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Regulatory requirements for Drug master file in context to Canada and Australia

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ABSTRACT

Drug Master Files 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. Canada and Australia which are consider as highly regulated markets (HRMs). In CANADA, DMF filing was done through New Drug Submission (NDS) for both drugs and biologic products. They use MF terminology for DMF which contain four types of MASTER FILE- ASMFs, CCS MFs, Excipient MFs, Drug product MFs. In AUSTRALIA different application processes and regulatory requirements apply depending on the type of therapeutic goods that is applied. They consist of eight phase for DMF registration. Where EU guidelines adopted in Australia include references to EU legislation. Now from 2016 onwards most of the regulated countries will use eCTD or their electronic format for their DMF submission. Compare DMF regulatory requirements in the above-mentioned countries so that reader can have clear idea on how to file DMF.

Keywords: DMF, HRMs, NDS, ASMFs, CCS, EU, eCTD.

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1. Introduction

Drug Master File

The Drug Master File (DMF) filing allows a firm to protect its intellectual property from its partner while complying with regulatory requirements for disclosure of processing details. DMF contain detailed 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. The information contained in the DMF may be used to support an IND, a NDA, an ANDA, and another DMF. DMF is provided for in 21 CFR 314.420 (1).

DMF are divided in two parts:

The Applicant's Part: which contains all the information that the license-holder needs to assess the quality and submit a license or amendment application.

Restricted Part: This contains confidential information that disclosed to the authorities.

Role of Drug Master File

1. Supporting documents for the registration / approval of drug products.
2. In the Chemistry, Manufacturing and Controls (CMC) sections of the drug. DMF documents the drugs identity, purity, strength and quality.
3. Protect Proprietary and Confidential Information (2).

Types of Drug Master Files

Type I: Production Site, Facilities, Procedures, and Personnel
Type II: Drug Substance, Intermediate, and Material Used in their Preparation, Drug Product
Type III: Packaging Material
Type IV: Excipient, Colorant, Flavor, Essence, Material Used in Their Preparation
Type V: FDA Accepted Reference Information (3).

2. Regulatory Guidelines in Canada

Health Canada is the department of government of Canada with responsibility for national public health.

Canadians and their health care providers use pharmaceutical drugs that have been approved by Health Canada to treat or prevent an array of diseases and disabling physical conditions. Enabling timely access to safe and effective drugs, and ensuring that these products remain safe and effective is critical to improving and maintaining the health of Canadians. Drugs are regulated under the Food and Drugs Act, which is administered by Health Canada.

Health Canada's responsibilities include the following core activities

- Reviewing clinical trial applications, for clinical trials to be conducted in Canada.
- Reviewing drug submissions from manufacturers for market authorization and for post-market changes.
- Monitoring the safety of drugs in the Canadian market and communicating safety risks to health care professionals and the public, in collaboration with industry.
- Enforcing the pharmaceutical industry's compliance with regulations, including those related to clinical trials, drug manufacturing, and the reporting of adverse drug reactions (4).

3. Regulatory Guidelines in Australia

The TGA administers the Therapeutic Goods Act 1989 Act, applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy. The work of the TGA is that benefits to customer and provides risk free medicines and medicines devices. The TGA regulates therapeutic goods through Pre and post market monitoring and enforcement of standards, Licensing of Australian manufacturers and verifying overseas manufacturer's compliance with the same standards as their Australian counter parts (5).

The TGA's approach to risk management involves identifying, assessing and evaluating the risks, applying for treating the risks posed, monitoring and reviewing risks over time, the risk-benefit approach gave confident that medicine which used by consumers that are safe and good for health (5).

4. Regulatory Guidelines for DMF as per Canada

Health Canada is pleased to announce the release of the revised the 2008 Draft Guidance Document - Drug Master Files (DMFs) is outdated and not in line with international efforts to standardize MF terminology and MF procedures. The revised draft is administrative in nature and was developed to facilitate information sharing initiatives that are ongoing in collaboration with the International Generic Drug Regulators Programmed (IGDRP).These initiatives include bringing efficiencies to MF practices. It also introduces process changes that are less cumbersome on industry and Health Canada (6).

Table 1 MFs are classified according to the following types (6)

	For pharmaceuticals
Type I Active Substance Master Files (ASMFs)	Active Pharmaceutical Ingredients (API) (drug substances), starting materials or intermediates used in the manufacture of a drug substance. **For biologics** Drug substances can include bulk process intermediates, vaccine antigens, excipients of biological origin, adjutants, albumin and critical raw materials for radiopharmaceuticals or vectors for gene therapy.
Type II Container Closure System Master Files (CCS MFs)	Packaging material, Container closure systems components Description Suitability-protection, safety, compatibility, performance Quality control
Type III Excipient Master File	Capsule shells, coating ingredients, colourants, Flavours, and other additives.
Type IV Dosage Form Master Files	Dosage forms and drug product intermediates.

