drug master file contains general information about the product quality, shelf life and purity of the drug. The Drug Master File supports Investigational New Drug (IND) applications, Abbreviated New Drug Applications (ANDA) applications, and NDA applications. All country has its personal medication refill format and content. In the current competition, different countries apply for Master of Medicine, and the content and format of Master of Medicine application respects the country. This review revealed about DMF , it's parts contents , role & it's mechanism of filling procedure.

**KEYWORDS –** Drug Master File , DMF Types , Mechanism of DMF , DMF in Various Country , DMF Filling in Various Country

## I. INTRODUCTION

A Drug Master File (DMF) is a document prepared by a drug or excipient manufacturer and submitted to the regulatory authorities of the target market. It contains information on the chemistry, stability, purity, excipient profile and packaging, as well as cGMP status of each API. (3)

It is not a mandatory requirement for regulatory bodies like DMF USFDA, European Medicines Agency (EMA) etc. DMFs are used only to support marketing applications such as NDAs, ANDAs, and Biologics License Applications (BLAs). By using the DMF, applicants can comply with legal requirements while maintaining the confidentiality of information.(4)

**Role of DMF :-**

- The DMF documents the purity, strength and suitability of the drugs in the Chemistry, Manufacturing and Control (CMC) department.
- Drug registration/approval document support.
- To protect Confidential and Proprietary Information.(2)

**Current Types of DMF's:**
Now four types are present, they are:

I. Pharmaceutical products, formulations, intermediates and materialsused in production
II. Packaging Material
III. Excipients, Colorant, Flavour, Substance or Material Used in theirPreparation
IV. Other Sterile Plants, Biotech Contracts, clinics, toxins(18)

**DMF PROCEDURE:-**

- Module-1

Regional & Administrative Information

- Module-2

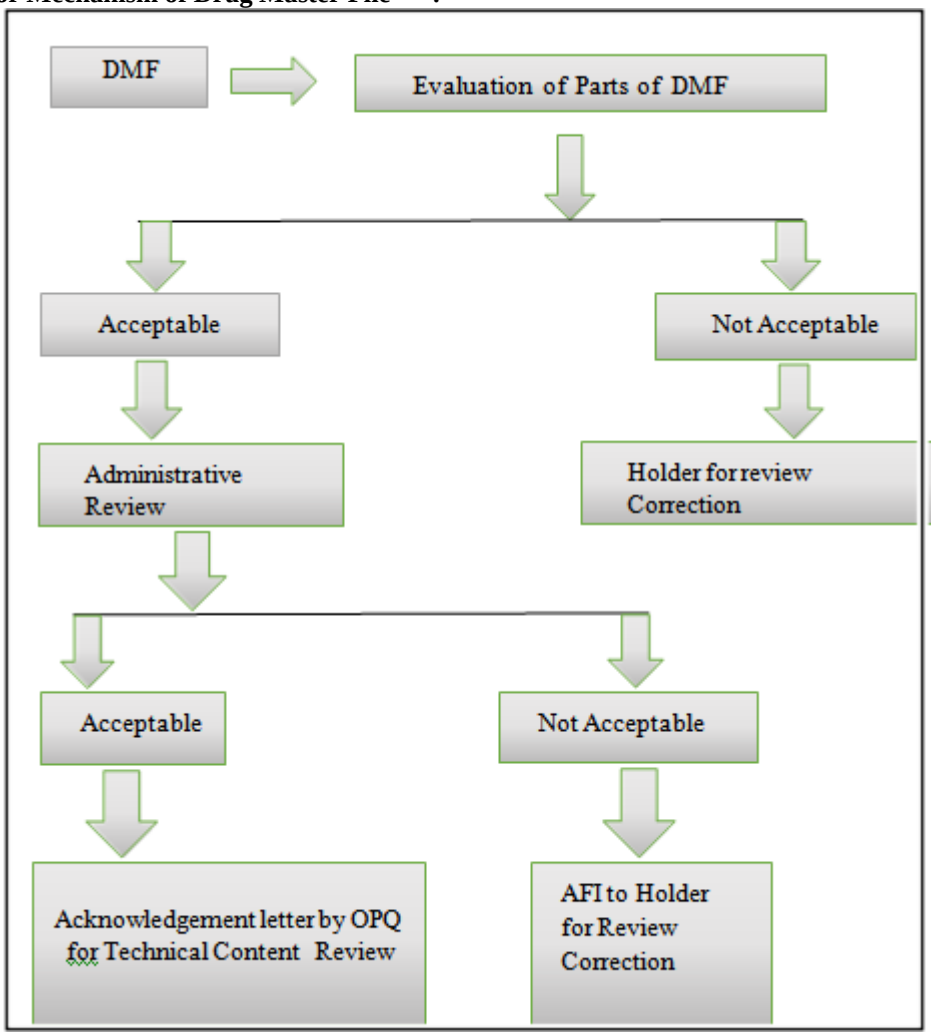
QUALITY OVERALL SUMMARY (QOS)

