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An Overview of Registration of API (DMF) in Regulated Markets (USFDA, CANADA, EU and EDQM (CEP)

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ABSTRACT

The purpose of this article is to present a concise overview registration of Active pharmaceutical ingredient (API) for Generic Drugs in various regulatory authorities such as USFDA, TPD, EU and EDQM as per ICH-CTD. A regulatory process, by which a person/organization/sponsor/innovator gets authorization to launch a drug in the market, is known as registration process. The registration process will be done by submitting technical information to the authority i.e., Drug Master File. A Drug Master File or DMF is a reference source that provides drug evaluator's confidential information not available to drug product manufacturer about the specific process and components used in the manufacturing, processing and packaging of a drug meant for Human /Animal use(1). A DMF is submitted solely at the discretion of the holder.

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INTRODUCTION

The US Food and Drug Administration (FDA) already for several decades has had an extensive and complex set of API requirements in place covering the areas of Drug registration(2) and current Good Manufacturing Practice (cGMP) (3) and new FDA regulations and guidelines are still continually being issued. The United States - Food and Drug Administration (U.S. FDA) has its own regulatory strategy to approve and allow generic drugs into the market, which is named as Office of Generic Drug Submission Review (OGD). FDA has introduced Generic Drug User Fee amendment (GDUFA) program in October 2012.

Recently USFDA has issued Completeness Assessments for Type II API DMFs under GDUFA (4).

Since about 1990, the authorities within Europe especially have also acknowledged the importance of APIs, as illustrated by a steep increase in the amount of information on the manufacture and control of APIs to be included in marketing authorization application within the EU(5). In addition, legal provisions are being developed by the European commission for the mandatory application of cGMP principles in API manufacture (6).

In 1994 European Directorate for the Quality of Medicines (EDQM) is created and started new procedure called CEP (‘Certification of Suitability to the monographs of the European Pharmacopoeia') and EU/EDQM regulations and guidelines are still continually being issued for better control and improvement(7).

TPD., CANADA the draft version of this Health Canada guidance document Drug Master Files (DMF) is made available for comment in September 2008. The guidance document has been updated to incorporate revisions and terminology resulting from the adoption of International Conference on Harmonization (ICH) guidelines. Where terminology is defined in the ICH guidance documents, no definition is given and the reader is referred to these guidelines. The guidance document includes direction on biotechnological/biological products, veterinary drug products and natural health products in addition to pharmaceuticals. Administrative requirements and procedures have been updated and clarified, and content requirements for all types of DMFs are more detailed or cross-referenced to relevant ICH and Health Canada guidelines where they exist (8).

Role of DMF submission in API:

1. DMF plays a crucial role for the manufacturers of Drug products and to support the documents for the registration/approval of Drug products.

2. Registered APIs will be published in websites helps in the marketing of APIs to all drug product manufacturers

3. In the Chemistry, manufacturing and Controls (CMC) sections of the drug submission, the DMF documents the drugs identity, purity, strength and quality.

4. To protect proprietary and confidential information. (9)

Drug Master filing system

US Drug Master filing system:

Types of Drug master in US:

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, Flavor, Essence or Material Used in Their Preparation

Type V-FDA Accepted Reference Information. Used for sterile manufacturing plants and contract facilities for biotech products.

Filing of DMF

Recent update regarding USFDA DMF is now we can submit e-CTD via ESG (Electronic Submission Gateway). The deadline for the conversion of Paper format to e-CTD is beginning May 5, 2017, all submission types NDA, ANDA, BLA and Master Files must be submitted in eCTD format.

Organization of the eCTD

Module 1 – Administrative Information

FDA Regional eCTD Backbone Files Submissions to CDER and CBER can be made using either version 2.01 of the us-regional.xml backbone file or, the newer and preferred version 3.3.

Cover Letter: Cover letters contain pertinent information which aid communication within the review process. It is recommended the cover letter include the following information: Regulatory description of the submission, including appropriate regulatory information, and any desired hyperlinks to submitted information. Technical description of the submission, including the approximate size of the submission up to 2GB. Certifying statement that the submission is virus free, with a description of the software (name, version, and company) that was used to check the files for viruses. A regulatory and technical point of contact for the submission, including email address should be mentioned.

