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REGULATORY DOSSIERS OF ASEM COUNTRIES

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ABSTRACT: Demonstration of safety and efficacy of the drug product for human use is important before the drug product gets approval for import or manufacturing of new drug by regulatory authority in any country. Once the clinical and preclinical data have been collected, a New Drug Application (NDA) must be submitted to regulatory authority for approval. Globalization of pharmaceutical industry has created the need to develop the recommendations for development of new pharmaceuticals as well as the regulatory requirement of various countries. Thus, a common format of submission will help in overcoming these difficulties. Through International conference on Harmonization (ICH), Common Technical Document (CTD) guidance's have been developed for Japan, EU and United States and the Research based industry and more recently its electronic version the electronic Common Technical Document (eCTD). The CTD application format is now favored by USFDA as well as Worldwide regulatory authorities. Implementation of CTD is expected to reduce time and resources needed by the industry to compile applications for global registrations. Asia-Europe Meeting (ASEM) is an informal process of dialogue and cooperation bringing together 27 European Union member states, 2 European countries and the European commission with 20 ASEAN secretariats.

INTRODUCTION: Dossier is a collection or a file of documents on the same subject especially files containing detailed information about a person or a subject.

The primary process for pharmaceutical companies is to submit the information or data related to the project will be by dossier submission. Submitting a completed dossier will make sure that the information submitted by a company will be fully reviewed.

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Dossiers help you create, assemble, update and publish a composite document. Any preparation for human use that is intended to modify the physiological system or pathological states for benefit of the patient is called as pharmaceutical product for human use. Process of reviewing and assessing the dossier of a pharmaceutical product is a document that contains all the technical data (administrative, quality, nonclinical and clinical) to be approved or registered or marketed in a country is called as registration dossier. It is commonly known as New Drug Application (NDA) in the United States or Marketing Authorization Application (MAA) in the European Union and other countries simply a registration dossier. The main objectives of dossiers are to provide enough information to regulatory agencies to permit reviewers to review the submissions.

Asia-Europe Meeting (ASEM) [1] is an informal process of dialogue and cooperation bringing together 27 European Union member states, 2 European countries and the European commission with 20 Asian countries and the ASEAN secretariat. Initially the ASEM partnership was started in 1996 consisted of 15 EU member states and 7 ASEAN member states plus china, Japan, Korea and the European commission.

The ASEM expanded during 5th summit in 2004 in Hanoi (Vietnam), where 10 new EU member states (Cyprus, Latvia, Malta, Slovenia, Slovakia, Hungary, Poland, Estonia, Czech Republic) and 3 new ASEAN countries (Laos, Myanmar and Cambodia) became the part of ASEM process in official[2].

The second enlargement of ASEM in 2008 at 7th summit in Beijing (china) brought in India, Pakistan, Bulgaria, Mongolia and Romania and the ASEAN Secretariat, expanding the total ASEM membership to 45 partners.

The 8th ASEM summit of Heads of Government and state in Brussels (Belgium) held in October 2010 welcomed 3 member states to the ASEM process: New Zealand, Australia and Russia. This third round expanded the ASEM membership to 48 partners.

In November 2012, during the 9th summit of Heads of Government and state in Vientiane (Laos) ASEM joined officially by Switzerland, Norway and Bangladesh. This round expanded the total ASEM membership to 51 partners.

As the Human dimension is the major part of ASEM process it includes various forums [2]:

1) Asia-Europe Business Forum (AEBF)
2) Asia-Europe Parliamentary Partnership Meeting (ASEP)
3) Asia-Europe Peoples Forum (AEPF)
4) Asia-Europe Innovation Centre (ASEIC)

The ASEM addresses the economic, political and cultural issues to strengthen the relationship between the Asia and Europe. ASEM work is organized by ASEM coordinators.

METHODOLOGY:

COMMON TECHNICAL DOCUMENT: A process by which an organization/ sponsor/ innovator gets authorization to introduce a drug in the market is known as drug approval process. Drug approval is the long process of drug development. A drug approval process undergoes various stages: conducting clinical trials, filing of NDA and post marketing studies. Once clinical and preclinical data have been collected a NDA must be submitted to the regulatory authority for approval. Every country has its own regulatory authority which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of drugs. Drug registration guidelines provide guidance to applicants who may wish to market their product in the markets. Through International Conference on Harmonization (ICH) [3] process, the Common Technical Document (CTD) guidance's have been developed for Japan, European Union and United States.