- Module-3

QUALITY (1)

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2079-2084 www.ijprajournal.com ISSN: 2249-7781

**Flow chart for Mechanism of Drug Master File[3] :-**




**DMF are classified into 2 parts -**

1. Open part (Applicant's part):
Production, possible additives, production systems, etc.

2. Closed Part (Restricted part):
It includes extractions, validations, processes, solvents used, reactions, temperatures, conditions, critical manufacturing steps and more. Contains API manufacturing confidential information such as.[16]

**DMF in Various Country :-**

**1. India** –

There are no guidelines for drug master documents issued by the Central Drug Standards Organization. The DMF format is commonly used in the United States to deliver confidential data about drugs and pharmaceuticals to regulatory authorities in India. A DMF can be sent for bulk or prescription drugs. [7]

**2. United States** –

In the United States, Drug Master File are submitted to the USFDA. The primary purpose of a DMF is to support regulatory requirements and demonstrate the quality, safety and efficacy of pharmaceutical products to receive IND applications, NDA applications, ANDA applications, other DMFs or export applications.[14]

**Types of DMF in United States :-**

Type I - Manufacturing Site, Facilities, Working Procedures, and Personnel. This is no longer accepted by the FDA.

Type II – Pharmaceutical products, intermediats

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2079-2084 www.ijprajournal.com ISSN: 2249-7781

and susbstances or agents used in their manufacture.
Type III – Packaging
Type IV – Excipients, Colors, Flavors, Essences or Ingredients Used in Preparation. Type V – FDA approved references are Used for sterile manufacturing.[17]

**United States DMF Filling System :-**

Latest Updates on USFDA DMF You can submit an e-CTD through the Electronic Submission Gateway (ESG). The deadline to transition from paper to e- CTD format is May 5, 2017, and all NDA, ANDA, BLA and master file submissionsmust be submitted in eCTD format.[5]

**Comparative Study Of DMF in India and US[7] :-**

| Requirement | US FDA | India |
|---|---|---|
| **RegulatoryAuthority** | Food And Drug Administration (FDA) | Central Drug and Standard ControlOrganization (CDSCO) |
| **Use Of DMF in Support of Application** | IND, NDA,ANDA | MAA |
| **Provide Information** | Drug Substance Intermediate, Drug Products , Flavors Etc | API, Drug Products, Flavors, Colorants, Etc. |
| **Fees For Assessment** | ANDA Case Only | No Fee |
| **Forms For DMFFilling** | Not ApplicableExcept Type Ii DMF, Form FDA 3794 | Not Applicable |
| **Letter Of Authorization** | Applicable | Applicable |
| **Electronic Submission** | eCTD | eCTD |

## 3. Australia –

The purpose of the Drug Master File is to provide the Food and Drug Administration (FDA) with detailed information about the facilities, processes, or materials used in the manufacture, processing, packaging, and storage of one or moredrugs for human use. Providing a DMF is not essential through law or FDA regulations. Awarded at the pleasure of the DMF owner. Current work provides detailed information on how drug master files are submitted in Australia.[6]

**Types of DMF in Australia :-**

**Type 2**: Drug substance and substance intermediate.
**Type 3**: Packaging material.
**Type 4**: Inactive substance, colorant, flavour, essence or ingredients used in theirpreparation.
**Type 5**: FDA accepted correct reference information.[6]

**Australia DMF Filling system:-**

The Australian DMF registration system contain of the following steps.

- Phase 1: Pre - Shipment
- Phase 2: Transmission phase
- Phase 3: First step in evaluation
- Phase 4: Response period for combined applicaton under section 31
- Phase 5: Second evaluation period
- Phase 6: Evaluation period of expert advice
- Phase 7: The decision-making phase
- Phase 8: Positioning[9]

## 4. Canada –

A drug master file is a reference file that deliver data about particular procedures or constituents used in the manufacture, processing and packaging of pharmaceutical products. DMF is useful for providing information to healthcare organizations where that information is proprietary and not existing to the formulary manufacturer or

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2079-2084 www.ijprajournal.com ISSN: 2249-7781

participating sponsors.[10]

**Types of DMF in Canada -**

**A) Type 1-** Active Substance Master File (ASMF)

For pharmaceuticals, it includes API in the manufacturing of a drug substance.

