Review Article

Regulatory Requirements for Registration of API in US and EU

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ABSTRACT

To submit a marketing authorization application (MAA) in all countries, it is important to know exactly the pharmaceutical legislations (regulations, directives and guidelines) and the regulatory requirements in each of the country in advance. For registration of drug product we need to know about the requirements for the registration of active pharmaceutical ingredient (API) which is the part of drug product and influences the quality of drug product. Due to the fact that the European Union (EU) and the United States (US) are the biggest and most potential markets for medicinal products in the world. Therefore within this dissertation a scientific requirements and recommendation for the registration of a active pharmaceutical ingredient is provided within these regulatory regions. The different pharmaceutical legislations and regulatory requirements for a new MAA of an API of EU, United States (US), are discussed and analyzed in detail. The analyses are made especially concerning the aspects required for marketing authorization and accepted dossier requirements for the registration of API in US and EU.

Keywords: MAA, API, DMF, ASMF, FDA, EMEA.

INTRODUCTION

Medicinal products, pharmaceuticals, veterinary medicines, medical devices, and food supplements – all these products are subject to regulations designed by governments to protect public health. For producing drug product of high quality, safety and efficacy every industry need to follow regulations. The Regulatory Affairs department is an important part of the organizational structure of pharmaceutical companies. At the late stage of product development regulatory professionals are responsible for the submission of the dossier for registration, e.g. Marketing Authorization Applications (MAA) in the EU or New Drug Applications (NDA) in the US.

ACTIVE PHARMACEUTICAL INGREDIENT (API OR DRUG SUBSTANCES)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when used so, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body .

General work profile of a Regulatory Affairs professional in an API (Active Pharmaceutical Ingredient) manufacturing company

- Filing a DMF/ASMF with regulatory agencies in support of the NDA / ANDA/ INDA /MAA filed by a Formulator (Drug Product manufacturer who uses API of that particular API manufacturing company).
- Filing dossier of API with EDQM for obtaining CEP.
- Assessing and filing amendments/variations to the information (which may be related to manufacture, control, stability studies etc) in DMF/ASMF/Dossier of particular API with the Regulatory agencies. Major amendments are to be reported prior to their implementation while minor amendments may be reported annually.
- Taking approval of customers of API before implementing any major changes regarding the information mentioned in DMF/ASMF/Dossier. The updated DMF/ASMF may be submitted to the customer simultaneously along with amendments/variations filed with the agency.[6]

REGULATORY AUTHORITIES: Regulatory bodies are responsible for approving whether a drug can proceed to clinical trials and whether it should be allowed on the market. The regulatory body has to evaluate the scientific and clinical data to ensure that the drug can be produced with consistently high purity, that it has the clinical effect claimed, and that it does not have unaccepted side effects. It must also approve the labeling of the drug and the directions for its use. In general, the regulatory body is interested in all aspects of a drug once it has been identified as a potential useful medicine.

USFDA (United Sates of Food and Drug Administration): The U S. Food and Drug Administration is a scientific, regulatory, and public health agency that oversees items accounting for 25 cents of every dollar spent by consumers. The agency grew from a single chemist in the U.S. Department of Agriculture in 1862 to a staff of approximately 9,100 employees and a budget of $1.294 billion in 2001, comprising chemists, pharmacologists, physicians, microbiologists, veterinarians, pharmacists, lawyers, and many others. About one-third of the agency's employees are stationed outside of the Washington, D. C. area, staffing over 150 field offices and laboratories, including five regional offices and 20 district offices.

Organization of FDA: The FDA's organization consists of the Office of the Commissioner and four directorates overseeing the core functions of the agency: Medical Products and Tobacco, Foods, Global Regulatory Operations and Policy, and Operations.
It consists of following centers/offices, which are listed below that review and approve FDA regulated products:

1) ORA-Office of Regulatory Affairs CDER-Center for Drug Evaluation and Research
2) CBER-Center for Biological Evaluation and Research
3) CDRH-Center for Devices and Radiological Health
4) Center for Tobacco Products
5) CVM-Center for Veterinary Medicine
6) CFSAN-Center for Food Safety and Applied Nutrition
7) NCTR-National Center for Toxicological Research
8) OFC-Office of Commissioner
9) ORA-Office of Regulatory Affairs [11]

European Medicines Agency –EMEA: The European Medicines Agency (EMEA) is a decentralised body of the European Union with headquarters in London.
• Its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use.
• The EMEA is responsible for the scientific evaluation of applications for European marketing authorisation for medicinal products (centralised procedure). Under the centralised procedure, companies submit one single marketing authorisation application to the EMEA.

