Review Article

Drug Master File Filing in US, Europe, Canada and Australia

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DOI:10.18579/jpcrkc/2017/16/2/116432

ABSTRACT

Purpose: A Drug Master File (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 drugs. The submission of a DMF is not required by law or FDA regulation, it is submitted solely at the discretion of the DMF holder. 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. The present work gives the Detailed idea on how to file Drug Master File in US, EUROPE, CANADA, AUSTRALIA.

Approach: A Drug Master File is a submission of information to the FDA to permit the FDA to review this information in support of a third party's submission without revealing the information to the third party. In US, DMF filing was done through NDA for drugs, ANDA for generics and BLA for Biologics. In Europe, DMF filing was done through MAA via centralized procedure for eligible products and for other products via decentralized procedure was used. In CANADA, DMF filing was done through NDS for both drugs and biologic products, where as in AUSTRALIA different application processes and regulatory requirements apply depending on the type of therapeutic goods that is applied.

Findings: This gives you clear vision on how to file Drug master file in US, EUROPE, CANADA and AUSTRALIA. This paper also gives you the comparison of DMF fling procedure in the above-mentioned countries so that reader can have clear idea on how to file DMF and different concerns on DMF among the above counties.

Conclusion: 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 Drug product for humans. The content and the format for Drug Master File is used to obtain marketing Authorization. The main objective of the DMF is to support regulatory requirements of a medicinal product to prove its quality, safety and efficacy. This helps to obtain a marketing authorization grant. Now from 2016 onwards most of the regulated countries will use eCTD or their electronic format for their DMF submission.

Key words: DMF, FDA, CDR, CMC, CEP, LOA, TGA, ACPM, ACSOM, NDS, MAA, ANDA

INTRODUCTION

Drug Master File (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 drugs[1].

DMFs usually cover the Chemistry, Manufacturing and Controls (CMC) of a component of a drug product e.g. drug substance, Excipients, packaging material. Drug product information or non-CMC information may be filed in a DMF.

A DMF is required to supply bulk Drugs to the United States but the FDA does not require all manufacturers to submit a DMF. However, the information contained in a DMF may be used to support an Investigational New Drug Application (IND), a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA),

Received on: 07/04/2017
Revised on: 21/05/2017
Accepted on: 28/06/2017
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another DMF, an Export Application, or related documents.

Before going to the details of DMF submission in different countries, an understanding between differences prevailing in Application procedures and DMF are given below :

Points to be noted in the Process of DMF submission :

- DMF Does not come under regulatory status as it is not mandatory to file it.
- DMFs are entered into database as per their types. (Separate database for each type of DMF).
- Submitted to Central Drug Registration (CDR).
- No assignment to a reviewer, no due date.
- DMFs are reviewed only when referred by an application or DMF.
- If the anniversary date for annual update is missed FDA will not send a reminder.

Types of DMF Submission:

Therapeutic goods can be very beneficial, but to be effective they must be modified the way they work on body systems. This means there are risks, as well as benefits, associated with their use.

Because of these risks, these products must be regulated in order to protect public health.

The following information gives you an idea of Drug submission types in US, Europe, Canada and Australia.

USA:

- New Drug Application (NDA), for new drugs.
- Abbreviated New Drug Application (ANDA)-for generics.
- Biologic License Application (BLA), for biologics[2].

EUROPE:

- Marketing Authorization Application (MAA) via the centralized procedure for eligible products.
- For other products, via the decentralized, mutual recognition or national authorization are applicable.

CANADA:

- New Drug Submission (NDS) •for both drugs and biologic products.

AUSTRALIA:

Different application processes and regulatory requirements apply depending on the type of therapeutic good that is to be supplied.