Registration Requirements for MFs (6)

- One signed cover letter.
- MF Agent Authorization Letter from MF Holder.
- MF Application Form, Master File Fee Form and appropriate fees.
- Certificates of Suitability to the Monographs of the European Pharmacopeia (CEPs) – It should be filed by the drug substance supplier in an Active Substance Master File (ASMF) with full information on the drug substance. MF Holders are requested to confirm at the time of filing if no CEP is available.
- Letter(s) of Access (LoA)-The information in the MF will only be used if the MF Holder provides Health Canada have a signed actual LoA to the MF Applicant. LoA grants Health Canada permission to access the information contained in the MF.

  Information to include in the LoA that MF number, if assigned by Health Canada, if not yet assigned state "to be assigned", name of MF manufacturer's internal code, applicant's name being granted access to the MF the appropriate Master File fee form and fees.
- The MF must include the Applicant and the Restricted Parts.
- The Certified Product Information Document (CPID) in Word format, if applicable. It should be completed to provide a condensed summary of the key Quality information for New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) containing drug substances and their corresponding

products of synthetic or semi-synthetic origin that are filed with Health Canada.

- A Copy of Quality Overall Summary (QOS) in Word format.

Processing of MFs

- MFs are processed in sequence according to the date of receipt. When a MF registration package received the following activities are performed.
- Assigning an MF number and a dossier ID to the MF.
- Verifying that the correct information, documents and forms have been filed.
- Once the MF registration package is administratively complete.
- A Filing date is assigned.
- An Acknowledgement letter is sent to the designated MF contact.

MF Fees

Refer to the Master File Fee Form regarding fees for the processing of a New MF, LoA and Update. Fees are increased annually by 2% on the first of April. The revised fee structure increases the cost of filing a new DMF to $424 (Canadian), the cost of filing a biannual update to $191 (Canadian), and the cost of filing a Letters of Access to $191 (Canadian).

Format and Structure of the MF

March 2016, all MFs previously registered with Health Canada must have filed a complete conversion to replace their paper MF with a Non-eCTD Electronic-Only (NeeS) which includes guidance on MF structure and content as well as the breakdown of the Applicant and the Restricted Parts. The navigation through a NeeS Format dossier is based on electronic tables of contents, bookmarks, and hypertext links. MF Holders may also file their MFs in eCTD format and. All documents should be provided in Portable Document Format (PDF) or Microsoft Word. Documents may also be provided in Microsoft Excel where applicable. (7)

5. Regulatory Guidelines for DMF as Per Australia

In the case of an API used by a producer for a medicine who's origin is a third party manufacturer, data about its fabrication, quality control and stability can be presented by a Drug Master File (DMF) The European style relevant for the procedure of a Active Substance Master File, adopted by Australia's Therapeutic Goods Administration (TGA) (8).

DMF Filing System *(9, 10)*

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 uses for category 1 and category 2 applications. Pre-submission Planning Form should be lodged at least 2 ½ months prior to the intended lodgments date for the submission. A complete PPF identifies quality, nonclinical, and clinical evidence to be included in the dossier. TGA assign resources for the evaluation process. Within six weeks of receipt of a PPF the TGA will send the sponsor a TGA Planning Letter that provides the expected submission date.

The PPF is divided into three parts

Part 1 - Applicant and product details

1.1 -Applicant details
1.2 - Product details
1.3 - Indications
1.4 – planning

Part 2 - Details of application

2.1 - General information
2.2 - CTD Modules 1–5
2.3 - Justifications and further information
2.4 - Summary of attachments

Part 3 – Declaration

Phase 2: Submission

The TGA will send a planning letter to the sponsor, identifying whether the submission is accepted for evaluation. After receipt of the TGA Planning Letter, lodgement of submission and supporting data is within a month. Sponsors must lodge well-planned, high quality, complete submission dossiers.

The Application fee is non-reimbursable from the time of submission. If submissions are not accepted due to deficiencies amount will be remaining by the TGA, covering administrative costs.

Evaluation fee ($100,000): 100% of the evaluation fee is required when the submission is lodged.

Phase 3: First Round of Assessment

All dossier data would evaluate by the evaluators. It necessary section 31 request for documentation. Report prepared by clinical, non clinical evaluators. The period is 90 days for completion, with an additional 30 days for prepare question.

Phase 4: Consolidated section 31 request response

Prepare a response and send the response to the TGA. 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 review the first round assessment reports and advise the TGA for major omissions.