- The EMEA takes appropriate actions if adverse drug reaction reports suggest changes to the benefit-risk balance of a medicinal product. In 2001, the Committee for Orphan Medicinal Products (COMP) was established, charged with reviewing designation applications from persons or companies who intend to develop medicines for rare diseases (so-called 'orphan drugs').

• The Agency is also involved in referral procedures relating to medicinal products that are approved or under consideration by Member States.

Organisation of EMEA:

a. Committee for orphan medicinal products (COMP)
b. Pediatric committee (PDCO)
c. Committee for veterinary medicinal products (CVMP)
d. Committee on advanced therapies (CAT)
e. Committee for medicinal products for human use (CHMP)
f. Committee for herbal products (HMPC)
g. Pharmacovigilance Risk Assessment Committee (PRAC)[12]

ICH (International Conference On harmonization): For most countries, whether or not they had initiated product registration controls earlier, the 1960s and 1970s saw a rapid increase in laws,

regulations and guidelines for reporting and evaluating the data on safety, quality and efficacy of new medicinal products. Harmonisation of regulatory requirements was pioneered by the European Community (EC), in the 1980s, as the EC (now the European Union) moved towards the development of a single market for pharmaceuticals. The birth of ICH took place at a meeting in April 1990, hosted by EFPIA in Brussels. Representatives of the regulatory agencies and industry associations of Europe, Japan and the US met, primarily, to plan an International Conference but the meeting also discussed the wider implications and terms of reference of ICH.

The CTD is organised into five modules. Module 1 is region specific and Modules 2, 3, 4 and 5 are intended to be common for all regions. In July 2003, the CTD became the mandatory format for new drug applications in the EU and Japan, and the strongly recommended format of choice for NDAs submitted to the FDA.[13]

OBJECTIVE:

The objective of this study was

- To know about the Regulatory agencies present in the US and EU and registration procedures for pharmaceuticals.
- Study and analyse on the Requirements for registration of API in US (FDA) and EU(EMEA)
- Comparison of regulatory requirements of API in US and EU on what basis the registration requirements are varying.
- Simplifying the registration procedure for API in US and European Union.

METHODOLOGY

Each and every study has some patterns and follows certain pathways in order to reach the Destination. The study was analysed by dividing the whole study into 4 steps:

1. Type of study
2. Source of data
3. Registration of API in US and EU
4. Study process

1. Types of study:

The study was conducted with an objective to chalk out the regulatory requirements for the registration of API and difference of those regulatory requirements and registration process in US and EU.

2. Source of data:

Major part of secondary data collection was done by means of following sources:

- Literature review
- Regulatory agencies and related websites of particular country i.e US and EU.
- Guidelines framed by government authorities

a. Literature review:

Academic journals, online journals, Market research reports, news paper articles, and other resources. And direct communication with Regulatory authorities. Online books also served as a good source of information.

b. Regulatory agencies and related websites of particular country i.e US and EU.

Typically covered the regulatory guidelines published officially by agencies and websites related to the registration requirements for different countries.

c. Guidelines framed by government authorities:

Guidelines must give the most useful information and the information mentioned in the guideline was standard, every one try to follow these guidelines.

