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Importance of Drug Master File in Processing of Active Pharmaceutical Ingredients (APIs)

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Mithun E G*[1], Satyavir Singh[2]

[1]*Research scholar OPJS University, Churu, Rajasthan, India*

[2]*Research Guide OPJS University, Churu, Rajasthan, India*

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ABSTRACT

Active Pharmaceutical Ingredient registration is a demanding task in the regulated market. Although the requirements are harmonized in regulated countries by CTD (Common technical document) filing, others have enormous diversity in requirements. ICH International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) brought regulatory authorities and pharmaceutical industries of Europe, Japan and the US together for various aspects of drug registration. The optimization of requirements is mandatory and can be judged by the incidence of higher costs involved in the availability of drugs, research and development facilities. For better treatment safety and efficacy the drugs must be justified and rationalized for public security. The quality, safety and efficacy data have their own importance in the registration Drug Master File.

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INTRODUCTION

The commercial significance of markets is increasing globally[1-2]. It is vital for the pharmaceutical industry to cope with the regulatory requirements for the betterment of public and to ensure their place in the market. This project approaches the registration requirements in the form a Drug Master File for market authorization. It also has drawn a comparative statement on various approaches for harmonization of registration requirements for pharmaceuticals.

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

2. Registered APIs will be published on websites that helps in the marketing of APIs to alldrug 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.

Regulation of API in USFDA:

Types of Drug Master Files in US[3-6]:

- 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.

Regulation of API in Europe:

Marketing Authorization Application is an application to the relevant authority to market a drug or medicine in the Europe market. (Typically, the UK's MHRA or the EMA's Committeefor 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).

Table 1: List of European Union Countries

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.

- **Restricted Part** (Closed / Confidential): Confidential information on themanufacturing of Active Pharmaceutical Ingredient[20].

European Directorate for the Quality of Medicines & HealthCare (EDQM)[7-10]

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.)

Regulation of API in Canada:

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 has divided into two sections:

- Sponsor's (Open)
- Restricted (Closed)[11-14]

As per the 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)[22].

MARKET SCENARIO:

The global active pharmaceutical ingredient market is estimated to reach USD 245.2 billion by 2024 from USD 182.2 billion in 2019, at a CAGR of 6.1% during the forecast period. The increasing incidence of chronic diseases, the growing importance of generics, and the increasing uptake of biopharmaceuticals are some of the major factors driving the growth of the global APIs market. On the other hand, the unfavourable drug price control policies across various countries and the increasing penetration of counterfeit drugs are expected to restrain the growth of this market in the coming years.

In 2019, the prescription drugs segment is expected to account for the largest share of the APIs market.

Based on the type of drug, the APIs market can be classified into two segments prescription drugs and over-the-counter (OTC) drugs. In 2019, the prescription drugs segment is expected to account for the largest share of the APIs market. The demand for drugs falling under this category has increased significantly in recent years due to the rising prevalence of target diseases. Additionally, the largest share of the prescription drugs segment can also be attributed to the increased focus of innovator companies on the development of specialty drugs and the affordability of healthcare. The implementation of significant federal reforms to improve the affordability of healthcare, especially in the US, has expanded the consumption of both traditional and specialty drugs. Also, inflation has played a key role in enhancing revenue from the sales of prescription drugs, particularly specialty drugs. All these factors are collectively responsible for a large share of this segment.