Phase 5: Second round assessment

Complete the evaluation of the data. Response should be send to TGA by Sponsor within 30 days.

Phase 6: Expert Advisory Review

The main advisory group is the ACPM, PSC and some ACSOM for prescription medicine. All data

evaluate by advisor and give their suggestion in different issues.

Phase 7: Decision

The TGA will decide whether the application is to be approved or rejected. In this there so many objection that related to PI, CMI or RMP and general registration information. Sponsor prior to making a decision within 28 days.

Phase 8: Post Decision

Time line for this phase is 90 days. All regulatory activities administrative procedure completed.

Registration requirements for DMF (11)

- **Cover letter:** A description of the submission, including appropriate regulatory information, regulatory activity category and regulatory activity types.
- **Application form:** It is the basis of the new/revised ARTG entry. It should enter accurately information.
- **Pre–submission details:** PPF is required for category 1 and 2 not for category 3 application.
- **Patent certification:** Forms is required to satisfy legislative requirements under section 26B of the Act when before newly approved registration.
- **Letter(s) of Access**

6. Categories of Applications for Prescription Only Medicines (12)

***Category 1 applications*:** include applications for a new chemical entity or a new indication for a registered prescription product as well as other major changes such as changes to product information or approval of a new generic medicine.

Category 2 applications: When an application has been previously approved in two acceptable countries these applications have a shorter statutory time frame for evaluation. For this two independent evaluation reports from acceptable countries, where the product is already approved, are required to be provided at the time of application.

Category 3 applications: Involve a change to a product that is already registered on the ARTG, Where the change does not require quality data (clinical, toxicological or bioavailability data) to support the change.

Category 1 and 2 requests to vary the entry in the Australian Register of Therapeutic Goods (ARTG) of registered therapeutic goods are made under section 9D of the Act. Section 9D requires that applications are made in a manner approved by the Secretary. The currently approved manner is the CTD format. It is a set of specification for a dossier for the registration of medicines. It is internationally agreed "well structured common format".