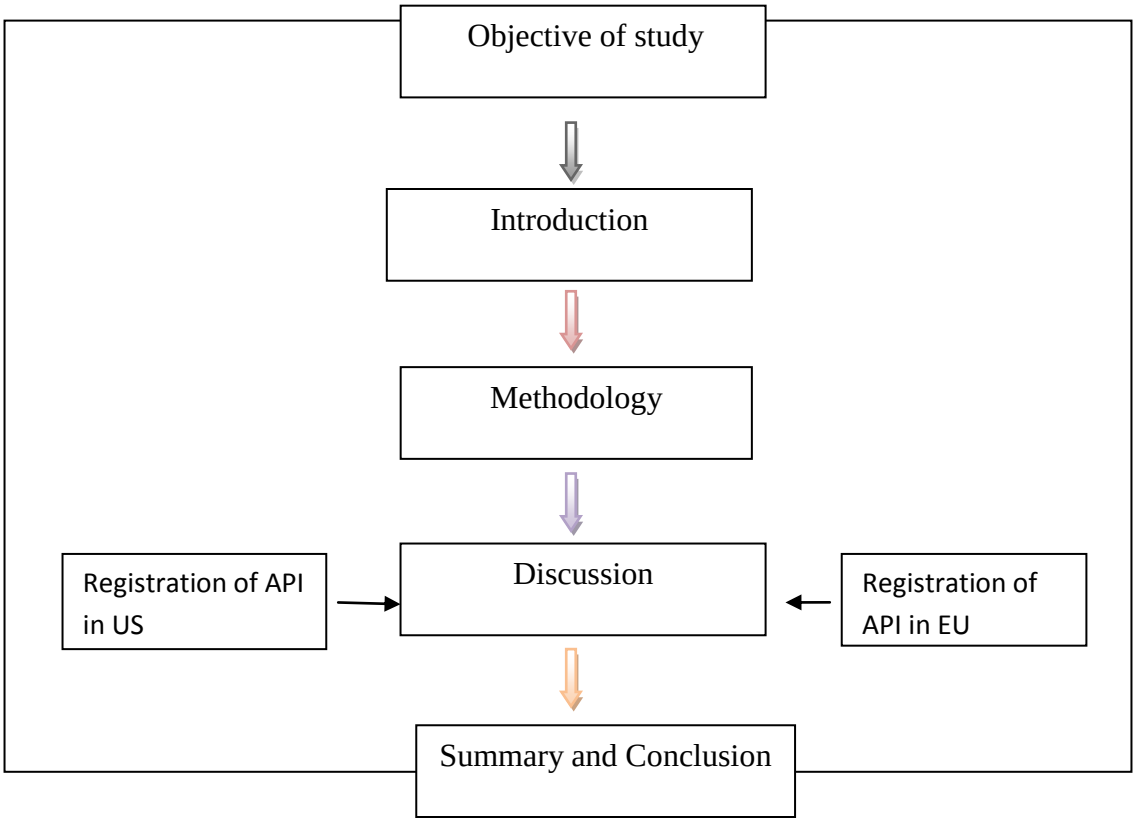
3. Registration of API in US and EU:

In India most of the drugs are exported to US and EU. These study parameters are selected to understand the

- Basic requirements for the registration of API in US and EU.

- Registration procedures for API in US and EU. In US registration is carried out through drug master file process (type-2), while in EU, the registration is done by filing of active substance master file (ASMF).
- By knowing the requirements it may allow us to make easy for registration of single API in both US and EU countries.

4. Study process:



DISCUSSION

REGISTRATION OF API IN US

Registration of pharmaceuticles: All new drugs are subject to FDA pre-market approval; it is the responsibility of the new drug's manufacturer to demonstrate the safety and effectiveness of its particular product to FDA. The regulations relating to the approval of new drugs require that the application (*e.g.,* the New Drug Application (NDA)) include a description of the manufacturing procedures and in-process controls for the new drug product including all its components, as well as complete details about the drug's composition. In preparing an NDA, the drug manufacturer must include adequate data to demonstrate that the drug substance used for the particular drug of interest will not in any way affect the safety or efficacy of the drug.

While filing ANDA we need to mention matter related to drug substance. All the information was registered as DMF.[23]

USDMF: Drug Master File (DMF) is a document containing complete information on an Active Pharmaceutical Ingredient (API) or finished drug dosage form. It is known as Active Substance Master File (ASMF) in EU and US-Drug Master File (US-DMF) in United States. 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.[17]

Role of Drug Master Files

The Drug Master File (DMF) system was developed to permit suppliers to make this information on their products directly available to FDA for its review of drug company applications that involve the use of the supplier's material.

DMF can be submitted in support of:

- Investigational New Drug Application (IND)
- New Drug Application (NDA)
- Abbreviated New Drug Application (ANDA)
- Another DMF
- Export Application
- Supplements or Amendments to any of these

A DMF is NOT a substitute for an IND, NDA, ANDA, or Export Application. It is not approved or disapproved. Technical contents of a DMF are reviewed only when referenced in other regulatory filings, such as an IND, NDA or ANDA or Export Application. If requested by FDA headquarters, an FDA inspection may take place at an API manufacturing site after a review of the DMF.

Types Of DMF's

Table 1: Types of Drug Master Files Type I Manufacturing Site, Facilities, Operating Procedures, and Personnel (no longer applicable)

Type II: Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product

Type III: Packaging Material

Type IV: Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation

Type V: FDA Accepted Reference Information

Requirements for Registration of API

In US active pharmaceutical ingredient is referred as drug substance. Registration of active substance takes palace along with pre marketing approvals like NDA & ANDA. That means there is no separate registration process for API .The manufacturer of API need to submit the information in the form of DMF. The FDA reviews the information and gives the DMF number. When the drug product manufacturer wants to get approval for the product, they mention the DMF of drug substance as supporting document for the applications like NDA & ANDA.