- The Australian Regulatory Guidelines for Prescription Medicines (ARGPM) will assist sponsors to prepare applications to register new prescription or other high risk medicines for human use in Australia.
- The Australian Regulatory Guidelines for OTC Medicines (ARGOM) will assist sponsors to prepare applications for a new OTC medicine for human use in Australia.
- The Australian Regulatory Guidelines for Complementary Medicines (ARGCM) will assist sponsors to prepare applications for new complementary medicine for human use in Australia.
- The Australian Regulatory Guidelines for Medical Devices (ARGMD) will assist manufacturers and sponsors of medical devices in meeting the regulatory requirements for legally supplying a medical device in Australia.
- The Australian Regulatory Guidelines for Biological (ARGB) will assist sponsors to prepare applications to register a new biological for human use in Australia.
- Another therapeutic good (OTG) includes things such as disinfectants and tampons.

DMF types:

Drug Master Files (DMFs) are required in most countries as supporting documents for the registration of drug products. DMFs generally contain information pertaining to the chemistry, manufacturing and controls (CMC) sections of the drug submission and reflect the drug's identity, strength, purity and quality.

The DMF procedure exists all over the world, from

highly regulated markets (HRMs) through nearly regulated markets (NRMs). The HRMs, such as the US, EU, Japan, Canada and Australia, exclusively use DMF procedures, whereas NRMs, including Brazil, Russia and South Africa, utilize a system called a technical package. In less regulated markets (LRMs), no DMF procedure exists. For example, India, which is classified as an LRM, has neither a DMF system nor a technical package.

All these issues are covered by guidelines, published by the various international regulatory authorities such as the US Food and Drug Administration, European Medicines Agency, Australian Therapeutic Goods Administration, Canadian Health Protection and Foods Branch and several others.

US DMF – TYPES

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

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

Type III – Packaging

Type IV – Excipients, Colorant, Flavour, Essence, or Material Used in Their Preparation

Type V – FDA Accepted Reference Information Used for sterile manufacturing plants and contract facilities for biotech products[3].

US DMF Filing System

Filing the DMF

- Holder sends two copies of the DMF to FDA[2]
- DMF is reviewed for administrative purposes only by Central Document Room staff.
- DMF entered into database, assigned a number and acknowledgment letter sent to holder
- A DMF is neither approved or disapproved

Accessing the DMF: Letter of Authorization (LOA)

- The DMF will be reviewed only when it is referenced in an Application or another DMF.
- The Holder must submit two copies of the LOA to the DMF, plus a copy to the Applicant.
- The Applicant submits a copy of the LOA in their Application.
- The LOA is the only mechanism to trigger a review of the DMF by the FDA.

DMF Review Procedure

- The DMF is reviewed only if referenced by an Applicant or another DMF
- If the reviewer finds deficiencies in the DMF, the deficiencies are detailed in a letter to the Holder.
- The Applicant will be notified that deficiencies exist, but the nature of the deficiencies is not communicated to the Applicant.

Format, Font, Font Size and Paper used for submission to USFDA

- Electronic DMF should be filed. In Common Technical Document, the display of information should be unambiguous and transparent, in order to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents.
- Text and tables should be prepared using margins that allow the document to be printed on both A4 paper (E.U. and Japan) and 8.5 x11" paper (U.S.). The left-hand margin should be sufficiently large that information is not obscured by the method of binding. Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying[4].
- Times New Roman, 12-point font is recommended for narrative text. Every page should be numbered, according to the granularity document. Acronyms and abbreviations should be defined the first time they are used in each module.
- DMF neither approved nor disapproved by USFDA.
- U.S. standard paper size (8.5 by 11 inches) is preferred.
- Paper length should not be less than 10 inches nor more than 12 inches. However, it may occasionally 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.

Referral letters required for FDA submission:

In CTD (Common Technical Document), in Module 1 – Administrative Information provide information about referral letters for FDA submission.

Letter of Authorization (LOA)

Submission by the owner of information, giving authorization for the information to be used by another. An Agent Appointment Letter is NOT an LOA and should not be called "Letter of Authorization[5]"

Statement of Right of Reference

Submission by recipient of a Letter of Authorization with a copy of the LOA and statement of right of reference. Submitted in a DMF only when another DMF is referenced. If a DMF holder references other DMFs a list of those DMFs can be provided in this section. This is not the same as the list of authorized parties.