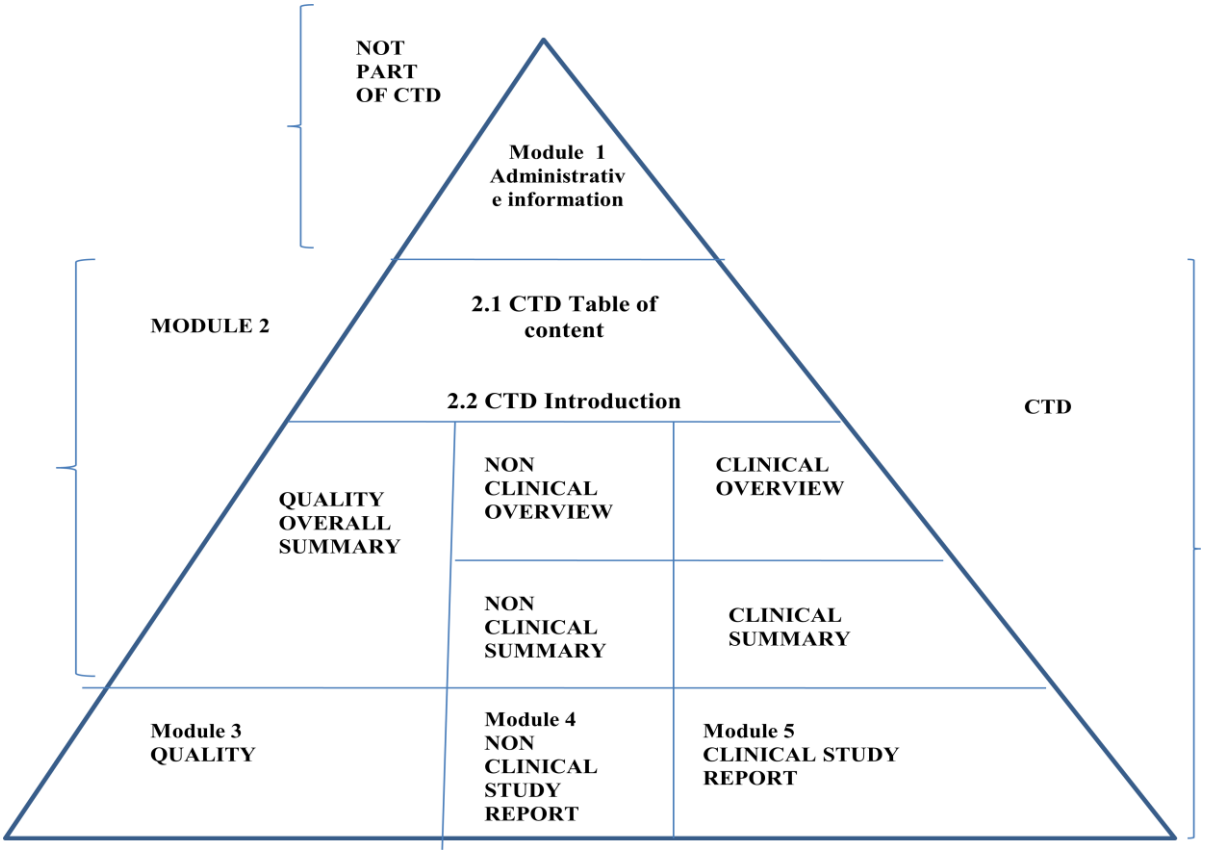

Figure 1. ICH Common Technical Document Format (13)

Table 2 Comparison of DMF's of Canada and Australia

DMF Requirement	CANADA	AUSTRALIA
Health Authority	Health Canada	Australian government-TGA
Definition of DMF	A DMF is a reference that provides information about specific processes or components used in the manufacturing, processing, and packing of a drug	In the case of an API used by a producer for a medicine whose origin is a third party manufacturer, data about its fabrication, quality control and stability can be presented by a Drug Master File (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(Excipient MFs) **Type IV**-Dosage Form Master	No type for drug master file
Format	MFs must follow the filing and formatting requirements outlined in the Guidance Document Preparation of Drug 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.
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 chemical entity is $46,900. No cost for filing a letter of Access.
Updation	Bi- annually	Five years once
Forwarding Address	Health Canada Health Products and Food Branch Therapeutic Products Directorate **Master File Administration Unit** Address Locator 0201D promenade Tunney's asture Driveway Ottawa Ontario K1A 0K9 Canada Email:dmf_enquiries@hc-sc.gc.ca Fax number: 613-941082	**Postal add-** **Prescription Medicines Authorisation Branch** Therapeutic Goods Administration PO Box 100 Woden ACT 2606 Australia **Street Add-** Therapeutic Goods Administration 136 Narrabundah Lane Symonston ACT 2609 Australia Email: info@tga.gov.au
Submissions along with DMF	The DMF Should include the following information The Name and Address of the agent if applicable. The Name and Address of the DMF owner. The Name and Address of manufacturing processing and packaging facilities.	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 general submission information as well as information about the proposed application type and details of the quality, non clinical and clinical evidence that will be provided in the dossier. The PPF provides the TGA with the necessary information for effective resource planning.
Format Difference	ICH CTD Module 3-Quality and QOS. When providing MF Types I& IV, two separate documents should be included in the folder. "Quality Overall Summary", a "QOS (Restricted Part RP)" and a "QOS (Applicant's Part AP)" files.	The currently approved form is the CTD format. CTD Module 1-Administrative information and prescribing information for Australia. ICH M4Q - Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality (14). ICH M4E - Common Technical Document for the Registration of Pharmaceuticals for Human Use: Efficacy (15). ICH M4S - Common Technical Document for the Registration of Pharmaceuticals for Human Use: Safety (16).

Closure of DMF	MF withdrawn by the MF holder. The MF holder should advise Health Canada in writing of the reason for the closure, including a statement that their obligations have been fulfilled and provide a list of the Canadian Customers using their MF. Health Canada will close a MF 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 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.
Clinical and Non Clinical data	In Nees format Clinical and Non Clinical data included in separate Clinical Trial Application (CTA).	In CTD format overview and summary of Clinical and Non Clinical included in module 2 and study report included in module 4 and module 5.
ICH Zone Requirements	Zone I	Zone II
Sterilization Process	Autoclave program, Use gamma radiation, Terminal sterilization, Depyrogenation of packaging components, Aseptic condition, Use ethylene oxide gas.	Bioburden test, Pre-use and Post-use filter integrity test, Aseptic manufacturing process, Container Closure Integrity test, Finished drug substances sterility testing.

7. Conclusion

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. The content and the format for Drug Master File is used to obtain marketing Authorization. In Canada DMF filing was done through New Drug Submission (NDS) for both drugs and biologic products. By March 31, 2016, all existing DMFs in paper format must be replaced by a complete DMF conversion in "non-eCTD electronic-only" format. In Australia there is TGA guidelines, different application processes and regulatory requirements apply depending on the type of therapeutic goods that is applied. Under the registration process, applicants provide the TGA with planning data in the Pre-submission planning form (PPF) at the pre-submission phase with details of the quality, non clinical and clinical evidence that will be provided in the dossier. The European style Active Substance Master File adopted by TGA. The currently approved form is the CTD format which contains 5 Modules.

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Conflict of interest

The authors declare no conflicts of interest.

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