Submissions Requirements:

As mentioned above the requirements include

- Module 1 - includes administrative information
- Module 3 - include quality information

Module 1: Administrative Information

Forms are not required for all types of DMF.

Section 1.2

- ✓ Cover Letter
- ✓ Statement of Commitment
- ✓ Generic Drug User Fee (GDUF) Cover Sheet (3794), where applicable

Section 1.3: Administrative Information

- ✓ Contact/sponsor/Applicant information
- ✓ Change of address or corporate name: Can be used to supply addresses of DMF holder and manufacturing and testing facilities
- ✓ Change in contact/agent: Can be used to supply the name and address of contact persons and/or agents, including Agent Appointment Letter.

Section:1.4 Reference Section

- ✓ Letter of Authorization: Submission by the owner of information, giving authorization for the information to be used by another.

  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 DMF that REFERENCES a DMF)

- ✓ List of persons authorized to incorporate by reference: Submitted in DMF annual reports.
- ✓ Environmental Analysis [25]

Section 1.2:

i) Cover letter(transmittal letter)

The following should be included

• Identification of Submission:

Original: which means that the DMF submitting is original or any amendment DMF for previously submitted drug substance.

Type of DMF and its subject: in present we are going to know about the registration of API and it is **type II** DMF. The subject mainly relates to the quality part of drug substance.

Identification of the applications: if known that the DMF is intended to support which application i.e NDA or ANDA including the name and address of each sponsor, applicant or the holder and all relevant document holders.

• Signature of the holder or authorized representative.

• Type written name and title of the signer.

ii) Statement of commitment

"A signed statement by the holder certifying that the DMF is current and that the DMF holder will comply with the statements made in it."

iii) Generic drug user fee cover sheet:

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).

Section 1.3: Administrative Information

Should include the following;

Original Submission

- The name and address of the holder
- The name and address of manufacturing facility
- For the contact person:
  - Name
  - Mailing Address
  - Telephone number
  - Fax number
  - E-mail address
- Statement of Commitment
- The name and address of the agent (if applicable)
- For the contact person at the agent (if applicable):
  - Name
  - Mailing Address
  - Telephone number
  - Fax number
  - E-mail address
- Statement of Commitment

Section: 1.4 - Reference Section:

Letter of Authorization: All Letters of Authorization (LOAs) should be submitted in two copies to the DMF, if the DMF is in paper format. . A copy of the LOA must then be sent by the DMF holder to the Authorized Party (company or individual authorized to incorporate the DMF by reference). Failure to submit the LOA to the DMF may result in a delay in review of the DMF. LOAs should specify the name of

the specific item being referenced and the date of the submission of information about that item. The LOA should not be called a "Letter of Access."
An LOA is required even if the DMF holder is the same company as the authorized party. LOAs should NOT be submitted with original paper DMFs (unless the DMF has received a pre-assigned number) because the LOA should contain the DMF number. Therefore DMF holders should wait before submitting an LOA until they have received an acknowledgment letter containing the DMF number.
It is not necessary to reissue LOAs if there have been no changes in the holder, authorized party, subject of the DMF or item referenced.

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. And those DMF's are mentioned as right of reference. [25]

List of persons authorized to incorporate by reference
This is required when the authorized person was going to update the DMF annually. In this they need to mention all the persons who are authorized by FDA and those persons are mentioned as reference member. "A DMF is required to contain a complete list of persons authorized to incorporate information in the DMF by reference [21 CFR 314.420(d)]."
The language in the CFR is more explicit:

> "The drug master file is required to contain a complete list of each person currently authorized to incorporate by reference any information in the file, identifying by name, reference number, volume, and page number the information that each person is authorized to incorporate".[26]

Environmental analysis: Since DMFs are neither approved nor disapproved, there is no need to file an Environmental Assessment. For this we need to mention statement of commitment on environmental system around the manufacturing area.

- The National Environmental Policy Act (NEPA) requires that all government agencies prepare an Environmental Impact Statement (EIS) or a Finding of no Significant Impact (FONSI) when they take an action e.g., approving a drug application.
- DMF should include a statement that holder will comply with all local environmental regulations
- DMF holder's responsibility is to provide sufficient information to customer to permit customer to file an EA. [25]

MODULE 3: QUALITY INFORMATION OF API: According to ICH CTD format module 3 is related to quality of drug substance and drug product. In present review I am going give quality information drug substance.