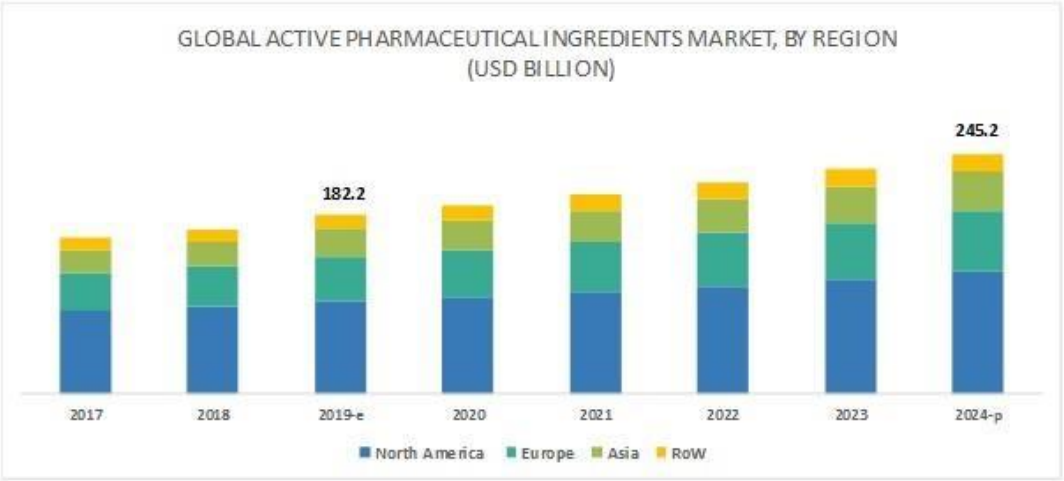

Figure 1: Global API Market by Region

Key players in the global APIs market

The global APIs market is competitive in nature, with several big as well as emerging players. The prominent players in the market are Pfizer, Inc. (US), Novartis AG (Switzerland), Sanofi (France), Boehringer Ingelheim (Germany), Bristol-Myers Squibb (US), Teva Pharmaceutical Industries Ltd. (Israel), Eli Lilly and Company (US), GlaxoSmithKline plc (UK), Merck & Co., Inc. (US), AbbVie Inc. (US), F. Hoffmann-La Roche Ltd. (Switzerland), and AstraZeneca plc (UK).

Pfizer is one of the leading players in the global **API industry**. The leading position of the company is majorly attributed to its exhaustive product portfolio. The company has a strong brand image, which gives it a competitive edge over other players. In order to remain competitive and strengthen its market position, the company primarily focuses on adopting both organic and inorganic growth strategies such as agreements, partnerships, collaborations, product approvals, and acquisitions. In accordance with this, in June 2016, Pfizer acquired Anacor Pharmaceuticals, Inc. (US), a leading biopharmaceutical company developing small molecule therapeutics[23].

MANUFACTURING PROCESS OF ACTIVE PHARMACEUTICAL INGREDIENT:

The active pharmaceutical ingredient (API) of medicine is the substance that exerts a therapeutic effect. In everyday language they are often referred to as drugs. Drugs are a wide range of different substances and can be classified as natural products, semisynthetic or synthetic, or biotechnological products. While the majority of drugs until now have been

synthetic molecules, the number of new medicines of biotechnological origin, including genetically modified molecules, has been increasing.

In the case of synthetic drugs, stereochemical aspects often play a role; often only certain enantiomers have the desired biological effect. Such drugs require either the specific synthesis of only one enantiomer or the separation of enantiomers after synthesis.

Synthetic drugs are manufactured using a large number of process steps; these need to be coordinated as well as possible. On the one hand there is the need to use production lines flexibly and on the other, cross-contamination of the different APIs must be avoided. It is increasingly important to utilize the capacities of production plants worldwide as efficiently as possible. The key to meeting these challenges lies in the optimization of the processes. Integration of the whole process from incoming goods to the finished product reduces costs and cycle times; the safety of personnel can be improved, even in Ex zones; and impurities in the product can be reduced to a minimum[24].

A General Manufacturing process of API is provided below as process flow;

