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REGULATORY REQUIREMENTS OF DRUG MASTER FILES BY FOOD AND DRUG ADMINISTRATION (USA), EUROPEAN MEDICINES AGENCY (EUROPE) AND HEALTH CANADA (CANADA) AND THEIR COMPARISON

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ABSTRACT

The pharmaceutical industry is one of the most regulated industries; no drug would be marketed without the teams of medical researchers and other specialists who worked to make sure it receives regulatory authority's approval. A regulatory authority is an agency of the government that is responsible for protecting public health in safety aspects. A Drug Master File is a confidential document used to provide detailed information about facilities, processes or articles used in the manufacturing process, packaging and storing of one or more human drug. A drug master filecomprises 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; and the Restricted Part, which contains confidential information about the manufacturing procedure that only needs to be disclosed to the authorities. This review article provides information on regulatory requirements of Drug Master Files by Food and Drug Administration (USA), European Medicines Agency (Europe) and Health Canada (Canada) and their comparison.

Keywords: European Drug Master File, Active Substance Master File, US-Drug Master file. DMF Canada

INTRODUCTION

The pharmaceutical industry is one of the most regulated industries; no drug would be marketed without the teams of medical researchers and other specialists who worked to make sure it receives regulatory authority's approval. Regulatory affairs professionals are key players in drug development for obtaining approvals and maintaining lifecycle management of both branded and generic drugs[1].They are the primary communications link between the company and agencies such as USFDA, MHRA, CDSCO and TPD etc. A regulatory authority is an agency of the government that is responsible for protecting public health in safety aspects. The present study focuses on API filing (DMF System) in United States, Canada and Europe[2]. Drug Master File or DMF is a document prepared by a pharmaceutical manufacturer andsubmitted solely at its discretion to the appropriate regulatory authority in the intended drugmarket. There is no regulatory requirement to file a DMF. However, the document providesthe regulatory authority with confidential, detailed information about facilities, processes, orarticles used in the manufacturing, processing, packaging, and storing of one or more humandrugs[3]

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Typically, a DMF is filed when two or more firms work in partnership on developingor manufacturing a drug product. The DMF filing allows a firm to protect its intellectual property from its partner while complying with regulatory requirements for disclosure of processing details.

DMF GUIDELINES HISTORY IN USA, EUROPEAND CANADA[4]

Guidelinesin USA:

In USA DMF guidelines are established in September 1989 Guideline for Drug Master Files.

Guidance for Industry: Generic Drug User Fee Amendments of 2012

Guidelines in EUROPE:

31 May 2013- This guideline replaces guideline CPMP/QWP/227/0Committee of Human Medicinal Products CHMP/QWP/227/02Rev3/Corr *

Committee of Veterinary Medicinal Products EMEA/CVMP/134/02Rev3/Corr Discussion at the HMPC November 2005 – January 2006

Adoption by the HMPC – 22 January2006

Draft agreed by Quality Working Party –9 February 2006 Adoption by CHMP for release for consultation-23 March 2006 Adoption by CVMP for release for consultation-20April 2006 End of consultation (dead line for comments) – 30 August 2006 Agreed by Quality Working Party-1 December2011

Adoption by CHMP for release forconsultation-15 December 2011Adoption by CVMP for release

forconsultation-12 January 2012End of consultation (deadline for comments) - 12 March 2012
Rev. 03 Agreed by Quality Working Party -04 May 2012
Rev. 03 Adoption by CVMP- 14 June2012
Rev. 03 Adoption by CHMP - 21 June 2012
Rev. 03 Date for coming into effect-1October2012

Guidelines in CANADA: September 05,2008

The draft version of this Health Canada guidance document Drug Master Files (DMF) is now available for comment. This guidance document is a revised version of the guidance document Product Master Files published in 1994 which will replace the 1994 document when it is officially adopted.

EuropeanDMF/ASMF[5]

EC procedure where information can be provided to the authorities and the applicant, where the active substance manufacturer is not the applicant for a product marketing authorization, with a view to protecting valuable manufacturing know-how. Established in 1989-1991 Revised in 2005 and became ASMF (Active Substance Master File) after implementation of CTD in EU Applicable only to active substances has been divided into 2 parts-An applicant's part and an ASM Restricted Part. 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.