1. General Information :
    a. Nomenclature
    b. Structure
    c. General Properties
2. Manufacturer :
    a. Manufacturer
    b. Description Of Manufacturing Process and Process Controls
    c. Control of Materials
    d. Controls Of Critical Steps and Intermediates
    e. Process Validation and/or Evaluation
    f. Manufacturing Process Development
3. Characterization
    a. Elucidation Of Structure and other Characteristic
    b. Impurities
4. Control Of Drug Substances:
    a. Specification
    b. Analytical Procedure
    c. Validation of Analytical Procedures

d. Batch Analysis
e. Justification of Specification

5. Reference Standards or Materials
6. Container Closure System
7. Stability
    a. Stability Summary and Conclusions
    b. Post- approval Stability Protocal and Stability Commitment
    c. Stability Data

DMF FILING PROOCESS

Paper submission

- An original and duplicate copy is to be submitted for all DMF submissions. The original and duplicate copy must be collated, fully assembled and individually jacketed.
- Standard paper size is preferred (e.g., 8-1/2 by 11 inches for US DMF). Paper length should not be less than 10 inches nor more than 12 inches. However, it may occasionally be necessary to use individual pages larger than standard paper size to present a floor plan, synthesis diagram, batch formula, or manufacturing instructions.
- Those pages should be folded and mounted to allow the pages to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved.
- The Agency's system for filing DMFs provided for assembly on the left side of the page. The left margin should be at least three fourths of an inch to assure that text is not obscured in the fastened area.

Drug Master File with one signed original of the covering letter and other necessary documents are send to the FDA's Central Drug Evaluation and Research (CDER).

• The Drug Master File staff will audit the nontechnical information for completeness and adequacy for submission. If the key elements are missing, the staff will contact the proposed holder to try to obtain the necessary documents in order to file the DMF.

• Once the DMFs are determined to be acceptable for filing, the document room staffs assigns a DMF number and a letter is sent to the contact person listed in the DMF.

DMF submissions and Correspondence should be addressed as follows:

Drug Master File Staff
Center for Drug Evaluation and Research
Central Document Room
Food and Drug Administration
5901-B Ammendale Rd. Beltsville,
MD 20705-1266
Delivery charges for the above address must be prepaid. [24]

ELECTRONIC DRUG MASTER FILE (EDMF)

- Most of the health authorities require paper copies of the documents. The size of DMFs easily approaches or exceeds 1000 pages. Each master file is made up of several volumes as well as duplicate copies.
- ALL electronic applications must follow the Electronic Common Technical Document. eCTD is a structured format that permits life cycle management, which is important for DMFs.
- US marketing applications are submitted in electronic CTD format.
- There is no requirement to submit any type of application in electronic format but encouraged to submit in electronic format. Submitting the information in the eCTD backbone files will result in greater efficiency.
- The absence of electronic datasets in an acceptable format to permit review and analysis may be considered as inadequate and resulting in refuse-to-file an application.

The following file formats should be used

- PDF for reports and forms.
- SAS XPORT (version 5) transport files (XPT) for datasets.
- ASCII text files (e.g., SAS program files, NONMEM control files) using txt for the file extension.
- XML for documents, data, and document information files.

- Style sheets (XSL) and document type definition (DTD) for the XML document information files.
- Microsoft Word for draft labeling.

DMF currently in paper format is being converted to electronic format, it is not necessary to request a pre-assigned number. Once the DMF holder has made an electronic submission every subsequent submission should be in electronic format. Electronic DMFs may be submitted either:

- Through the Electronic Submission Gateway (ESG) or
- Via Physical Media (CD-ROM, DVD, Digital linear tape, linear tape open or USB drive) to the same address as paper DMFs.

Steps for Filing A DMF

1. Set the document margins at 3/4 inch for the left (at least) and 1/2 inch for the right.
2. Print the transmittal page, administrative information and DMF information on standard letter-size paper. If a larger sheet of paper is required for a diagram or schematic, fold the sheet and attach it to a letter-sized page in a manner that will allow for the page to be opened and refolded. At a maximum, each volume of a DMF should be no more than 2 inches thick.
3. Number multiple volumes for one submission according to the total number of volumes (if more than one). (For example, 1 of 3, 2 of 3, etc.)
4. Sign all documents requiring signature (only if you are the DMF holder or authorized representative).
5. Copy and collate the document; FDA requires you submit both.
6. Punch documents with a standard hole-punch.
7. Cover each original and copy of each volume with a document jacket. Prepare the submission for shipping and mail to:

Drug Master File Staff
Food and Drug Administration
5901-B Ammendable Rd.
Beltsville, MD 20705-1266 27 [1]

Annual Update: The holder should provide an annual report on the anniversary date of the original submission. All changes and additional information incorporated into the DMF since the previous annual report on the subject matter of the DMF should be provided. If the subject matter of the DMF is unchanged, the DMF holder should provide a statement that the subject matter of the DMF is current. Type II active pharmaceutical ingredient (API) 20 drug master files (DMFs) that are or will be referenced in an abbreviated new drug application 21 (ANDA) or an amendment or prior approval supplement (PAS) to an ANDA (generic drug 22 submissions).