"Common Technical Document[4] is a set of specifications for application dossier for the registration of medicines and designed to be used across Europe, Japan and United States."

Common Technical Document provides a common format for the submission of information to the regulatory agencies for the registration of the pharmaceutical product. Most of the countries have adopted the CTD format.[5]

Common Technical Document is divided into five modules [6]:

1) Administrative and Prescribing information
2) Overview and summary of module 3 to 5
3) Quality(pharmaceutical documentation) [7]
4) Safety (toxicology studies) [8]
5) Efficacy (clinical studies) [9]

Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

Module 1: Administrative Information & Prescribing Information

1.1 Table of contents of submission including module 1

1.2 Documents specific to each region

Module 2: Common Technical Document Summaries

2.1 CTD table of contents

2.2 CTD Introduction

2.3 Quality overall summary

2.4 Nonclinical overview

2.5 Clinical overview

2.6 Nonclinical written & tabulated summary

- Pharmacology
- Pharmacokinetics
- Toxicology

2.7 Clinical summary

- Bio pharmaceutics & associated analytical methods
- Clinical pharmacology studies
- Clinical Efficacy
- Clinical Safety
- Synopses of individual studies

Module 3: Quality

3.1 Module 3 Table of contents

3.2 Study Reports

3.3 Literature References

Module 4: Nonclinical Study Reports:

4.1 Module 4 Table of contents

4.2 Study Reports

4.3 Literature References

Module 5: Clinical Study Reports:

5.1 Module 5 Table of contents

5.2 Tabular Listing of All Clinical Studies

5.3 Clinical Study Reports

5.4 Literature References

The CTD is organized into five modules [10]:

MODULE 1: Regional Administrative Information

Module 1 is for administrative information and prescribing information and should contain documents that are specific to each region for Example, application forms or labeling etc.

MODULE 2: Overview and Summary of modules 3 to 5

Module 2 contains the CTD summaries and should begin with the general introduction to the drug including its pharmacological class, mode of action and proposed clinical use. It should also provide the overall summary of the 'quality' information provided, the clinical overview and the nonclinical overview as well as nonclinical written summaries and the tabulated summaries and the clinical summary.

MODULE 3: Quality (Pharmaceutical Documentation) [11].

The quality section of the CTD provides a harmonized structure and format for presenting CMC (Chemistry, Manufacturing and Controls) information in a registration dossier. The table of contents includes sections on drug substance and drug product. There are also sections for regional specific information as well as some appendices.

MODULE 4: Safety (Toxicology Studies-Non Clinical Study Report) [12].

The CTD safety guideline describes the structure and format of the nonclinical summaries in module

2 of the CTD, and provides the organization of module 4, the nonclinical study reports. The nonclinical overview should present an integrated and critical assessment of the pharmacologic, pharmacokinetic and toxicological evaluation of the pharmaceutical and generally should not exceed 30 pages. The nonclinical written summaries (100-150 pages) are recommended to provide more extensive summaries and discussions of the nonclinical information on pharmacology, pharmacokinetics and toxicology.

MODULE 5: Efficacy (Clinical Study Report) [13]

CTD Efficacy describes the structure and format of the clinical data in an application including summaries and detailed study reports. There are two high level clinical summaries in module 2 of CTD[14]: the clinical overview, a short document that provides a critical assessment of the clinical data and clinical summary, a longer document that focuses on data summarization and integration. Clinical study reports and raw data are included in module 5 of the CTD.

The Electronic CTD- Modern concept [15]: The electronic Common Technical Document (eCTD) is an interface for the pharmaceutical industry to agency transfer of regulatory information's. The content is based on the Common Technical Document (CTD) format [16].

It was developed by the International Conference on Harmonization (ICH) Multidisciplinary Group 2 Expert Working Group (ICH M2 EWG) [17].