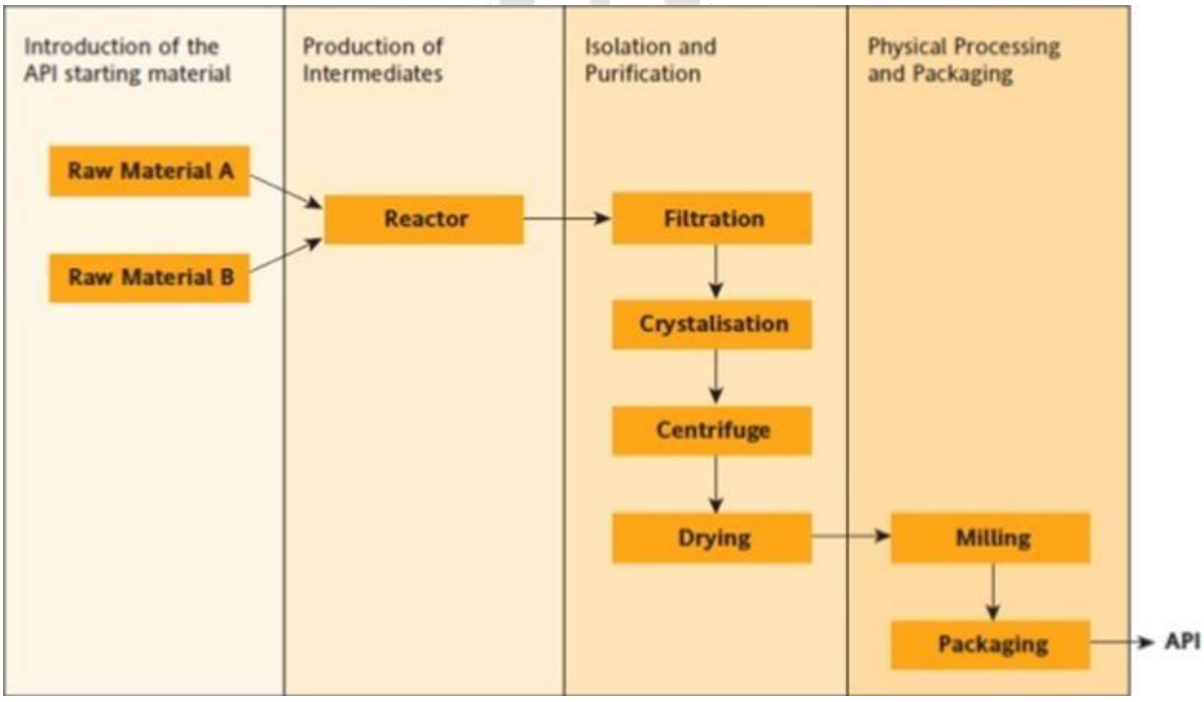

Figure 2: Manufacturing Process of Active Pharmaceutical Ingredient

DRUGS AND MEDICAL DEVICES:

Drugs and Medical Devices are both regulated by the Food and Drug Administration (FDA) through each by a separate division. All drugs must go through a long, rigorous process demonstrating safety at each juncture. The below table gives us some differences between a drug and a medical device.

Table 2: Differences between Drugs and Medical Device.[25]

Drugs	Medical device
Pure molecules based on pharmacology, chemistry, biotechnology, genetic engineering etc.	Physical objects, complex components and assemblies. Generally based on mechanical, electrical and materials engineering
Administered by mouth, skin, eyes, lungs etc. and act through metabolic, pharmacologic or immunologic means	Most act through physical interaction withbody or body parts
Typically, short half-life in body	Duration and nature of exposure varies widely
Long market life	Short market life (~ 18 to 24 months)
Very large multiple companies dominate	Over 80% small and medium sized enterprises
No service or maintenance	Some require service and repair

SUMMARY, RECOMMENDATION AND CONCLUSION:

Active pharmaceutical ingredient (API) is the driving force of the pharmaceutical industry. A combination of API and excipients makes a medicine i.e., Finished product. An API is a propeller of the healthcare industry. The manufacture of Active Pharmaceutical Ingredients (API) involves high-end technologies and strategies. Production of an API is a very critical task due to the necessary action of execution of hazardous chemical reactions. Active Pharmaceutical Ingredients are not only the heart and brain of drug products, but are also crucial to the regulatory filing success of drug applications.

Review of the Regulated markets like the United States, Europe and Canada in Pharmaceutical industries, it is evident there are significant differences between the old and new regulations for Active Pharmaceutical ingredients. Drug approvals are the most demanding in the world. The primary purpose of the rules governing medicinal products in Regulated markets is to

safeguard public health. It is the role of public regulatory authorities to ensure that pharmaceutical companies comply with regulations. There are legislations that require drugs to be developed, tested, trailed, and manufactured in accordance to the guidelines so that they are safe and patient's well - being is protected.

The drug master file contains complete & correct information about active pharmaceutical ingredient or finished drug dosage forms and CMC data i.e., chemistry, manufacture, stability, purity, impurity profile, packaging of any drug product or excipient. The main purpose of DMF is to support regulatory requirements of a medicinal product to prove its quality, safety and efficacy and this helps in obtaining a market authorization grant.

Drug regulations are becoming more and more stringent. Every now and then new amendments or new regulations are introduced to combat falsifications/shortcuts/ noncompliance by the industry. The regulations for Manufacturing, data integrity, validations, Impurity profiling, Import, export, storage and distribution are becoming complex.