Registration of API in EU : The European Medicines Agency's (EMA) main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. The registration of pharmaceuticals in EU is referred as marketing authorization **(MA).**

Marketing authorizations : The Agency is responsible for the scientific evaluation of applications for European Union (EU) marketing authorizations for human and veterinary medicines in centralized procedure. Under the centralized procedure, pharmaceutical companies submit a single marketing-authorization application to the EMA. Most of the EMA's scientific evaluation work is carried out by its scientific committees, which are made up of members from EEA countries, as well as representatives of patient, consumer and healthcare-professional organizations. [31]

Marketing Authorization Procedure: In the European Union (EU), medicines can be authorized by the centralized authorization procedure or national authorization procedures**.** The European system for the authorization of medicinal products for human and animal use was introduced in January 1995 with the objective of ensuring that safe, effective and high quality medicines could quickly be made available to citizens across the European Union.

According to European Generic Medicines Association (EGA), the marketing authorization for a pharmaceutical product in more than one country in the European Union must currently be applied for through one of two procedures:

- Centralized Procedure"
- "Mutual Recognition Procedure" (MRP).
- "Decentralized Procedure," came into force with the newly revised EU pharmaceutical Directive in November 2005 [33]

Centralized Procedure

Notification to EMEA

Appointment of Reporter and Co-Rapporteur

↓

CPMP meeting, validation of dossier by EMEA and delivery to Rapporteurs ⇨ starts **Day 1**

↓

Preparation of two separate assessment reports by the Rapporteurs ⇨ **Day 70**

↓

Reports sent to all CPMP members, EMEA and applicant ⇨ **Day 100**

↓

Comment of CPMP members

↓

Reports sent to applicant with or without modification by CPMP ⇨ **Day 120 clock stop**

↓

Response by the applicant ⇨ Within 180 Days

↓

Preparation of Joint assessment report by the Rapporteurs ⇨ Clock restarts Day 150

