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A Comparative Study on the Dossier Submission for Pharmaceutical Products: Global Review

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ABSTRACT

The Dossier is a series of papers on various topics. The process of reviewing and analyzing the pharmaceutical product dossier, which has administrative, quality, non-clinical and clinical data. The Drug Regulatory Authority in a specific country regulates and authorizes this process and the process is known as New Drug Application in the United States of America, Marketing Authorization Application in the European Union and other countries simply as the Registration Dossier. For dossier preparation, there are essentially two formats, i.e., Asean Common Technical Dossier and International Conference on Harmonization- Common Technical Dossier. International Conference on Harmonization- Common Technical Dossier is followed by International Conference on Harmonization countries and low economic or developing countries where Asian countries follow the Asian Common Technical Dossier. Asian Common Technical Dossier serves as the bridge between developed and emerging countries' regulatory requirements. To harmonize both Common Technical Dossier and Asian Common Technical Dossier guidelines, discrepancies and variations in both guidelines can be reduced. As a result, the clear regulatory strategy should be carefully understood and established through an examination of the target regions, the various terms and conditions of the patent and its extension, the various implementation options, the data needs, and the potential schedule for marketing launches in the various regions.

As a result, less testing is required, drug approvals are launched more quickly, and the overall cost of manufacture is reduced. A high-quality dossier is required for any export market and can be created through the methodical production of formulas. A consistent dossier and responses to regulatory authorities' questions could benefit from careful planning and formulation production. It is challenging for pharmaceutical companies to design therapeutic formulations that can be concurrently submitted for approval in many countries because the regulatory standards of various nations differ from one another. Therefore, there are ongoing procedures of harmonization around the world.

Keywords: ICH- CTD; ACTD; eCTD; Dossier Submission

Introduction

Dossier submission is a set of records and data summarizing the entire history of product production and evolution. The marketing approval of a product depends upon the dossier, and it is the vehicle to the regulatory agency for the product approval. The dossier submission is done after the successful completion of the phase III clinical trial. The information presented in the dossier includes product chemistry, formulation, manufacture, toxicology, pharmacology, pharmacokinetics, and clinical studies. Another part of the dossier contains the companies dedicated work in phase IV. For example, in US and Europe, companies must include the pediatric study plan [1]. The steps involved during and after the dossier submission is given in (Figures 1 & 2).

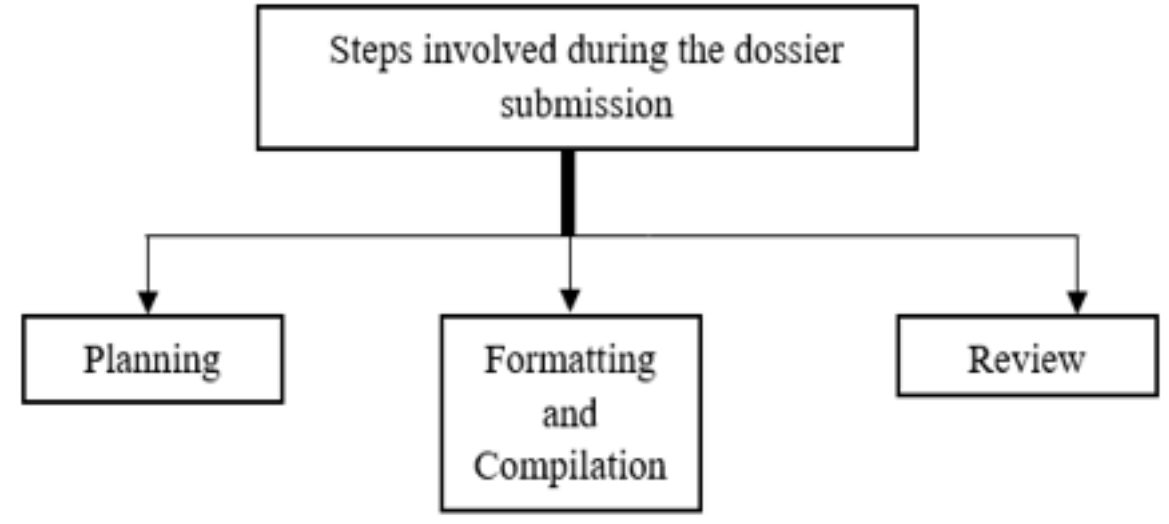

Figure 1: Steps involved during the dossier submission.