The electronic Common Technical Document will be a transport format intended to be moved into an agency's review environment and will facilitate electronic submissions. The electronic Common Technical Document specification lists the criteria that will make an electronic submission technically valid.

The electronic Common Technical Document represents a major advance in the submission of information to support a New Drug Application[19]. In the future, companies might be able to send their submissions to several regulatory authorities simultaneously.

Drug Master File: A drug master file (DMF) [20] 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 Files are provided for in 21CFR 314.420. This guideline is intended to provide DMF holders with procedures acceptable to the agency for preparing and submitting a DMF. The information contained in DMF may be used to support an Investigational New Drug Application (IND), a New Drug Application (NDA), Abbreviated New Drug Application (ANDA), another DMF, an export application or amendments and supplements to any of these.

Types of DMF [21]:

There are five types of DMF's:

- Type I Manufacturing Site, Facilities, Operating Procedures and Personnel
- Type II Drug Substance, Drug Substance Intermediate and Materials used in their preparation or drug product.
- Type III Packaging Material
- Type IV Excipient, Colorant, Flavor, Essence or Materials used in their preparation
- Type V FDA Accepted Reference Information

Submissions to Drug Master Files:

- Each DMF submissions should contain a transmittal letter, administrative information about the submission and the specific information to be included in the DMF.
- 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 DMF should be dated and consecutively numbered.

Drug Master File Contents [22]:

Types of Drug Master Files:

TYPE I: Manufacturing Site, Facilities, Operating Procedures and Personnel: A Type I DMF is recommended for a person outside of US to assist FDA in conducting site inspections of their manufacturing facilities, the DMF should describe the manufacturing site, equipment capabilities and operation layout.

TYPE II: Drug Substance Intermediates, Drug Substances and Materials Used In Their Preparation or Drug Product: A Type II DMF should, in general be limited to a single drug intermediate, drug substance and materials used in their preparation.

Drug substance intermediates, drug substances and materials used in their preparation: Summarize all the significant steps in the manufacturing and controls of drug intermediate or substance. What should be included in type II DMF may be found in following guidelines?

- Guideline for Submitting Supporting Documentation in Drug Application for the Manufacture of Drug Substances.

- Guideline for the format and content of Chemistry, Manufacturing and Control Section of an Application.

Drug Product:

Manufacturing procedures and controls for finished dosage forms should ordinarily be submitted in IND, ANDA, NDA or export application, if not submitted it should submit in DMF. When a Type II DMF submitted for a drug product the applicant/sponsor should follow the guidelines:

- Guidelines for Format and Content of the Chemistry, Manufacturing and Control Section of an Application.

- Guidelines for Submitting Documentation for the Manufacture of and Controls for Drug Product.

- Guidelines for Submitting Samples and Analytical Data for Method Validation.

TYPE III: Packaging Material

Each packaging material should be identified by its intended use, components, composition and controls for its release. The names of the suppliers and fabricators of the components used in preparing the packaging material and the acceptance specifications should also be submitted in DMF. Data supporting the acceptability of packaging materials for its intended use should also be submitted as outlined in the:

- Guidelines for Submitting Documentation for Packaging for Human Drugs and Biologics.

TYPE IV: Excipient, Colorant, Flavor, Essence or Materials Used in their Preparation

Each additive should be identified and characterized by its method of manufacture, release specifications and testing methods. Toxicological data on these materials would be included in DMF, if not otherwise available by cross reference to another document.

TYPE V: FDA Accepted Reference Information

FDA discourages the use of Type V DMF for miscellaneous information, duplicate information or the information that should be included in one of the other types of DMF. If any holder wishes to submit the information in a DMF that is not covered by Type I through IV, a holder must first submit a letter of intent to the DMF staff. FDA will then contact the holder to discuss the proposed submission.

General Informations and Suggestions:

Environmental Assessment: Type II, Type III and Type IV DMF's should contain a commitment by the firm that it facilities will be operated in compliance with applicable environmental laws.

Stability: Stability study design, data, interpretation and other information should be submitted, when applicable, as outlined in the:

- Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics.