List of authorized persons to incorporate by reference:

This list should be submitted in DMF annual reports.

EUROPEAN DMF – TYPES

European DMF was established in 1989-1991. It was revised in 2005 and became ASMF (Active Substance Master File) after implementation of Common Technical Document (CTD) in EU. DMF is applicable only to active substances.

The content and the format for DMF used in United States differ from that used in European Countries to obtain market authorization (MA). The Main Objective of the EDMF is to support regulatory requirements of a medicinal product to prove its quality, safety and efficacy. This helps to obtain a Marketing Authorisation grant.

European DMF has been divided into 2 parts

- Applicant Part (Open): Contains all the required information including an outline of the manufacturing method.
- ASM Restricted Part (Closed / Confidential): Confidential information of on the manufacturing of Active Pharmaceutical Ingredient[5].

European DMF Filing System

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 the applicant's part and the ASM Restricted Part of the DMF are submitted to the authorities.

The main objective of the Active Substance Master File (ASMF) procedure, formerly known as the European Drug Master File (EDMF) procedure, 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 Authorisation (MA) holder to take full responsibility for the medicinal product and the quality and quality control of the active substance. National Competent Authorities/EMA thus have access to the complete information that is necessary for an evaluation of the suitability of the use of the active substance in the medicinal product[6].

The ASMF procedure can be used for the following active substances, including herbal active substances/preparations. i.e.:

- **New active substances**
- **Existing active substances** not included in the European Pharmacopoeia (Ph. Eur.) or the pharmacopoeia of an EU Member State

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

Applicant's part of a DMF – Open part

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 the 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 – Closed 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[7].

CANADA DMF – TYPES

Canada has 4 Types of DMFs

Type I (Active Substance Master Files (ASMF)):

For pharmaceuticals:

Drug substance or intermediate in the manufacture of a drug substance. This can include Active Pharmaceutical Ingredients (API).

For biologics:

Drug substance can include bulk process intermediates, vaccine antigens, Excipients

of biological origin (with the exception of gelatine) - Drug Substance, Drug Intermediates and materials used in their preparations.

Type II - Container Closure System Master Files (CCS MFs)

Type III - Excipients Master Files (EMFs)

Excipients, capsule shells, coating ingredients, colorants, flavours, and other additives, including alum and growth media.

Type IV - Dosage form Master Files (DFMFs)

Dosage forms and drug product intermediates[8].

Canadian DMF Filing System:

Filing the DMF:

Type I ASMFs and Type IV Dosage Form Master Files are divided in two parts:

The "Restricted Part" and the "Applicant's Part" which is provided to the Applicant and is usually included as part of the applicants drug submission or clinical trial application (CTA), with the accompanying Letter of Access (LoA).

For Type I ASMFs, the Applicant's Part contains the information that the ASMF Holder regards as non-confidential to the applicant, whereas the Restricted Part contains the information that the ASMF Holder regards as confidential. An MF will not be considered complete if both parts have not been provided to Health Canada.

Registration requirements:

For New MF Registrations, the following electronic documents are required:

- One signed cover letter, including the MF name
- MF Agent Authorization Letter from MF Holder, if applicable
- MF Application Form
- Master File Fee Form and appropriate fees
- Certificate of Suitability (CEP) and Attestations (for Type I MFs only), if applicable
- Letter(s) of Access
- For Type I ASMFs and Type IV Dosage Form Master Files, the following additional electronic documents are required:
- The MF must include the Applicant and the Restricted Parts
- A Copy of Quality Overall Summary (QOS) in Word format

- The Certified Product Information Document (CPID) in Word format, if applicable.