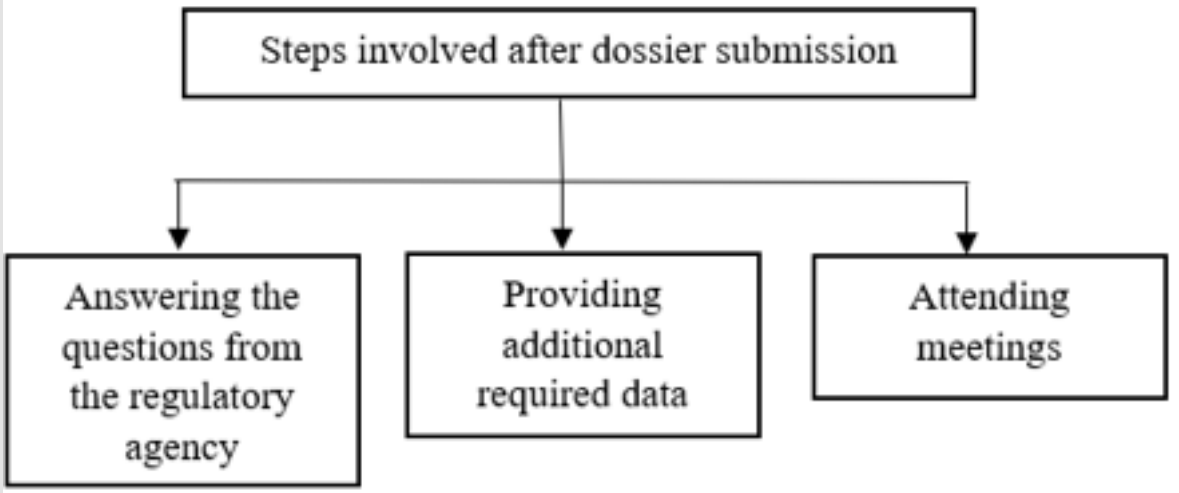

Figure 2: Steps involved after the dossier submission.

Planning

1) Plan the submission according to the given timeline.

2) Gain complete knowledge about the respective agencies and their submission requirements and format

3) Listing down all the requirements to be submitted to the agency and distributing it to the respective department.

Formatting and Compilation

Formatting the dossier according to the country specific requirements and compile all the documents.

Review

The documents are again re-checked, and cross verified before

submitting to the agency. The delay in the following and the meeting can jeopardies the time to market the drug, which is a great loss for the company [2].

Dossier Submission Types

The dossier submission may vary from one country to another. The types of dossier submission include: CTD, eCTD, ACTD, NeeS, paper submission.

Common Technical Document (CTD)

The CTD is a well-structured, globally accepted common format maintained by the ICH with regard to technical criteria for the registration of human pharmaceuticals. The ICH-CTD is a collaborative project of three regulatory agencies, Europe, the USA and Japan. The CTD is one of the cross-cutting themes that does not fall into one of the categories of efficiency, protection and effectiveness, and is part of the multidisciplinary guideline [3].

CTD Modules:

Module 1: Regional and Administrative Information: It is not considered to be a section of CTD. It includes regional information. It includes administrative documents such as application forms, legal documents, proposed label etc [4].

Module 2: CTD Overview and Summaries: This module consists of the common technical document summary containing information from module 3 to 5 which consists of seven sections.

- Section 1 – Table of contents
- Section 2 – Introduction
- Section 3 – Quality overall summary
- Section 4 – Non-clinical overview
- Section 5 – Clinical overview
- Section 6 – Non-clinical written and tabulated summaries
- Section 7 – Clinical summary
- Module 3: Quality
- Module 3 contains information about Drug Substance, Drug Product, Literature References [5].
- Module 4: Non-clinical
- Module 4 contains information about reports on pharmacologic, pharmacokinetic, and toxicological studies [6].
- Module 5: Clinical
- Module 5 contains information about safety and efficacy reports of clinical studies.

eCTD – Electronic Common Technical Document

It is the electronic form of a common technical document which is submitted by the applicant to the regulator in order to obtain approval for marketing the product. It is made up of individual PDF documents that are structured in accordance with the CTD structure. The information is provided by cross linking the document using XML backbone. The electronic submission is very useful for the reviewer of the regulatory authority [6]. It is superior technology and is a single application format for all applications [7].

eCTD Structure

1) Modules: 1 to 5

2) Documents: PDF linked via XML backbone

3) The submissions are highly transparent, easy to navigate and review.

