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A COMPARITIVE STUDY OF DMF (USFDA) AND EDMF (EU) AND IN BETWEENPARA IV FILINGS (USFDA) AND IPR (EU): A REVIEW

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ABSTRACT

Pharmaceutical manufactures need to prepare a document and submitted solely at its discretion to the appropriate regulatory authority in the intended drug market. The file is known as the DMF in US and EDMF in EU the work into compare the drug master files between USFDA and EU for drug registration process and also vision to gain the research about Para IV filling in US and IPR in EU which is useful for the knowledge on drug patents.The literature work, the comparison parameters, difference in filing process of DMF and EDMF requirements has been studied and explained in detailed in this work, which gives the clear over view of the role of filing the DMF and EDMF. It also gives an outline work of PARA IV filings and IPR Studies.

KEYWORDS: DMF, EDMF, PARA IV filings, IPR Studies and regulatory authority.

US FDA (DMF)

- **Drug Master File** or **DMF** is a document prepared by a pharmaceutical manufacturer and submitted solely at its discretion to the appropriate regulatory authority in the intended drug market. There is no regulatory requirement to file a DMF. However, the document provides the regulatory authority with confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. Typically, a drug master file is filed when two or more firms work in partnership on developing or 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.
- Drug Master File (DMF) is a document containing complete information on an Active Pharmaceutical Ingredient (API) or finished drug dosage form.
- An Active Substance Master File (ASMF) is the currently recognised term in Europe, formerly known as European Drug Master File (EDMF) or a US-Drug Master file (US-DMF) in the United States.
- Drug master files (DMFs) are submissions to FDA used to provide confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drug products.

Para IV filing

- A generic company is rewarded for a Para IV filing. The first applicant to submit a substantially completed ANDA (Abbreviated New Drug Application) is given marketing exclusivity for 180 days. Exclusivity means that no company is allowed to launch its product during this period.
- *As a result, there isn't any competition. As the first mover, this helps the manufacturer have an advantage. It can garner a market share. This is a valuable opportunity to maximize profit margins without any competition.*

Guideline on EDMF

- 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 Authorization (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 has 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.

  Pharmaceuticals: EU refines intellectual property rules
- The regulation will entitle EU-based companies to manufacture a generic or bio similar version of an SPC-protected medicine during the term of the certificate, if done either for the purpose of exporting to a non-EU market where protection has expired or never existed, or for stockpiling during the final 6 months of an SPC ahead of entry into the EU

market. It will thus remove a major competitive disadvantage of EU manufacturers compared to manufacturers based in non-EU countries and ensure a better deal for patients.

AIM

- To compare the drug master files between USFDA and EU for drug registration process and also vision to gain the research about Para IV filling in us and IPR in EU which is useful for the knowledge on drug patents

Dmf Procedure Usfda And Eu

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

Role of DMF

- To support the documents for the registration / approval of drug products.
- In the Chemistry, Manufacturing and Controls (CMC) sections of the drug submission, the DMF documents the drugs identity, purity, strength and quality.
- To protect Proprietary and Confidential Information.

Differences between Applications and DMFs

Application	DMF
Submitted to a review division	Submitted to CDR
Each submission is assigned to a reviewer	Each submission is NOT assigned to a reviewer New in database: Reviewer can get automatic assignments
database links particular submission with volume	Pre-database: No link between submission and volume New in database: Entries linked with volume
Reviewed on receipt. Each submission has a due date.	Reviewed ONLY when referenced. No due date except for the Application supported by the DMF.
ALL post-approval submissions assigned to a reviewer	All changes NOT assigned to a reviewer New in database: Reviewer can choose to be notified.

Country	**Submission Types**
USA	New Drug Application (NDA), for New Drugs accelerated New Drug Application (ANDA)- for Generics Biologic License Application (BLA), for biologic.
EU	Marketing Authorization Application (MAA) - via the Centralized Procedure for eligible products. For other products, via the decentralized, mutual recognition or national authorization are applicable.

TYPES OF DMF

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, 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.
- EUROPEAN DMF - TYPES

Unlike US-Drug Master file, the scientific information of EDMF or ASMF is physically divided into 2 parts as per European filing procedures.