For Type II CCS MFs and Type III Excipient MFs, multiple components may be included in a single MF provided that the components are similar (e.g., a complete container closure system, different stopper formulations, multiple flavours). A limit of 50 components will be enforced per MF. Additional components should be filed in a new MF.

Naming an MF:

For Type I ASMFs, the preferred name of the MF should be the generic name (e.g., the International Non-proprietary Name (INN) for an active pharmaceutical ingredient) followed by any manufacturer's internal API brand names or codes to identify a particular product.

A Type IV Dosage Form Master File may have more than one product strength with the same formulation except for changes necessary to accommodate the different strengths. However in such cases, the information in the MFs for each product should be clearly differentiated within the Dosage Form Master Files.

If the MF Holder has more than one MF for a similar product, the cover letter should state this explicitly and provide information to distinguish the different products. The MF Holder should provide an MF name that distinguishes the MF from any previously registered MFs.

Accessing the DMF: Letter of Authorization (LOA):

MF Holders file confidential business information (CBI) directly with Health Canada that may be referenced to support an applicant's drug submission or CTA with respect to Quality information. The information in the MF will only be used if the MF Holder provides Health Canada with a signed original LoA to the MF Applicant. The LoA grants Health Canada permission to access the information contained in the MF.

Information to include in the LoA:

The following information should be included in the LoA:

- MF number, if assigned by Health Canada, if not yet assigned state "to be assigned"
- Name of MF
- Manufacturer's Internal Code, if applicable
- Applicant's Name being granted access to the MF
- The appropriate Master File Fee Form and Fees

LoA Filing:

A separate LoA is required for each applicant who cross-references the MF in their drug submission or CTA and each letter is subject to the applicable fees. A LoA needs to be signed by the MF Holder. A copy of the LoA should be sent to the applicant prior to filing their drug submission or CTA.

For Type I and IV, a LoA is for an MF in its entirety and is valid for all products from the applicant cross-referencing the MF.

For Type II or III, a LoA can be filed to grant access for an entire MF or specific components within a MF. Only one LoA is required, per applicant, if granting access to the entire MF or for multiple components within a MF. When granting access for an additional component, not included in the first LoA, a new LoA is required with the applicable fee.

When a MF Holder is filing a Type IV Dosage Form Master File that references a Type I ASMF, the MF Holder for the Type I ASMF must file a LoA granting access to the MF Holder of the Type IV Dosage Form Master File. Separate LoA's must be filed granting the applicant access to the Type I ASMF and to the Type IV Dosage Form Master File as well[8].

Processing of DMF:

MFs are processed in sequence according to the date of receipt. When a MF registration package is received the following activities are performed:

- Assigning an MF number and a dossier ID to the MF (only for New MF registration submissions)
- Verifying that the correct information, documents and forms have been filed and that all submitted information, documents and forms are complete for administrative purposes (including those related to cost-recovery).

Once the MF registration package is administratively complete:

- A filing date is assigned (which is the date when the MF is considered administratively complete), and
- An acknowledgement letter is sent to the designated MF contact as listed on the MF

Application Form

If required information, forms or fees are missing or incomplete, the MF will be placed on Administrative Hold, in which case the Office of Submissions and Intellectual Property (OSIP) will issue an MF transaction rejection letter to the MF contact requesting the missing information(8).

Administrative Holds

At different stages during the administrative processing of MFs it may be necessary to place the MF transaction on Administrative Hold when the MF package is incomplete (i.e. missing required information and material). This hold will remain in place until the required information is submitted.

There are two categories of administrative holds:

A. Process Hold

OSIP will place the MF on Process Hold when the MF is considered incomplete, or when the information is filed as the wrong transaction type (i.e., New MF should have been filed as an Update). When the reason for the Process Hold is addressed, the MF transaction is considered administratively complete and a filing date will be applied.