↓

Comments of CPMP ⇨ **Day 170**

↓

Any outstanding issues communicated to applicant and opinion is deferred by CPMP

↓

CPMP Opinion ⇨ **With or without further clock stop** Day 210

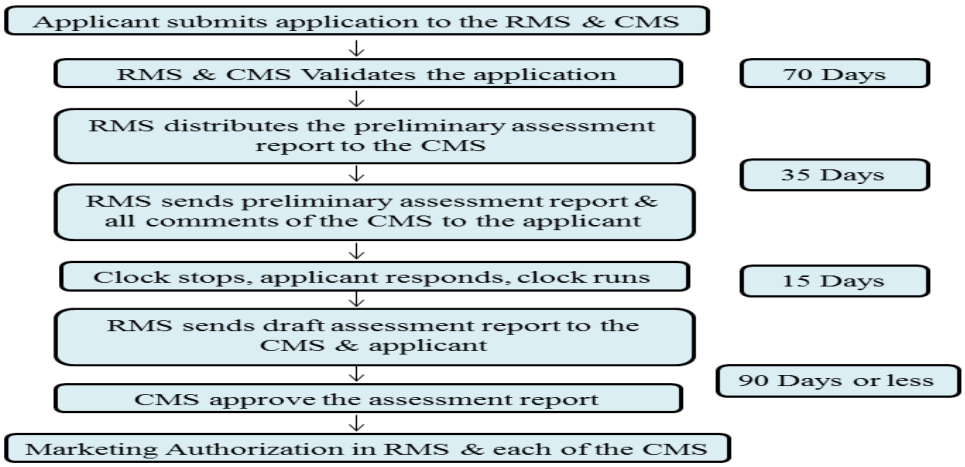
↓

Assessment report to Commission ⇨ **Day 240**

↓

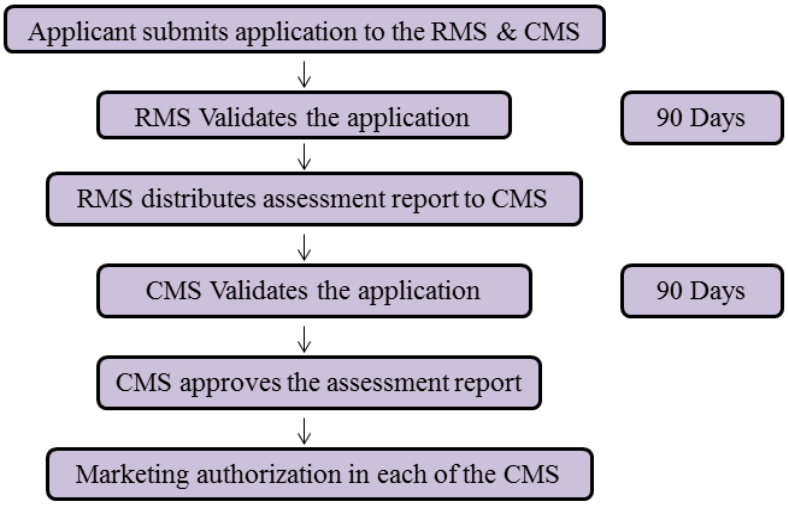
If positive opinion by CPMP, then marketing authorization is issued ⇨ **Day 300**

Decentralized Procedure



Decentralized Procedure

Mutual-recognition procedure



Mutual Recognition Procedure

Registration of API in EU

Active Pharmaceutical Ingredient

- **Definition**

Any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to effect the structure or any function of the body of man or other animals.

- **Classification of active substances**
  - New active substance used for the first time
  - Existing active substances not included in the European Pharmacopoeia (Ph.Eur.) or the pharmacopoeia of an EU Member State
  - Active substances included in the Ph.Eur. or in the pharmacopoeia of an EU Member State[41]

Active substance master file

It should be emphasized that the concept of the ASMF shall only apply to a well-defined active substance and cannot be used for excipients, finished products and biological active substances.

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 AP contains the information that the ASMF holder regards as non-confidential to the Applicant/MA holder, whereas the RP contains the information that the ASMF holder regards as confidential. It is emphasized that the AP is still a confidential document that cannot be submitted by anyone to third parties without the written consent of the ASMF holder. The RP may contain the remaining information, such as detailed information on the individual steps of the manufacturing method (reaction conditions, temperature, validation and evaluation data of critical steps) and the quality control during the manufacture of the active substance.

The registration of ASMF requires the quality data of active substance. Nowadays EU also follows CTD format which is referred as EU-CTD. CTD contains five modules. The present work aims to discuss about registration of active substance and it includes

Module 1

Administrative, regional or national information

Module 2

Quality information of drug substance

The overall content of the ASMF should contain detailed scientific information as indicated under the various headings of the relevant Notice to Applicants for Marketing Authorizations for Medicinal Products in the Member States of the European Union (NtA).[45]

Submission requirements of ASMF

In the first submission of an ASMF with an allocated EMEA ASMF reference number, the ASMF holder is required to submit:

i). MAA application form stating the correct EMEA ASMF reference number
ii). Letter of Access
iii). Submission Letter and Administrative Details
iv). ASMF dossier (Applicant's part, Restricted part, Quality Overall Summary and Expert's *curriculum vitae*).[46]

i). **EMEA/ASMF reference number**

- From 1 September 2013, ASMF holders submitting their ASMF dossiers relating to a Centralized and national MAA are asked to send it to the Agency and Committee Members only once.
- According to the new ASMF submission rules the Agency will assign a reference number on request prior to submission of the ASMF that can cover multiple CAPs.
- The EMEA/ASMF/XXXXX number is an internal reference number sequentially assigned by the EMA to enable an appropriate data lifecycle management of ASMFs used in one or more centralized Marketing Authorization.
- The EMEA ASMF reference number does not replace the responsibility of the ASMF holders to version control their ASMF (in accordance with GMP) nor replaces their own ASMF numbering system.
- Up to two weeks before submitting a complete ASMF, or an update to an already submitted ASMF, the ASMF holder should request the EMEA ASMF reference number.
- It is the responsibility of the ASMF holder to inform the applicant of a MAA or MAV of the allocated EMEA ASMF reference number. Failure to state a valid EMEA ASMF reference number on the MAA or MAV form will trigger validation questions and may delay the start of procedure.
- For previously submitted ASMFs, in cases where the ASMF is used in more than one MA the ASMF Holder should only request one EMEA ASMF reference number, when applicable.

ii).Letter Of Access :(Annexure-6)