Across most regional pharmaceutical markets, generics are emerging as strong challengers to branded medications. The demand for generic drugs is also set to increase following the imminent loss of patent protection for several blockbuster drugs. North America (USA & Canada) is the largest pharma market and has least restrictions. America has larger funding than European and Asian countries, and the growth is expected to continue. Japan is also a large market but it is one of less penetrable market. Japan and India also has its own guidelines for approval of generic drugs. Indian generic players are seen as a major threat by European generic companies. The Indian pharmaceutical market is one of the most advanced among the developing countries. The ranking of Indian market is 4th in volume and 13th in value. Currently different countries have to follow different regulatory requirements for approval of new drug. It is time consuming for the participating countries. For marketing authorization application (MAA) a single regulatory approach is applicable to various countries is almost a difficult task. But now harmonization exists in many Regulated & semi regulated countries.

The implementation of GDUFA program is yielding good improvements in FDA's division of Office of Generic Drugs (OGD) i.e., advancing / improving the review pattern of a generic application without compromising quality and efficacy for intended use of generic product. Further, FDA is planning to increase the staff to assess the Risk based quality approach and make every effort to allow generic drugs in to the market for availability of patients/customers.

Thus, the implementation of Generic Drug User Fee program benefits customers economically and benefits generic industries in facilitating early launch of generic products into the market.

Formal meetings provide an important forum for the sponsor or applicant to present information, and for FDA to provide specific and targeted advice. FDA promotes innovation through intense and well-timed interactive communication with sponsors during drug development. The ultimate goal of the FDA is to smooth the conduct of development programs efficiently and effectively. Formal meetings are classified into different types by FDA and it is very important to request right meeting at right time for the questions sponsors or applicants have in the development phase. Formal Meetings are done earlier in the development phase and later meetings show high impact on success at best. These meetings can be particularly helpful for orphan drug products, new chemical entities, drugs having novel indications and biologics, where the Regulatory pathway is not plotted and/or aspects of the clinical trials are uncertain. The success of these meetings depends on the particularity of the sponsor's meeting agenda, objective and ability in asking questions regarding the format and content of their upcoming IND/BLA/NDA submission. Preparation for the meeting is very crucial for sponsors and applicants. A formal meeting facilitates the understanding of product development and regulatory related doubts to the sponsor or applicant.

FDA can get benefits from these type of productive meetings as well. FDA gets better knowledge of the data submitted by sponsor or applicant and can have collaborative expectations with the sponsor or applicant and among the review team. These meetings discussions also enhance predictability, communications and transparency between the applicant or sponsor and FDA.

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 are used to obtain marketing Authorization. In Canada DMF filing was done through New Drug Submission (NDS) for both drugs and biologic products.

Marketing Application is an application for approval for generic drug product. Application is submitted to ICH regions for marketing authorization, which provides for the review and ultimate approval of generic drug product. Once approved, the applicant may manufacture and market the generic drug product to provide safe, effective and stable drug product with low cost effectiveness to public.

After studying & analysis the process of new drug registration in European Union its take approximately 33 to 35 weeks. Each & every company should follow the stages, rules & regulations which are given by the government of the European Union. For the approval of a new drug firstfile the application for clinical trial after that apply for marketing authorization of the new drug in the European Union.

From the current scenario of the regulatory requirements, it is important to keep in mind that FDA is scrutinizing DMFs more closely than ever before. With the considerable increase in the number of DMF submissions and FDA's interest in keeping track of such filings electronically and FDA more stringently insists on uniformity in DMF submissions in accordance with its current administrative guidelines. Thus, more than ever before, it is important to consult FDA's current DMF guidance when preparing DMF submissions and to adhere to FDA's requirements for various types of DMF filings.

Moreover, to maintain the active status of a DMF and ensure that it is not retired by FDA making it unavailable for review, it is important to regularly comply with FDA's Annual Report requirement. In the end, 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 complete it are of the same quality as the actual drug application.

European Medical Agency provides detailed guidance for the submission of application including established timelines where as in US FDA has limited guidance for the process of submission and related aspects. Saudi Arabia classification of variation is quite similar to EU but there are minor changes in terms of classification and timelines for approval of applications.