B. Cost Recovery Hold

In the event that the Master File Fee Form or applicable fee is not provided or the applicable fee is insufficient, OSIP will request the fee form and payment from the MF contact. Pending receipt of the fee form or payment, the transaction will be placed on a Cost Recovery Hold. If the fee form or payment is not received in the timeframe indicated in the letter issued by cost recovery, the transaction will not be accepted. When the reason for the Cost Recovery Hold is addressed, the submission is considered administratively complete and a filing date will be applied.

Failure to respond to a request for additional or corrected information in the prescribed time will result in the MF being shredded and/or closed[8].

Format and Structure of the MF:

MFs must follow the filing and formatting requirements outlined in the *Guidance Document Preparation of Drug Regulatory Activities in the "Non-eCTD Electronic-Only" Format* which includes guidance on MF structure and content as well as the breakdown of the Applicant and the Restricted Parts

All documents should be provided in Portable Document Format (PDF) or Microsoft Word. Documents may also be provided in Microsoft Excel where applicable.

Official Language of Correspondence

The MF can be filed in either of Canada's official languages (English or French)(8).

AUSTRALIA DMF:

AUSTRALIA DMF – TYPES

- **Category 1**
- **Category 2**

Category 1 and 2 applications for new registrations are made under section 23 of the Act. Section 23 requires that applications are made in a form approved by the Secretary. The currently approved form is the CTD format[9].

AUSTRALIA DMF Filing System

An Australian DMF registration system consists of the following stages.

- Phase 1 : Pre Submission
- Phase 2 : Submission
- Phase 3 : First Round of Assessment
- Phase 4 : Consolidated section 31 request response
- Phase 5 : Second round assessment
- Phase 6 : Expert Advisory Review
- Phase 7 : Decision

- Phase 8 : Post Decision

Phase 1: Pre Submission

- The pre-submission phase applies to category 1 and category 2 applications, excluding requests for additional trade names.
- The pre-submission phase begins with the lodgement of the *Pre*-submission planning form (PPF). The PPF provides the TGA with the necessary information on the scope and scale of an application to arrange appropriate resourcing for the processing and evaluation of the application. Once a PPF has been considered complete and acceptable, the TGA begins the process of securing appropriate evaluators for the dossier.
- A complete PPF identifies the proposed application type, and contains general information about the quality, nonclinical, and clinical evidence to be included in the dossier. The information provided in the PPF allows the TGA to commit to timeframes for the evaluation of the application[9].

Milestone 1:

If the PPF is considered complete and acceptable, a TGA Planning letter is sent to the applicant identifying the expected dossier lodgement date and target milestone dates for the application.

Phase 2: Submission

The submission phase involves processing activities in preparation for application evaluation.

- confirmation of dossier delivery by the expected lodgement date
- verification that any application fee has been paid
- workflow planning and IT administration
- consideration of the application against the TGA regulatory requirements
- Issuing of a Notification letter, including notice of evaluation fee payable, if applicable.

Milestone 2:

The TGA sends a letter to the applicant identifying whether the application has been considered effective and accepted for evaluation, or considered 'not effective'.

Phase 3: First Round of Assessment

- All data provided in the dossier are considered by the evaluators during the first round assessment phase.
- Where there are issues or questions about any component of the application, a consolidated section 31 requests for information containing requests from all evaluation areas within the TGA is compiled and sent to the applicant by the date specified in the Planning letter.
- Within this phase, TGA evaluators may directly contact the applicant to seek clarification or ask questions informally if they determine that waiting for the formal consolidated section 31 request on a minor clarification is unnecessary. This type of informal question will not change the timeline for the consolidated section 31 request.

Milestone 3:

Applicants will be sent a Milestone 3 letter including:

- 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 RMP evaluators.

Phase 4: Consolidated section 31 request response

- The consolidated section 31 request response phase allows applicants time to consider the TGA's consolidated section 31 request for information or documents, prepare a response and send the response to the TGA.

Milestone 4

Applicants will send TGA a response to:

- Any consolidated section 31 request for Information or documents
- The first round assessment reports prepared by the quality, nonclinical and clinical evaluators, if required.