Annual Reports: Sponsors and applicants should include a bookmark for each study or trial described in the postmarketing requirement/commitments files. The reporting period covered by the annual report should be included in the eCTD leaf title. Information Amendments Documents for information amendments should be included in the applicable eCTD module using the appropriate eCTD heading to describe the document's subject matter.

Letters of Authorization (LOAs): 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" and should not be submitted in Section.

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 to be provided in 1.4.3.

1.4.3 - List of authorized persons to incorporate by reference: This list should be submitted in DMF annual reports.

Module 2

Quality Over summary which comprises a precise summary of Module-3 (Quality).

Module 3

Quality (Drug Substance)

Which consists of seven sections namely General Information, Manufacture, Characterization, Control of Drug Substance, Reference standard or materials, Container closure system and Stability.

Module-3 which contains detailed information of the drug substance (CMC). (10)

DMF Review Procedure

1. The DMF is reviewed only if referenced by an Applicant or another DMF. The LOA is the only mechanism to trigger a review of the DMF by the FDA.

2. If the reviewer finds deficiencies in the DMF, the deficiencies are detailed in a letter to the Holder.

3. The Applicant will be notified that deficiencies exist, but the nature of the deficiencies is not communicated to the Applicant. (11)

DMF holders are required to pay a DMF fee when first authorizing the reference of their DMF in a generic application Type II API DMFs must undergo an FDA completeness assessment (CA)

Under GDUFA, beginning October 1, 2012, the holder of a Type II API DMF must pay a one time DMF fee when the DMF is first referenced in a generic drug submission submitted to FDA on the basis of a letter of authorization (LOA) from the DMF holder. Also under GDUFA, holders of Type II API DMFs that were evaluated before October 1, 2012, must pay a one-time fee for the DMF when their DMF is first referenced in a new ANDA, an ANDA or Prior Approval Supplements (PAS) amendment, or an ANDA PAS on or after October 1, 2012. Only Type II API DMFs for use in generic drug submissions incur this one-time fee.

DMF Fee for FY 2017; (12)

Fee category	Fee rates for FY 2017 in US $
Applications	
Drug Master File (DMF)	$ 51,140
Facilities:	
API-Domestic(US)	$ 44,234
API-Foreign	$ 59,234

CANADA Drug Master filing system:

Canada has 4 Types of DMFs

1. DMF Type I - Drug Substance
2. DMF Type II - Container Closure Systems and Components
3. DMF Type III – Excipients
4. DMF Type IV- Drug Product

Type I DMF for API have divided into two sections:

- Sponsor's (Open)
- Restricted (Closed) (13)

Recent notification from Health Canada dated October 5, 2015, with file number: 15-110442-152

Health Canada is pleased to announce the acceptance of Drug Master Files in "non-eCTD electronic-only" format.

Electronic documents will be uploaded onto the Health Canada viewing tool, where they will be immediately accessible to Health Canada staff involved in the review of the regulatory activities. This will contribute to effective record management and ensure authenticity, integrity, availability, traceability, and non-repudiation of the data.

Effective immediately the following should be provided in "non-eCTD electronic-only" format:

- New DMFs;
- Transactions related to existing DMFs (for example, letters of access, administrative information);
- DMF updates (the first update must include a **complete** DMF conversion in "non-eCTD electronic-only" format for the existing DMF in paper format).

As of **January 1, 2016**, Health Canada will no longer accept paper copies of DMF transactions. Any paper received after this date will be shredded or returned at the owner's expense.

By **March 31, 2016**, all existing DMFs in paper format must be replaced by a complete DMF conversion in "non-eCTD electronic-only" format. Failure to provide the complete electronic copy of the DMF will result in the DMF being suspended (no further access for review will be granted and no update will be accepted for the DMF). (14)

Format Comparison Table (13)

Issue	Paper format (CTD) along with electronic data	Non-eCTD electronic -only format	eCTD electronic-only format
Portion of regulatory activity provided electronically	Complete regulatory activity provided in paper format, along with partial/complete electronic data.	Complete regulatory activity provided in "non-eCTD electronic only" format.	Complete regulatory activity provided in eCTD electronic-only format.
Legal record	The regulatory activity in paper format remains the legal document.	The regulatory activity in "non-eCTD electronic-only" format is the legal document.	The regulatory activity in "non-eCTD electronic-only" format is the legal document.
Signature	Scanned copy of signed document (or a digital signature where applicable) is Required		
Letter of Attestation	Letter of Attestation stating that material in the regulatory activity or additional information provided electronically is exactly matching the material in paper format.	Not applicable	Not applicable
Plan for format requirement	Health Canada is phasing out this format.	This format is an interim option for filing regulatory activities.	Health Canada is considering a date for mandatory filing of this format for regulatory activities in scope of the eCTD guidance document.