Canadian DMF's[6]

A Drug Master File (DMF) is a reference that provides information about specific processes or components used in the manufacturing, processing, and packaging of a drug. The DMF is a useful vehicle for providing information to Health Canada, where that information is of a proprietary nature and is not available to the manufacturer of the dosage form or to a Sponsor of a submission when they are not the dosage form manufacturer. The DMF can be referenced by drug manufacturers in support of their New Drug Submissions (NDSs), Abbreviated New Drug Submissions (ANDSs), Supplement to a New Drug Submission (SNDS) Supplement to an Abbreviated New Drug Submission (SANDS), DIN submissions, Notifiable Changes (NCs), New Product Number (NPN) applications and Clinical Trial Applications (CTAs). DMFs may be referenced by more than one drug manufacturer. Canadian DMF: division of formation to Sponsor's (Open) and Restricted (Closed) part for DMFs type I and IV

Canadian DMFs:

Type I- Drug substance or intermediate in the manufacture of DS
Type II- Container-closure systems or components
Type III- Excipients, colorants, flavors and other additives
Type IV-Dosage forms and drug product intermediates (e.g. blend of drug substance and excipients)

Fees for DMF Filling[7]

Under GDUFA, the DMF fee is owed by each person that owns a type II active pharmaceutical ingredient DMF that is referenced, on or after October 1, 2012, in a generic drug submission by an initial letter of authorization. This is a one-time fee for each individual DMF. This fee is due no later than the date on which the first generic drug submission is submitted that references the associated DMF.

Under section 744 B (a) (2)(D)(iii) of the FD&C Act, if a DMF has successfully undergone an initial completeness assessment and the fee is paid, the DMF will be placed on a publicly available list documenting DMFs available for reference. Thus, some DMF holders may choose to pay the fee prior to the date that it would otherwise be due in order to have the DMF placed on that list. In order to calculate the DMF fee, FDA assessed the volume of DMF submissions overtime.

The statistical forecasting methodology of power regression analysis was selected because these models how very good fit to the distribution of DMF submissions overtime. Based on the 8 months of available data representing the total paid DMFs from FY2013 and projecting a5-year timeline (October 2013 to October 2017), FDA is estimating 583 fee-paying DMFs for FY 2014. The FY 2014 DMF fee is determined by dividing the DMF revenue by the estimated number of fee-paying DMFs in FY 2014. Section744B (b) (2) (A) specifies that the DMF fees will make up 6 percent of the $305,659,000, which is $18,340,000 (rounded to the nearest thousand dollars). Dividing the DMF revenue amount ($18,340,000) by the estimated fee-paying DMFs (583), and rounding to the nearest $10, yields a DMF fee of $31,460 for FY 2014

DMF Fees in Europe: [8]

Table 1: DMF fees for Registration of Active Substance Manufacturers & Importer/Distributor

Fees for Registration of Active Substance Manufactures		Fee	Notes
New Application	New application for registration as a manufacture of Active Substances	**£5006**	£3143 application fee plus £1863 assessment fee £2655 Inspection fee less £1863 assessment fee
	Additional fee if the risk assessment of the initial application triggers an inspection	**£792**	
	Inspection fee (per site if required)	**£2655**	Charged for inspections conducted post registration
Variations	Notification of changes (Variation)	**£257**	
	Inspection fee (per site if required)	**£2655**	

Table 2: DMF Fees in Canada[9] Drug Master File(DMF) Fee Form

Drug Master File Name:		
DMF Number (if issued):	**Customer/Client Account Number (if issued):**	
DMF Company Name:		
Calculation of Payment		
DMF for New Registration:	x $408 Cdn =	$
DMF Biannual Update:		
Number of Letters of Access Enclosed:		
Total Fee (sum of the above):		
Fees Paid by: ☐Owner ☐Agent ☐Other-For Letter of Access Only (specify):		
Method of Payment Cheques, money orders, international bank drafts or wires		

Table 3: Comparison of DMF's of USA, Europe and Canada:

DRUG MASTER FILE REQUIREMENTS	USA	EUROPE	CANADA
HEALTH AUTHORITY	U.S. Food And Drug Administration	EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH	Health Canada Santé Canada
FOR API	US DMF	EDMF/ASMF	DMF
DEFINITION OF DMF	A Drug Master File (DMF) Is A Submission To The Food And Drug Administration (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	EC Procedure Information Can Be Provided To The Authorities And The Application, Where The Active Substance Manufacture Is Not The Applicant For Product Marketing Authorization, With A View To Protecting Valuable Manufacturing Know-How	A Drug Master (DMF) Is A Reference That Provides Information About Specific Processes Or Components Used In The Manufacturing, Processing, And Packing Of A Drug.
TYPES OF DMF	Four Types Of DMF: I. Drug Substance, Drug Product, Intermediates and Material Used In Their Manufacture. II. Packing Material. III. Excipients, Colorants, Flavors, Essence, Or Material Used In Their Preparation. Other Sterile Manufacturing Plants, Biotech Contract Facilities, Clinical.	No Types Of DMF	Four Types Of DMF: TYPE I: Drug Substance Or Intermediate In The Manufacture Of Ds. TYPE II: Container-Closure System Or Components. TYPE III: Excipients, Colorants, Flavours And Other Additives. TYPE IV: Dosage Forms And Drug Product Intermediates (E.G. Blend Of Drug Substance And Excipients)
FORMAT	The United States Food And Drug Administration Required Two Copies Of Each Type DMF In The CTD Format, But Not In CTD Module Form. FDA Requires One Continuous Document In The CTD Format. Quality Overall Summary Is Also Required. Electronic Submission And Paper Submission.	ICH CTD Module 3-Quality And Quality Over All Summary. The Scientific Information In The ASMF Should Be Physically Divided Into Two Separate Parts, Namely The Applicant's Part (AP) And The Restricted Part (RP). The United Kingdom 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	ICH CTD Module 3-Quality And Quality Overall Summary, DMF Divided Into Two Separate Parts, Namely The Applicant's Part (AP) And The Restricted Part (RP) Paper Submission

		Version Is Identical To The Paper Copy. Several Other Countries Process Are In The Process Of Converting To The Non-ICH (Xml), Non-E-CTD Electronic Filing Format. These Include Belgium, Denmark, Germany, and France.	
SUBMISSIONS ALONG WITH DMF	A. <u>Transmittal Letters</u> a. Identification Of Submission: Original, The Type of DMF as Classified in Section Iii, And It's Subject. 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. <u>Administrative Information</u> 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	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. 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.	Name And Address The DMF Should Include The Following Information: • The Name and Address of the Agent If Applicable. • The Name And Address Of The Corporate Headquarters (DMF Owner); And The Name and Address of the Manufacturing Processing, And Packaging Facilities.
FORWARDING ADDRESS	Drug Master File Staff Food And Drug Administration 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 **Facsimile** +44 (0)20 7418 8416 **E-Mail** Info@Ema.Europa.Eu **Website** www.Ema.Europa.Eu	Drug Master File Administration Unit, Therapeutic Products Directorate, Finance Building, Al: 0201d, 101 Promenade Tunney's Pasture Driveway, Tunney's Pasture Ottawa, Ontario K1a 0k9 Canada Email:Dmf_Enquiries@Hc-Sc.Gc.Ca Fax Number: 613-957-3989
LETTER OF AUTHORIZATION	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 Drug Master File 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	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 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

	DMF By Reference And A List Of Changes Made Since The Previous Annual Report.		Update Within A 5years Period.
DMF FESS	Only For Type 2 DMF Fees Will Be Taken According To GDUFA-$31,460	New Applications- £5006	DMF For New Registration-$408Cdn

There is no fixed time for getting DMF number.

CONCLUSION

Drug Master File (DMF) is a document containing complete information on an Active Pharmaceutical Ingredient (API). The Drug Master File may be utilized either by the holder who establishes the file, or by one or more additional parties in support of their application. The Drug Master File filing allows a firm to protect its intellectual property from its partner while complying with regulatory requirements for disclosure of processing details. 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 DMF consists of non- confidential and closed part confidential.

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