Response to section 31 request

- Responses to a section 31 request for information or documents must be provided in CTD format. Applicants need to send both hard copy and electronic copy formats of the response to the TGA.
- Applicants should pay close attention to the questions raised in the s31 letter, as well as any requests in the letter for other information or documents, as this may be the sole opportunity that an applicant has to provide this information.

Response to first round assessment reports:

- Applicants should review the first round assessment reports and advise the TGA of any perceived errors of fact or major omissions. Each identified error of fact or omission must be referenced to information previously submitted

Phase 5: Second round assessment

- During the second round assessment phase, evaluators will consider the response provided by the applicant to the section 31 request (if applicable) and complete the evaluation of the data.

Milestone 5:

- All second-round assessment reports are completed[9]

Opportunity to review evaluation reports:

- Applicants will be given a period of 14 calendar days after the TGA issues the final evaluation report(s) in which to review and advise the TGA of any perceived errors of fact or major omissions outside the *Pre-ACPM* response.
- Applicants should also use this period to revise the draft PI based on recommendations in the evaluation reports.

Phase 6: Expert Advisory Review

- After completion of the second round assessment phase, the evaluation reports are considered by the delegate. The delegate may seek independent advice on issues concerning the application.
- The main advisory group for prescription medicines is the Advisory Committee on Prescription Medicines (ACPM). Specific issues may also be referred to the Pharmaceutical Subcommittee (PSC) of the ACPM, or to the Advisory Committee on the Safety of Medicines (ACSOM).
- Comments from the applicant in relation to perceived errors of fact or major omissions in the second round assessment reports for those applications referred to the ACPM are also considered.

Milestone 6:

The TGA notifies the applicant of the advice received from the ACPM.

Phase 7: Decision

- The TGA delegate will determine whether the application is to be approved (possibly modified or varied) or rejected. Where any outstanding issues may affect the decision, the delegate may liaise directly with the applicant during this phase before finalising the decision.
- For applications made under section 23 of the Act the applicant will be notified in writing of the decision within 28 days of it being made (Section 25(4) of the Act). The issuing of a decision ends the legislated evaluation period[10].

Milestone 7:

- A 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 sent to the applicant[11].

Phase 8: Post Decision

- During the post-decision phase, administrative and regulatory activities are completed.

Milestone 8:

- Administrative and regulatory activities are completed. Any outstanding
- Payments are finalised (if applicable) and the ARTG entry is finalised.

The following table gives you the complete details and comparison of DMF registration process in US, Europe, Canada and Australia.

Drug Master File Requirements	US	Europe	Canada	Australia
Health Authority	U.S. Food And Drug Administration	European Medicines Agency	Health Canada	Australian government-TGA
FOR API	US DMF	EDMF/ASMF	DMF	Prescription medicine registration process
Definition of DMF	A drug master file (DMF) 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).	A DMF is a reference that provides information about specific processes or components used in the manufacturing, processing, and packing of a drug	Application refers to the regulatory activity required in respect of a product (a specific set of formulations, strengths and presentations) as requested by the applicant of the product. • It is the specific set of information on the product submitted for review. • Examples include: – an application for the registration of a new medicine
Types of DMF	Five Types of DMF: I. Manufacturing Site, Facilities, Operating Procedures, and Personnel. II. Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product III. Packaging IV. Excipients, Colorant, Flavor, Essence, or Material Used in Their Preparation V. FDA Accepted Reference Information	No Types of DMF	Four Types of DMFs: I. Drug Substance, Drug Intermediates and Materials Used In Their Preparations II. Packaging Material III. Colorants, lavours and Other Additives IV. Dosage Form	**Category 1** **Category 2** Category 1 and 2 applications for new registrations are made under section 23 of the Act. Section 23 requires that applications are made in a form approved by the Secretary. The currently approved form is the CTD format.
Format	The USFDA require two copies of each type DMF in the CTD format, but not in CTD Module form.	ICH CTD Module 3-Quality and QOS. ASMF divided into two: **Applicant's Part(AP) and**	ICH CTD Module 3-Quality and QOS. DMF divided into two separate parts, namely the	Category 1 and 2 applications for new registrations are made under section 23 of the Act. Section 23 requires that