DMF filing fee –Type-I (API) (15)

Type of Submission	Fee in CDN*
DMF-New Registration	$433 Cdn
DMF Biannual Update	$196 Cdn
Number of Letters of Access (LOA)	$196 Cdn

* DMF fee will be increased by approximately by 5% in the month of April.

DMF Filing contents in Module -1 and Procedure:

1.0 Correspondence

1.0.1 Cover Letter

1.0.2 Life Cycle Management Table (*Only required for eCTD)*

1.0.3 Copy of Health Canada Issued Correspondence

1.0.7 General Note to Reviewer

1.2 Administrative Information

1.2.1 Application Forms

1.2.2 Fee Forms

1.2.3 Certification and Attestation Forms

1.2.5 Compliance and Site Information

1.2.5.2 Establishment Licensing

1.2.5.5 Good Manufacturing Practices

1.2.6 Authorization for Sharing Information

1.2.7 International Information

MODULE-2

Quality overall summary (QOS) will be divided into two parts Applicants part and Restricted part. Both word copy and pdf copy needs to be submitted to the authority.

MODULE-3

Quality part will be divided into two parts namely Applicant Part and Restricted Part. Applicant part can be shared with the customer/sponsor. Restricted Part which contains manufacturing (CMC) related details needs to be confidential and not to share with any customer. Restricted part is exclusively made to submit to the authority to get approval for the product dosage.

- DMF fee will be paid to the finance sections and mode of payment is detailed below;(16)

1. Cheques, money orders or international bank drafts should be made payable to the "Receiver General for Canada". Cheques drawn on non-Canadian banks MUST be issued in coordination with a referenced Canadian bank (that is, referenced on cheque), otherwise, they are NOT ACCEPTED.

2. Wire payments of fees paid in advance of the service will be accepted only when wired in CANADIAN FUNDS to:

Bank Name: Scotiabank

Toronto Business Service Centre

40 King Street West, Toronto

Ontario, Canada, M5H 1H1

SWIFT: NOSCCATT

Bank Number: 002

Transit Number: 47696

Beneficiary Name: HEALTH CANADA - CFOB

Beneficiary Account Number: 476961242210

Description Field: 022-22879

- Once the DMF fee is paid the DMF will be reviewed for both Administrative and Technical part.

- In case of any queries, will be sent through mail for the regulatory contact person provided in the DMF and also Fax.

- Referenced customer will be notified regarding queries by Authority.

- Queries need to be responded to the DMF holder and Applicant part changes related to the queries will be notified to Customer /Sponsor.

- Once the queries cleared, Approval letter will be sent to the DMF holder.

EU Active substance master file (ASMF) or EDMF

Marketing Authorization Application is an application to the relevant authority to market a drug or medicine in Europe market. (Typically, the UK's MHRA or the EMA's Committee for Medicinal Products for Human Use (CHMP).

Manufacturers can enter in EU market by using following authorized ways for application of MAA. European Economic Area (EEA) unites the 28 EU member states & EEA European Free Trade Association (EFTA) states (Iceland, Liechtenstein, Switzerland & Norway).

Austria	Belgium	Bulgaria
Croatia	Cyprus	Czech Republic
Denmark	Estonia	Finland
France	Germany	Great Britain
Greece	Holland	Hungary
Iceland	Ireland	Italy
Latvia	Liechtenstein	Lithuania
Luxembourg	Malta	Netherlands
Norway	Poland	Portugal
Romania	Slovakia	Slovenia
Spain	Sweden	Switzerland

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. (17)

European DMF Filing System

Marketing Authorization Application (18)

- Prior submission applicant should notify the European Medicine Agency (EMA) of their intention to submit an application and give a realistic estimate of month of submission.