A. Restricted part (Closed part)

Information regarded as to be confidential and to be submitted only to the Authority.

- Manufacturer(s)/site of manufacture
- Detailed description of the manufacturing process and process controls
- Control of materials (Starting material of the API, reagents, solvents, other materials used)
- Control of critical steps and intermediates
- Process validation and/or evaluation
- Manufacturing process development

B. Applicant's part (Open part)

Information regarded as to be non-confidential and to be given to the applicant. This information is also given to the authority as part of **DMF services**.

- These parts include:
- General information
- Characterization
- Control of API
- Reference standards or materials
- Container closure system
- Stability

RESULTS AND DISCUSSION

Drug Master File Requirements	Usa	Europe
Health Authority	Usfda	European medical agency
For api	Us dmf	Edmf/asmf
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).
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	A. Restricted part (closed part) B. Applicant's part (open part)

	Iv. Recipients, colorant, flavor, essence, or material used in their preparation V. Fda accepted reference Information.	

FORMAT	The USFDA require 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. QOS is also required. Electronic submission and paper submission.	ICH CTD Module 3-Quality and QOS. • ASMF divided into two: Applicant's Part (AP) and Restricted Part (RP). • The UK and the Netherlands will only accept Electronic copies each in their own separate electronic format, France requires both a Paper copy and an electronic copy. • Several other countries process is in the process of converting to the non-ICH (Xml), Non-etch electronic filing format.
Letter of authorisation	Required	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.	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),

SUBMISSIONS ALONG WITH DMF	➢ **Transmittal Letters** a. Identification of Submission: Original, The type of DMF as classified in Section III, and it's Subject. b. Identification of the Application 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.	➢ Letter of Access to the NCA/EMA. ➢ Applicant's Part ➢ Restricted Part Separate or Combined Quality Overall Summary (QOS) for the Applicant's and Restricted Parts
DMF FEES	Only for Type 2 DMF fees will be taken according to GDUFA-$31,460	New Applications- £5006

PARA IV FILING & 180 DAY's MARKETTING EXCLUSIVITY FOR FIRST SUCCESSFUL ANDA FILER

(Para Iv Anda Filing = Challenging Weak Patent)

- The Drug Price Competition and Patent Term Restoration Act (Hatch Waxman act) of 1984 streamlined generic drug approval process in US. HWA created an abbreviated process for generic drug approval without conducting costly and duplicative clinical trials. (Under the new legislation, generic entrants need to establish the bio equivalence of its drugs to the original).
- The rules created processes and incentives for both branded and generic companies involving challenges to patents.
- An important section of Hatch-Waxman Act actually encourages generic companies to challenge weak patents.
- If a generic company is the first to file its Abbreviated New Drug Application (ANDA) with a Paragraph IV certification and prevails in the subsequent lawsuit, that generic company is granted a period of market exclusivity of 180 days.
- So, it can price its product slightly below the branded version for six months, take market share from the branded product, and maintain its price point before other generics enter the market and erode the price and segment margins.
- The 180-day exclusivity incentive can be significant for a generic company as it would be the only generic version on the market.

PARA – IV Filing & 180 days exclusivity

- By making a Paragraph IV filing, the generic drug maker says the patent is at least one of the following:

(1) Invalid;

(2) Not infringed; or

(3) Unenforceable.

Basic Structure of PARA –IV Filing

CTD submission to USFDA by generic drug manufacturer

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Notice Letter to Patent Owner

⇩

45-Days for Patent Owner to Sue

⇩

30-Month Stay of FDA Approval of ANDA

⇩

180-Day Marketing Exclusivity for Successful First-Filer

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 human drug product. The content and the format for Drug Master File are used to obtain market authorization. The main objective of the DMF is to support regulatory requirements of a medicinal product to prove its quality, safety and efficacy.
- 180-day Marketing Exclusivity created to encourage Paragraph IV challenges by rewarding First Filers for undertaking the costs and risks of patent litigation, to challenge weak or improperly obtained patents, or to defend non-infringing generic products. Paragraph IV Certifications under Hatch-Waxman have spawned a tremendous number of legal conflicts between the generic drug makers and the owners of those patented drugs.

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