For biologics, it includes process intermediates, vaccines antigens, excipient ofbiological origin.

**b) Type 2-** Container Closure System Master File (CCSMF)

**c) Type 3-** Excipient Master File (EMF)

Includes information related to excipient, coating ingredients, colorants, flavorsand other additives.

**d) Type 4-** Dosage Form Master File (DFMF)

Includes information related to dosage form & their intermediates[12]

**Comparison of DMF's of Canada and Australia[8] :-**

| DMF Requirement | CANADA | AUSTRALIA |
|---|---|---|
| **Health Authority** | Health Canada | Australian government- TGA |
| **Definition of DMF** | A DMF is aninformative definition for a particular process or component used in the manufacture, processing and packaging of pharmaceutical products. | In the case of anAPI used by a producer for a medicine whose origin is a thirdparty manufacturer, dataabout its fabrication, quality control and stability can be presented by a DMF. |
| **Types of DMF** | Type I-Active Substance Master Files (ASMFs) Type II-Container Closure System Master Files (CCS MFs) Type III-Excipient Master Files(ExcipientMFs) Type IV-Dosage Form Master | No type for drugmaster file. |
| **Format** | MFs must followthe filing and formatting requirements outlined in the Guidance Document Preparation ofDrug Regulatory Activities in the "Non-eCTD Electronic-Only (NeeS)" Format. | The currently approved form is the CTD format. |
| **Letter of Authorization** | Letter of Access is required. | Letter of Access is required. |

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2079-2084 www.ijprajournal.com ISSN: 2249-7781

| | | |
|---|---|---|
| **Fees** | The revised fee structure increases the cost of filing a new DMF to $424 (Canadian), and the cost of filing a Letters of Access to $191(Canadian). | New chemicalentity is $46,900. No cost for filing aletter of Access. |
| **Updation** | Bi- annually | Five years once |

**5. EU –**

The European DMF was established in 1989-1991 and revised in 2005. After the introduction of the CTD in the EU, it became the Active Substance Master File (ASMF). ASMF in Europe is regulated by Directive 2001/83/EC. The ASMF application aims to protect intellectual property while giving applicants full responsibility for quality control of active substances.[3]

**Types of DMF in EU :-**

EDMF or ASMF scientific information is physically divided into two parts according to European archiving procedures.

**A. Restricted part (Closed part)**

This information is considered confidential and is provided only to authorizedorganizations.

Manufacturer(s)/site of manufacture

Detailed description of the production process and process control

Materials management (API raw materials, reagents, solvents and other materialsused)

Control of critical and intermediate steps Process verification and/or evaluation Manufacturing process development

**B. Applicant's part (Open part)**

Information that is not confidential and must be disclosed to applicants.Theinformation is provided to the authorities as part of the DMF service.

- These section include: Common information Characterization Control of API

Standards or reference material Container closure system Stability[11]

**6. Japan –**

Manufacturers of pharmaceutical substances may, at the option of the owner, register information about the quality and manufacturing method of their products with the PMDA through the MF system. From April 1, 2005, the MF applies according to the amended Pharmaceutical Business Law. A key goal of a pharmaceutical or medical device (MD) company is to share and protect informationthat is critical to MF approval reviews, such as manufacturing technology information.[15]

**DMF Filling in various country :-**

The following parameters have been selected to understand and navigate the regulatory requirements for DMF submissions in different countries.

- Get detailed information on the regulatory requirements for issuing DMFs in your chosen market.
- Addressing regulatory challenges in emerging markets (China, Brazil and

Korea) and underlines the strict requirements of regulated markets (US) and emergingauthorities.[13]

## II. CONCLUSION :-

DMF is a document prepared by the drug products manufacturer or excipient and submitted to the targeted market's regulatory authority. DMF is a submission to the FDA (Food Drug and Administration) covering information and chemistry, stability, purity, impurity profile, and packaging and cGMP status of any API.We have seen the role of DMF , it's types and procedure in this project.We also studied a comparison of DMF accross different countries.