A regulatory affair is also important for Research and development, Product management, Clinical trial, marketing authorization. Becoming a good regulatory affair officer executive some special skills which needed like sound knowledge about regulatory affair, good communication skill, knowledge about drug laws. All pharmaceutical companies have their own regulatory affair department those who don't have they concerts with regulatory consultancy for product approval and marketing authorization.

The DMF contains factual and complete information on a drug product's chemistry, manufacture, stability, purity, impurity profile, packaging, and the cGMP status of anyhuman

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. This helps to obtain a marketing authorization grant.

The only weak link for Indian companies has been market access to the US. To complete the value chain, Indian companies have been forming partnerships with US firms, acquiring US companies, or setting up marketing subsidiaries. Eight to ten companies are active in the US either on their own or through their partners. Most Indian acquisitions until now have been small. At the end of the day, the generic industry is price driven. Cost pressures are fuelling consolidation in the global generic industry. It will mean fewer competitors. It will also mean more pricing discipline. India is still a small player in the $25 billion US generic market with a share of only about $ 1 billion.India has a long way to go before emerging as a substantial player in the generics market but yes it has the qualities to become one. But above all to go global in the market US and EU, regulatory approval is crucial. Pharmaceutical company should keep a close eye on the changing regulation and should consult with regulatory consultants for proper filing, so that they can enter without any hurdles.

After comparing the requirements for genetic approval in the above stated countries, unlike US, the regulatory guidelines of EU are not that well defined. One can't draw or get desired requirements for approval from the official sites of these countries (EU). But FDAsite gives very well defined requirements.

The final thought of this strenuous study states, the four countries dealt with during the study have similar requirements for Registration of Active Pharmaceutical Ingredients and are striving toharmonize their requirements with the ICH Q-12 guidelines. The essential principles are mainly the same in most of the countries studied, but there are some differences and thereforeit is necessary to look at these requirements country by country.

During the process of product development, there is a lot of regulatory requirement from compliance to submission which the sponsor has to adhere with. The main requirements are usually a local representative, import license from the competent authority in the import country, registration of the company and the product. To accomplish this, it is necessary to fulfill the essential principles, classify the product, apply Good Manufacturing Practices and risk management, follow the labeling requirements and establish a documented post-market

surveillance system. Technical documentation is also necessary and shall in most cases be submitted with the registration application.

The comparison between the four countries identified the similarities and differences between each country. Each country has its own determined guidance to fulfill the requirements of Drugs for safety and efficacy. Although, different methods are used to determine the safetyand effectiveness of the drugs, each system is similar in the information that is required for approval to market.

It is also important to keep in mind that the different countries have different systems of premarket review. For example, in Canada, classifies Drug Master File in to Type –I especially for API registration. In the United States Type II for Drug substance under GDUFA.

The regulation regarding confirmation of safety and efficacy of API registration is differing from country to country. Different countries acknowledge satisfactory pre-market review in different ways. In Canada it is Approval given by the Therapeutic products directorate and in United States, in support of ANDAs from the Food &Drug Administration. Every country has its own national standard which should be adopted by the domestic and foreign manufacturers.

All regulated markets for the registration of Medicines should have common guidance to Industry and a common format to get approval easily and quickly. There needs to be well-defined guidelines in place for post-authorization market surveillance. Proper quality (permissible lower and upper limits) and safety guidelines are also missing from the new rules. Finally, the rule needs to better define the procedure(s) for identifying and correcting a deficiency in the performance or clinical evaluation, in its measuring or delivery accuracy, sterility or handling, or risk to the environment because of importance. Measures for determining the analytical performance and clinical performance and dossier evaluation parameters also should be provided in the new rules.

CONCLUSION:

The overall study concludes that there are interesting comparisons and differences between regulatory systems across the USA, Europe (EU), EDQM and Canada. In the process of API development lot of research work has to be carried out during the development phase. But the research related activities have to be in accordance with the procedures adopted by the health agency. During the classification of APIs registration, different countries have different classification systems, but the ICH harmonized guidance to be developed allows a universal

system. Significant improvements were made to the guidelines regarding classification because of multiple available sources in a regulated market. However, there are still review issues that may need to be resolved to avoid any unnecessary duplication of regulatory review by regulatory authorities and Notified Bodies.

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