	FDA requires one continuous document in the CTD format. QOS is also required. Electronic submission and paper submission	Restricted Part (RP). The UK and the Netherlands will only accept Electronic copies each in their own separate electronic format, while France requires both a paper copy and an electronic copy. France also requires special application forms to accompany the DMF as well as a letter certifying that the electronic version is identical to the paper copy. Several other countries process are in the process of converting to the non-ICH (Xml), Non-eCTD electronic filing format. These include Belgium, Denmark, Germany, and France.	**Applicant's Part** (AP) and the Restricted Part (RP) Electronic submission and paper submission.	applications are made in a form approved by the Secretary. The currently approved form is the CTD format. The CTD format is described in the following documents: • CTD Module 1: Administrative information and prescribing information for Australia • ICH M4Q Common technical document for the registration of pharmaceuticals for human use-Quality (CPMP/ICH/2887/99 Rev 1 Quality) • ICH M4S Common technical document for the registration of pharmaceuticals for human use-Safety (CPMP/ICH/2997/99 Rev 1 Safety) • ICH M4E Common technical document for the registration of pharmaceuticals for human use-Efficacy (CPMP/ICH/2887/99 Rev 1 Efficacy).
SUBMISSIONS ALONG WITH DMF	**A. Transmittal Letters** a. Identification of Submission: Original, The type of DMF as classified in Section III, and **it's Subject.**	Letter of Access to the NCA/EMA. A Copy of the Letter Of Access to the MA Holder for inclusion in the annexes To their MA/MAV Application.	The DMF Should include the following information: • The Name and Address of the agent if applicable. • The Name and Address	Under the registration process, applicants provide the TGA with planning data in the *Pre-submission planning form* (PPF) at the pre-submission phase. Planning data include

	b. Identification of the Application, 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. Type written Name and Title of the Signer. **B.ads.infmt** a. Names and Address of the following: 1) DMF Holder 2) Corporate Headquarters 3) Manufacturing Processing Facility 4) Contact for FDA Correspondence. 5) Agent(S), If any b. The Specific responsibilities of each person listed in any of the categories in Section A. Statement of Commitment.	A Submission details form to the NCA/EMA subsequent updates to an ASMF where the information in the form is the same for all. Application: **Applicant's Part** • Restricted Part • Separate or Combined Quality Overall Summary (**QOS) for the Applicant's** and Restricted Parts **Copy of the Expert's** Curriculum Vitae.	of the Corporate Headquarters (DMF Owner); and • The Name and Address of the Manufacturing Processing, and Packaging Facilities.	general submission information as well as information about the proposed application type and details of the quality, nonclinical and clinical evidence that will be provided in the dossier. The PPF provides the TGA with the necessary information for effective resource planning.
FORWARDING ADDRESS	Drug Master File Staff FDA, 5901-B Amendable Rd. Beitsville, Md 20705-1266	In Europe according to Marketing Authorization Procedures, DMF submitting address will be change. **EMA Address:** 7 Westferry Circus, Canary Wharf , London E14 4hb, United Kingdom **Telephone :** +44 (0)20 7418 8400	Health Canada, Health Products and Food Branch, Therapeutic Products Directorate, Master File Administration Unit, Address Locator 0201D, 101 promenade Tunney's Pasture Driveway, Ottawa Ontario, K1A 0K9 Canada	Street address: TGA, 136 Narrabundah Lane, Symonston ACT 2609, Australia Postal address: TGA, PO Box 100, Woden ACT 2606, Australia Email: info@tga.gov.au

