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A COMPARATIVE STUDY OF THE DRUG REGULATORY AND MARKET AUTHORIZATION FRAMEWORK OF THE EUROPEAN UNION AND UNITED STATES

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ABSTRACT

Pharmaceuticals must be regulated and approved in the European Union (EU) and the United States (US) to ensure their safety, efficacy, and quality. An analysis of key differences and similarities between these two regions' regulatory frameworks and approval processes is provided in this study. A single marketing authorization is valid in all EU member states under the centralised procedure overseen by the European Medicines Agency (EMA). Decentralized and mutual recognition procedures also allow national approvals to be recognized by other members. A New Drug Application (NDA) and Biologics License Application (BLA) are the approval processes managed by the US Food and Drug Administration (FDA). The regulatory requirements and timelines between the two regions differ, but both require rigorous preclinical and clinical testing. Drug safety and efficacy are monitored by robust pharmacovigilance systems at both the EMA and FDA after approval. Regulatory policies are also examined in the study in terms of their impact on pharmaceutical innovation and market access. Pharmaceutical companies seeking to navigate the complex processes of drug development and commercialization must understand these regulatory landscapes. The comparative analysis highlights the importance of harmonizing global regulatory standards to facilitate access to safe and effective medicines around the world

Key words: Drug regulatory process, pharmaceutical approval, marketing authorization, European Medicines Agency, EU, US, Food and Drug Administration.

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INTRODUCTION

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. Drug Master File is a Submission to the FDA of Information usually concerning the confidential, detailed Information about Chemistry, Manufacturing and Controls (CMC) of a Drug Product or a Component of a Drug Product .The submission of a DMF is not required by law or FDA regulation. A DMF is submitted solely at the discretion of the holder. The information contained in the DMF may be used to support an Investigational New Drug Application (IND), a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), another DMF, an Export Application, or amendments and supplements to any of these. As per the regulatory guidelines, it is mandatory to file a drug Master file and after being approved, releasing the drug into the market.

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A drug master file may be for a bulk drug or for a formulation. A drug Master file declared by the company provides in detail the manufacturing place, physicochemical properties, Pharmacodynamics/kinetic, toxicology studies of the bulk drugs and formulations, therapeutic class, dosage form, strength, route of administration, labeling, packaging etc. Filing a drug master file at USFDA by a company is an indication that the company is claiming its capability in manufacturing and having a facility complying USFDA rules and regulations guideline is intended to provide DMF holders with procedures acceptable to the agency for preparing and submitting a DMF. The guideline discusses types of DMF's, the information needed in each type, the format of submissions to a DMF, the administrative procedures governing review of DMF's, and the obligations of the DMF holder. DMF's are generally created to allow a party other than the holder of the DMF to reference material without disclosing to that party the contents of the file. When an applicant references its own material, the applicant should reference the information contained in its own IND, NDA, or ANDA directly rather than establishing a new Drug Master file.

METHODOLOGY

Types of Study

The study was conducted with an objective to chalk out the regulatory framework for Drug Master File registration legislations and guidelines. The major emphasis has been provided to regulatory requirements of United States.

Internet using the web page content:

The literature was collected using numerous search engines e.g. Pharmabiz, DMF search engine, Google Scholar and many more. Online books also served as a good source of information. Key words in the search involved Drug Master File Registration requirements along with the name of various parameters associated to pharmaceutical field, name of regulatory bodies and other variations were used.

Criteria for selection of study parameters: Part-I: Requirement for Drug Master Filing:

There is no legal or regulatory requirement to file a DMF. Information can be in an Application OR a DMF. A DMF may be filed to provide CMC information that the FDA reviews. The DMF must be submitted in English language. Whenever there is a submission in another language, an accurate certified English translation must also be included. Each page of each copy of the DMF should be dated and consecutively numbered. An updated table of contents should be included with each submission.

Part-II: Documents and study information required for Drug master File preparation. Each DMF submission should contain Transmittal letter, Administrative information about the submission. The DMF will be Reviewed only when it is Referenced in an Application or Another DMF. Holder must submit an LOA (Letter of Authorization-2 copies) to the DMF.

Part-III: Dossier compilation and submission. All the documents needed for Drug Master File submission should be compiled and should be submitted to USFDA and EMEA in US and Europe Respectively.

DISCUSSION

Requirements and Challenges to File A DMF

There is no legal or regulatory requirement to file a DMF. Information can be in an Application OR a DMF. A DMF may be filed to provide CMC information that the FDA reviews. Examples: drug substance, novel excipient. Conversely, there is no need to file a DMF for information that FDA does not Review.

DMFs are documents containing proprietary information concerning manufacturing facilities, production details and packaging. In the United States, Canada and elsewhere, DMFs may also cover proprietary support information and excipients. Prior to the initiation, acceptance and adoption of the International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) using their Common Technical Document (CTD) format, each of the major health agencies in the US, Canada, EU, Australia, and Japan had their own formats for the compilation of DMFs. With the adoption of the CTD format, the efforts for preparing a DMF have been simplified. The ICH CTD format has simplified the organization of DMFs for the world's major health agencies. However, there are still many differences in terms of application requirements, number of copies required and CTD Module 1 "Administrative Information and Prescribing Information" formats.

It is common knowledge that most health authorities are less than fond of dealing with DMFs However, protecting proprietary and confidential information is paramount to all. Many countries still require paper copies of these documents. The size of DMFs easily approaches or exceeds 1000 pages. Each master file is made up of several volumes (CTD Modules) as well as duplicate copies. The resulting amount of paper documents that must be generated and securely stored becomes quite large and onerous. Theadoption of electronic submission of these documents seems much more convenient. However, only certain European Union countries require electronic copies.