The Letter of Access is an important document in that it authorizes the NCA/EMA to refer to and review the ASMF in support of a MA application. The letter also notifies the NCA/EMA that the ASMF holder is informed and accepts that assessment reports of the ASMF may be shared amongst the NCA, EMA (including CHMP members and experts) and the Certification of Substances Division of the EDQM. The letter also confirms that the ASMF holder commits to ensure batch to batch consistency and to inform the MA holder of any changes to the ASMF.[32, 50]

iii).Submission Letter and Administrative details

- **Submission Letter:**
  The name of the active substance and the EU/ASMF reference number (when available) or national ASMF reference number, as appropriate, should be clearly stated in the subject heading. The Submission Letter should be signed by the authorized contact person for the ASMF holder. Their name, address (if different to the ASMF holder's address stated at the top of the letter) and position should be clearly stated. The EU/ASMF reference number will help identify and track where the same ASMF is submitted in multiple European procedures and/or Member States. Where the EU/ASMF reference number has not been allocated or if an ASMF is used in national applications only, a national ASMF reference number should be provided.
  Administration Details:
- recipients of the ASMF submission, the EU/ASMF or national reference number, ASMF version number, active substance name and internal (active pharmaceutical ingredient (API)) code.

- contact details of ASMF holder and companies responsible for manufacturing and quality control
- The ASMF holder should confirm, by ticking the appropriate box, whether the submission is a new ASMF in the NCA/EMA, an update to a previously evaluated ASMF or a response to a deficiency letter.
- format of the ASMF Submission
- list of submitted documents The ASMF holder should confirm they have provided the required documents by ticking the appropriate boxes. A copy of the NCA/EMA deficiency letter(s) should only be provided with any submitted response.[47]

ASMF dossier:

Quality Requirements for registration of API:

1. General Information:
    a. Nomenclature
    b. Structure
    c. General Properties
2. Manufacture:
    a. Manufacturer
    b. Description of Manufacturing Process and Process Controls
    c. Control of Materials
    d. Control of Critical Steps and Intermediates
    e. Process Validation and/or Evaluation
    f. Manufacturing Process Development
3. Characterization:
    a. Elucidation of Structure and other Characteristics
    b. Impuurities
4. Control of Drug Substances
    a. Specification
    b. Analytical Procedures
    c. Validation of Analytical Procedures
5. Reference standards or Materials
6. Container closure System
7. Stability
    a. Stability Summary and Conclusions
    b. Post-approval Stability Protocol and Stability Commitment
    c. Stability Data.

Certification of suitability: The procedure for 'Certification of Suitability to the monographs of the European Pharmacopoeia' was established in 1994 and was in the beginning restricted to controlling the chemical purity of pharmaceutical substances. In 1999, the procedure was extended to include products with a risk of transmissible spongiform encephalopathy (TSE), thus enabling their certification on the basis of the European Pharmacopoeia general chapter 5.2.8 'Minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products' and of the new monograph on 'Products with risk of transmitting agents of animal spongiform encephalopathy's (1483)'.

Submission Format: Paper or Electronic

Applicants are encouraged to submit electronic versions of their applications. Additionally, there are new requirements for paper submissions. This allows us to manage the applications more efficiently.[50]

Requirements for the registration of API in US and EU:

Basic differences between US AND EU:

REQUIREMENTS	US	EU
Agency	Food And Drug Administration (FDA)	European medical agency (EMEA)
Registration process	Single	Multiple 1)Cenralized 2)Decentralized
Braille Code	Not required	Required
Site registration	Required	Not Required
Plant GMP approval	US FDA audits of API manufacturer	Audit by any member state of EU

Administrative Requirements

Requirements	US	EU
Submission	Type 2 DMF for API	ASMF
Application	Type 2 DMF is submited as supporting document for NDA and ANDA	ASMF submission form for administrative information
No. of copies	2	1
Other requirements	1.Cover Letter 2.Statement of Commitment 3. Letter of Authorization 4. Statement of Right of Reference 5. Environmental analysis	1. EMEA/ASMF reference number. 2. Letter Of Access 3. Submission Letter

Quality Requirements

To market the drug substance the regulatory authorities mainly focus on the quality data of drug substance. After ICH harmonization every country follow the guideline framed by ICH member states (US, EU and Japan). For registration of API, US and EU authorities follow the quality guidelines framed by ICH. In US the quality data of drug substance was submitted as type II DMF and the quality requirements are as per ICH CTD module 3. And EU also follows the Module 3 of CTD but the quality part is divided into applicant part (AP) and restricted part (RP).

CONCLUSION

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. 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. At 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 compete it are of the same quality as the actual drug application.

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