- MAA can be filled in four ways. (19)

➢ Centralized procedure.

➢ National procedure.

➢ Mutual recognition procedure

➢ Decentralized procedure.

Centralized Procedure

- A marketing authorization granted under the centralized procedure is valid for the entire Community market, which means the medicinal product may be put on the market in all Member States.

- The Regulation (EC) 726/2004 lays down a centralized Community procedure for the authorization of medicinal products, for which there is a single application, a single evaluation and a single authorization allowing direct access to the single market of the Community.

National authorization procedures

- In order to obtain a national marketing authorization, an application must be submitted to the competent authority of the Member State.

- Each EU Member State has its own procedures for the authorization, within their own territory.

- The competent authorities of the Member States are responsible for granting marketing authorizations for medicinal products which are placed on their markets, except for medicinal products which are authorized under Regulation (EC) No 726/2004 (Community Authorizations).

- MA applications should be completed within 210 Days.

- If any organization wishes to market their product only in one EU country then this is preferred procedure. No need to book the slot, only need to inform relevant authority prior filing.

Mutual recognition procedure

- Companies that have a medicine authorized in one EU Member State (which would be through a National Procedure) can apply for this authorization to be recognized in other EU countries.

- Authorization of the medicines in several countries simultaneously.

- Quicker to first market.

- Can withdraw application from critical Concerned Member State (CMS).

Decentralized Procedure (DCP)

- For products that fall outside the scope of the European Medicines Agency (EMA [www.ema.europa.eu]) with regard to centralized procedures, a sponsor can submit under the decentralized procedure.

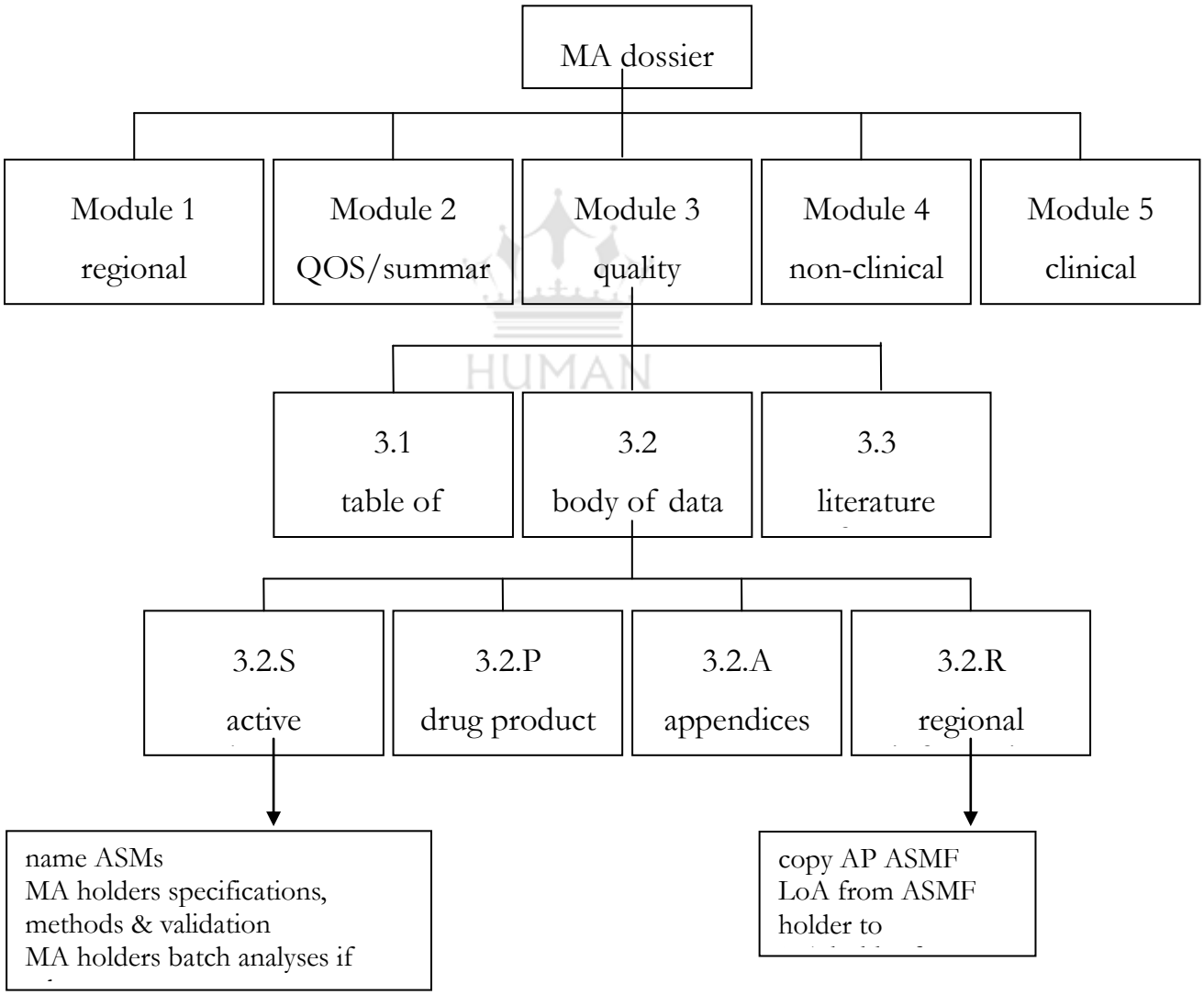
- Using this process, a sponsor can apply for simultaneous authorization in more than one EU country for products that have not yet been authorized in any EU country.