Format, Assembly, Delivery:

- An original and duplicate are to be submitted for all DMF submissions.
- The original and duplicate copies must be collated, fully assembled and individually jacketed.
- US standard paper size (8-1/2 by 11 inches) is preferred.
- Delivery to FDA:

DMF Submissions and correspondence should be addressed as follows:

Drug Master File Staff

Food and Drug Administration

5901-B Ammendale Rd.

Beltsville, MD 20705-1266

Authorization to refer to a DMF[22]

Letter of Authorization to FDA:

Before FDA can review DMF information in support of an application, the DMF holder must submit in duplicate to the DMF a letter of authorization permitting FDA to reference the DMF.

The Letter of authorization should include the following:

1) The date
2) Name of DMF holder
3) DMF number
4) Name of person(s) authorized to incorporate information in the DMF by reference
5) Specific product(s) covered by DMF
6) Submission date(s) of 5, above
7) Section numbers and/or page numbers to be referenced
8) Statement of commitment that the DMF is current and that the DMF holder will comply with the statements made in it.
9) Signature of authorizing official
10) Typed name and title of official authorizing reference to the DMF

Copy to Applicant, sponsor or Other Holder: The holder should also send a copy of the letter of authorization to the affected applicant, sponsor, or other holder who is authorized to incorporate by reference the specific information contained in the DMF.

Processing and reviewing policies:

- Policies related to processing Drug Master Files.
- Public availability of the information and data in a DMF is determined under 21 CFR part 20, 21 CFR 314.420(e), and 21 CFR 314.430.
- An original DMF submission will be examined on receipt to determine whether it meets minimum requirements for format and content. If the submission is administratively acceptable, FDA will acknowledge its receipt and assign it a DMF number.
- Drug Master File Review: A DMF is never approved or disapproved.

Holder Obligations [23]: Any change or addition, including a change in authorization related to specific customer, should be submitted in duplicate and adequately cross referenced to previous submissions.

The reference should include the date(s), volume(s), section(s) and/or page number(s) affected.

Notice Required for Changes to a Drug Master Files: A holder must notify each affected applicant/sponsor who has referenced its DMF of any pertinent Change in DMF. Notice should be provided well before making the change in order to permit the sponsor to supplement or amend any affected application as needed.

Listings of Persons Authorized to Refer to a DMF: A DMF is required to contain a complete list of persons authorized to incorporate information in the DMF by reference (21CFR 314.420(d)). The holder should update the list in annual update. The updated list should contain the holder's name, DMF number and date of the update. The update should identify by name the information that each person is authorized to incorporate and give the location of that information by date, volume and page number.

Annual Update: The holder should provide an annual report on the anniversary date of the original submission. Failure to update or to assure FDA annually that previously submitted material and lists in the DMF remain current can cause delays in FDA review of a pending IND, ANDA, NDA, export application or any amendment to such application and FDA can initiate procedures for closure of the DMF.

Transfer of Ownership: To transfer ownership of a DMF to another party, the holder should so notify FDA and authorized persons in writing. The letter should include the following:

1) Name of transferee
2) Address of transferee
3) Name of responsible official of transferee
4) Effective date of transfer
5) Signature of the transferring official
6) Typewritten name and title of the transferring official

Major reorganization of a DMF [24]: A holder who plans a major reorganization of a DMF is encouraged to submit a detailed plan of the proposed changes and request its review by DMF staff. The staff should be given sufficient time to comment and provide suggestion before a major reorganization is undertaken.

Closure of a drug master file: A holder who wishes to close a DMF should submit a request to the Drug Master File Staff stating the reason for the closure. The agency may close a DMF that does not contain an annual update of persons authorized to incorporate information in the DMF by reference and a list of changes made since the previous annual report. The holder will be notified of FDA's intent to close the DMF [25].

CONCLUSION: Every country has its own drug regulatory agencies which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of drugs. It is very difficult especially for the companies with global approach to develop one single regulatory authority approach for a marketing authorization application for a new drug on the basis of one dossier submitted simultaneously to different countries in the world. Regulatory standards in ICH countries have been progressively tighten. They have developed a common for submission for Marketing Authorization Application .All drug applications must be made in CTD format. Therefore, due to variations in the regulatory norms in the registration dossier in different countries of the world there is a strong need for harmonization by ICH as the regulatory agency for harmonized approval of drugs at global level.

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