Registration Requirements

Each DMF submission should contain Transmittal letter, Administrative information about the submission. DMF’s should contain a commitment by the firm that is facilities will be operated in compliance with applicable

environment laws. The DMF must in English language. Whenever there is a submission in another language, an accurate certified English translation must also be included. Each page of each copy of the DMF should be dated and consecutively numbered. An updated table of contents should be included with each submission.

Types of DMF

In the Unites States Drug Master Files are submitted to Food and Drug Administration (FDA).
There Are 5 Types of DMF'S in UnitedS tates.

TYPE I:
Manufacturing site facilities, operating procedures and personnel not specific to a drug substance are included in Type I. Type I DMFs are no longer accepted by the FDA but old ones remain on file.Type I DMFs are no longer accepted per a Final Rule published January 12, 2000 (65 FR 1776).
TYPE II:
Drug substances, substance intermediates and materials used in their preparation, or a Drug product. A Type II DMF, the most common form, canalso cover dosage form drugs manufactured under contract for another company which would file an Abbreviated New Drug Application.
TYPE III:
Packaging materials, from bottles and caps to PVC resin used in their manufacture must be covered in a DMF or other FDA document such as an NDA.
TYPE IV:
Excipients, colorant, flavor, essence or material DMF. Excipients are chemically inactive substances such as starches or cellulose used to bind drug powder together so that it can be pressed into a tablet. Other examples include flavorings in children's drugs, alcohol in liquids, etc.
TYPE V:
FDA accepted reference information not included in the other types.

Submissions to Drug Master Files

Each DMF submission should contain a transmittal letter, administrative information about the submission, and the specific information to be included in the DMF as described in this section. The DMF must be in the English language. Whenever a submission contains information in another language, an accurate certified English translation must also be included. Each page of each copy of the DMF should be dated and consecutively numbered. An updated table of contents should be included with each submission.

Transmittal Letters

A transmittal letter serves three purposes. It instructs the Agency that this is
An original submission and the Agency should assign a DMF number and hold the DMF for future reference in the filing of an application for a drug product. The submission is an amendment to a DMF on file with the Agency. The letter provides instructions on updating the DMF. The Letter is an Affirmation that the DMF Holder has reviewed the DMF and found that no Amendment is necessary.

The Following Should be Included in Transmittal letters.
A.1 Original Submissions
A.2 Amendments

DMFs UNDER GDUFA

The Generics Drug User Fee Act (GDUFA) section of the "Food and Drug Administration Safety and Innovation Act (S.3187) includes provisions for fees for DMFs, an initial completeness assessment, and communications with DMF holders. GDUFA applies only to Type II DMFs for drug substances (Active Pharmaceutical Ingredients (APIs)) used to support Abbreviated New Drug Applications (ANDAs). It does not apply to any other type of DMF or to Type II DMFs used to support NDA or INDs.

The Generic Drug User Fee Amendments of 2012 (GDUFA) is designed to speed access to safe and effective generic drugs to the public and reduce costs to industry. The law requires industry to pay user fees to supplement the costs of reviewing generic drug applications and inspecting facilities. Additional resources will enable the Agency to reduce a current backlog of pending applications, cut the average time required to review generic drug applications for safety, and increase risk-based inspections.

GDUFA is designed to build on the success of the Prescription Drug User Fee Act (PDUFA). Over the past 20 years, PDUFA has ensured a more predictable, consistent, and streamlined premarket program for industry and helped speed access to new, safe and effective prescription drugs for patients. GDUFA will also enhance global supply chain safety by requiring that generic drug facilities and sites around the world self-identify.

Initial Completeness Assessment (CA)

FDA will perform an initial CA once a DMF holder files a Type II API DMF with the generic drug user fee cover sheet (Form FDA 3794) and the fee payment has been verified. The initial CA does not replace the full scientific review, which is performed to determine the adequacy or inadequacy of the information contained in the DMF to support an ANDA review decision.

European Drug Master File

The European Drug Master File (DMF) procedure may be used when the active substance manufacturer (ASM) is not the applicant for a product marketing authorization (applicant), with a view to protecting valuable know-how on the manufacture of the active substance. European DMFs were established in 1989-1991,

revised in 2005 and became Active Substance Drug Master File after Implementation of Common Technical Document in Europe. A DMF is a document containing the information required to demonstrate that the quality of the active substance is adequately controlled by the specification proposed by the applicant. The applicant must, therefore, collaborate with the person submitting a separate DMF to ensure that all relevant information required is supplied. Furthermore it must be ensured that the applicant's part of the DMF contains all information needed for the applicant to take full responsibility for the preparation, including the suitability of the active substance (as supplied) for the intended route of administration.

CONTENTS OF DRUG MASTER FILE

Applicant's Part and ASM Restricted Part of a European DMF

The DMF contains information which includes valuable know-how which should be kept confidential and submitted to the authorities only. Therefore, it should be 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 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 competent authorities. The applicant's part of the DMF is still a confidential document which cannot be submitted to third parties without the written agreement of the ASM.

CONCLUSION

The Drug Master File is a critical document used to support a drug application. Deficiencies in the Drug Master File can result in the delay of approval of drug applications. It is important that the DMF be filed in a timely manner and that the standards used to compete it are of the same quality as the actual drug application. The DMF can be considered an extension of the drug application. The drug review process works best when the required information flows from the DMFs to the drug application.

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