**ACKNOWLEDGEMENT-**

I would like to express a specially thanks to my guide Ms.Atish B. Velhal for his affectionate encouragement, inspiring guidance and never ending enthusiasm.. An ostentatious use of words will not be sufficient to express my heartiest thanks to Prof.Dashrath Sagare (President), Prof. Ajinkya Sagare (Vice President). Prof. (Dr) V.K.Redasani (Principal, Yspm YTC, Satara) for their constructive suggestions, motivation.At last but not the least I am humbly grateful to all the team members who directly orindirectly played the role of a catalyst to bring out the lovely reaction of this work.

## REFERENCES :

[1]. Kiran CB, Nagabhushanam MV, Reddy DP, Sai GY, Ramakrishna G, Sindhu YR, Bonthagarala B. Drug Master Files

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2079-2084 www.ijprajournal.com ISSN: 2249-7781

Preparation and Requirements for Marketing Authorization of API in European Countries.

[2]. Divya MS, Swaroopa SN, Sanjana R, Reddy DN. A Review of Drug Master File and Active Substance Master File Approval Process and Their Comparision.

[3]. Sravanti VK, Bandla R, Juturi RK. Filing of DMF in the US, EU, and India, and its comparative review. International Journal of Drug Regulatory Affairs. 2021;9(1):22-32.

[4]. Patel Y, Pathan A. Drug Master File—Electronic Submission through eCTD: An Overview.

[5]. Mithun EG, Puranik SB, Hasija N. An Overview of Registration of API in Regulated Markets (USFDA, Canada, EU and EDQM). Int Journal of Pharm Pharm Res. 2016;8(1):216-31.

[6]. Shailaja P, Sunil K, Pushpalatha V, Snehalatha G, Ashok KS. A Review on DMF Filing in EU, USA and Australia. IJFMR-International Journal For Multidisciplinary Research. 2022 Sep 3;4(5).

[7]. Kumar P, Mangla B, Singh S. Arapna Rana,"Drug master file: global regulatory issues and challenges,". European Journal of Biomedical and Pharmaceutical Sciences. 2018Sep;5(1):623-6.

[8]. Meghna D, Dedania R, Gandhi S, Juhi R, Gaurav K. Regulatory requirements for Drug master file in context to Canada and Australia. International Journal of Drug RegulatoryAffairs (IJDRA). 2018;6(2):41-7.

[9]. Gurram I, Kavitha MV, Reddy N, Nagabhushanam MV. Drug Master File Filing in US, Europe, Canada and Australia. Journal of Pharmaceutical Research. 2017 Jun 1;16(2):160-73.

[10]. VaseemAkram M, Nagarjuna D, Ramaiah M, Nagabhushanam M, Venkateswarlu B. Regulatory requirements of drug master files by food and drug administration (USA), european medicines agency (Europe) and health canada (Canada) and their comparison.Journal of Global Trends in Pharmaceutical Sciences. 2014;5(4):2220-4.

[11]. Keerthi B, Nagarjunareddy D, Nagabhushanam MV, Kumar S. A Comparitive Study of DMF (USFDA) and EDMF (EU) and in Betweenpara IV Filings (USFDA) and IPR (EU): A Review.

[12]. Yamini Kanti, S.P. et al. (2019) "Filing of DMF in US, Canada & europe," Pharmaceutical Drug Regulatory Affairs Journal, 2(1).

[13]. Reddy, K.N. and Vasantharaju, S.G. (2020) "Comparison of regulatory requirements for Filing Drug Master File (DMF) in Emerging Markets - China, Brazil & South Korea," Applied Clinical Research, Clinical Trials and Regulatory Affairs, 7(1), pp. 71–81.

[14]. Kumar, V., Bist, M. and Rawat, S. (2018) "New Advancements in Drug Master Files Guidelines," Journal of Pharma Research, 7(11).

[15]. Shaikh, S.M.D. and Salunkhe, K.S. (2022) "Study on DMF Filling in Context to US , Europe , Japan and its Comparison," International Journal of Creative Research Thoughts, 10(3).

[16]. Aher, R. et al. (2021) "Regulatory requirement and step for registration and approval of Indian drug products in overseas market," International Journal of Pharmaceutical Sciences Review and Research, 68(2), pp. 54–62.

[17]. Agarwal, P. and Badjatya, J.K. (2018) "DMF filing in US, Europe and Canada," International Journal of Drug Regulatory Affairs, 3(4), pp. 9–17.

[18]. Ramasubramaniyan P et al. (2012) "Drug Master File and Processing : An Overview," International Journal for Pharmaceutical Research Scholars, 1(3), pp. 185–192.