- Need to book slot with choice of RMS via slot booking procedure.

- Once slot granted, application needs to be submitted to RMS & all CMS.[after payment of relevant fees]

- From July 1, 2015, new marketing authorization applications for decentralized procedures must be submitted (eCTD) format.

EUDMF / ASMF General Content



European Directorate for the Quality of Medicines & HealthCare (EDQM)

Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP)

CEP is the certificate given by EDQM for complying with European Pharmacopoeia (Ph.Eur.)

Major Advantages of CEP: (20)

- CEP can be applied if the substance name is published in Ph.Eur. and specification of the drug substance should comply with Ph.Eur.
- CEP can be applied without customers but EDMF/ASMF is purely customer driven.
- If Approved CEP is available we can give Letter of Access to any European countries irrespective of EU procedures and recently Canada and Australia also started accepting CEP.
- No need to submit analytical method validation only Ph.Eur. methods need to be verified.

Contents of CEP

Module-1:

- Complete application form with signed certificates
- Cover Letter
- Expert CV

Module-2:

Quality overall summary will be written by Expert in EDQM format available in website.

Module-3:

All sections as per ICH M4 and stability section is not mandatory, it's optional if retest needs to be captured on the Certificate then 3.2.S.7. Stability needs to be submitted.

EDQM Fee applicable; (20)

Item	Fee
Simple chemical certificate	5000 €
Simple TSE or herbal certificate	3000 €
Double certificate (chemical + TSE)*	8000 €
Certificate for chemical purity and sterility	8000 €
Certificate for chemical purity and sterility + TSE**	9000 €
Renewal	1500 €
Notification	1000 €
Minor revision	1500 €
Grouped revisions (affecting several dossiers)	2000 €
Major revision (may include minor changes and notifications)	2000 €
Transfer of Holdership	1500 €
Evaluation of sterility data	3000 €

DMF Requirements	USFDA	CANADA	EU	EDQM
Health Authority	FDA U.S Food and Drug Administration	Health Canada / Santé Canada	EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH	edqm European Directorate for the Quality of Medicines & HealthCare / Direction européenne de la qualité du médicament & soins de santé
FOR API	US DMF	DMF	ASMF / EDMF	CEP
Fee for DMF (New)	$ 51,140	433 CDN $	Will be paid by formulators except Italy.	5000 €
Fee type	One time including life cycle management	Fee for bi-annual update and LOA reference	Depends on EU countries requirements.	Fee for MAJOR changes, Minor changes and LOA Reference.
Updation	Annually	Bi-annually	5 years once or based on customer feed back	5 years once
LOA Fee	NIL	196 CDN $	Nil	Nil
Updation Fee	NIL	196 CDN $	Nil (Excpt Italy)	1500 €

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