		Facsimile :+44 (0)20 74188416 E- Mail: Info@Ema.Europa.Eu Web:www.ema.europa.eu		
LETTER OF AUTHORIZATION	Letter of Access is required	Letter of Access is required	Letter of Access is required	Letter of Access is required
CLOSURE OF DMF	A Holder who wishes to close a DMF should submit a request to the DMF Staff stating the reason for the closure. The agency may close a DMF that does not contain an annual update of persons authorized to incorporate information in the DMF by reference and a list of changes made since the previous annual report.	Where the active substance is no longer supplied to the MA Holder or the corresponding ASMF is replaced by a Ph. Eur. Certificate Of Suitability (CEP), The ASMF Holder should provide a withdrawal of access of letter to the NCA/EMA	A DMF be withdrawn by the Owner, The Owner should advise Health Canada in writing and provide a list of the Canadian Customers using their DMF. Health Canada will close a DMF that has not been update within a 5 years period.	Applications that do not meet the TGA's regulatory requirements will be considered 'not effective'. Applicants of applications considered 'not effective' will be notified in writing of the reasons the application was not accepted for evaluation. If the applicant wishes to proceed with the application they must lodge a new PPF and potentially a new dossier.
DMF FEES	Only for Type 2 DMF fees will be taken according to GDUFA- $31,460	New Applications- £5006	DMF for new Registration - $408Cdn	New chemical entity is $46,100

Appendix1

Comparison of DMF process in US, Europe, Canada and Australia

CONCLUSION

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 Drug product for humans. The content and the format for Drug Master File is used to obtain marketing Authorization. The main objective of the DMF is to support regulatory requirements of a medicinal product to prove its quality, safety and efficacy. This helps to obtain a marketing authorization grant. Now from 2016 onwards most of the regulated countries will use eCTD or their electronic format for their DMF submission.

REFERENCES

1. Guidelines for Drug Master Files [Internet]. CDER, FDA; 2005 Mar[cited 2015 Nov 15]. Available from: http://www.FDA.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122886.htm (Accessed on 15th march 2017)
2. Guidelines for drug master files, United States, Food and Drug Administration [Internet]. USFDA; 2011 Nov 14 [cited 2015 Nov 09]. Available from: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM279666.pdf (Accessed on 15th March 2017)
3. Guidelines for drug master files, CDER FDA [Internet]. FDA; 2015 [cited 2015 Nov 12]. Available from: http://www.FDA.gov/cder/guidancde/DMF.htm (Accessed on 20th march 2017).
4. Forms and Submission requirements [Internet]. FDA;2015 Nov [cited 2015 Nov 08]. Available from: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm090361.htm (Accessed on 20th march 2017)
5. Requirements/Drug Master Files DMF's [Internet]. FDA; 2013 Feb 11 [cited 2015 Nov 08]. Available from: https://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm339118.pdf (Accessed on 21st march 2017)

6. Guideline on Active Substance Master File Procedure - Europa.eu Available from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129994.pdf (Accessed on 21st march 2017)

7. Guideline on the European Drug From http://www.gmp-compliance.org/gmp-news/guideline-on-the-european-drug-master-file-procedure-updated (Accessed on 25th march 2017)

8. Draft Guidance Document: Master Files (MFs) - Procedures and Administrative Requirements. Available from http://www.hc-sc.gc.ca/dhp-mps/consultation/drug-medic/draft_guide_mf_fm_ld_ebauche-eng.php (Accessed on 30th march 2017).

9. Prescription medicine registration process , for the application lodged under the process of prescription registration process, Australian government, version 2 Available from https://www.tga.gov.au/sites/default/iles/pm-argpm-process.pdf (Accessed on 30th march 2017)

10. Australian regulatory Guidelines for prescription medicines from https://www.tga.gov.au/publication/australian-regulatory-guidelines-prescription-medicines-argpm (Accessed on 31st march 2017).

11. Standard and guidelines for Prescription medicines- e submissions from https://www.tga.gov.au/electronic-submissions (Accessed on 31st March 2017).