Significance of eCTD

1) It is a common format which is being accepted in all countries

2) Helps in reviewing the application and in order to avoid the omission of the data

3) The review or communication of the regulatory facilities are done in time

4) Since it is an electronic submission, the patient population receives the medicines at appropriate time [8] (Table 1).

Table 1: Comparison of Dossier Submission Requirements in US, EU and INDIA [9].

Module 1	USA: Information regarding Patent and exclusivity, administrative details of pediatrics and plans for risk assessment.
	EU: The information regarding clinical trials, Market exclusivity of orphan drugs, Pharmacovigilance, Environmental risk assessment, requirements for certain applications like generic summaries, hybrid applications, bibliographic applications.
	CANADA: Patent information, summaries of Health Canada, Environmental Assessment Statement, BE studies, Certified product information document
	AUSTRALIA: Experts' information, region specific requirements, Drug and Plasma Master file, GMP clearance letter, Summary Biopharmaceutical studies, Pediatric development program, Antibiotic resistant data.

Module 3	**USA**
3.2.S (Drug Substance)	a. 3.2.S The dossier may make reference to DMF data that was provided directly to FDA Substance by the manufacturer of the drug substance.
	b. 3.2.S.7 Stability: According to FDA standards, storage requirements must be indicated on labels.
	EU
	a. 3.2.S Drug substance data may be submitted as a reference to a European Pharmacopoeia Certificate of Suitability or as a reference to an EU 2-part DMF
	b. 3.2.8.7 Stability: To be mentioned in accordance with CHMP guidelines are the storage requirements.
	CANADA
	a. 3.2.S The dossier may make use of DMF information that was directly supplied by the manufacturer of the medicinal ingredient.
	AUSTRALIA
	a. 3.2.S A 2-part DMF or a reference to a European Pharmacopoeia Certificate of Suitability may be used to submit drug substance data.
3.2.P (Drug Product)	**USA**
	a. 3.2.P The dossier may make reference to DMF data that excipient and container/closure manufacturers directly provided to the FDA.
	b. 3.2. P.1 Colors included on the FDA's register of approved hues. Where there is a monograph, excipients must be marked as conforming to USP/NF.
	c. 3.2.P.4 Excipients: If specified in a monograph, to comply with USP/NF.
	d. 3.2. P.5 Control of Drug Product: Assay values may not exceed 10%. There may be just one regulatory (shelf-life) specification.
	e. 3.2. P.7 Container Closure System: Name of manufacturer(s)
	f. 3.2. P.8 Stability: FDA language standards for storage must be followed.
	EU
	a. 3.2.P.1 Description and Composition: Colors included on the register of authorised hues for the European Union. Where there is a monograph, excipients must be identified as adhering to European Pharmacopoeia.
	b. 3.2. P.4 Excipients: If described in a monograph, to adhere to Ph Eur/European national pharmacopoeia.
	c. 3.2. P.5 Control of Drug Product: Assay values should not exceed 5%. Products that adhere to European Pharmacopoeia general monographs
	d. 3.2. P.7 Container Closure System: Manufacturer(s) names are not necessary unless the product is crucial (e.g., parenteral).
	e. 3.2. P.8 Stability: Storage needs to comply with CHMP guidelines.
	CANADA
	a. 3.2.P.7 Container/Closure: One could mention a supplier's DMF.
	b. 3.2. P.8 Stability: Storage guidelines must follow Health Canada specifications (e.g., storage at controlled room temperature).
	AUSTRALIA
	a. 3.2.P.1 Description and Composition: Colors included on the Australian register of acceptable colors for oral products.
	b. 3.2.P.8 Stability: Store below 30°C, for example, is one of the permitted storage conditions listed on the TGA website.
Module 5	**USA**
	Ø 5.3.5.3 Reports of Analyses from More Than One Study to Include FDA Integrated Summaries of Safety and Efficacy (ISS/ISE) (these are typically required in addition to the Clinical Overview and Clinical Summary in 2.5 and 2.7).
	Ø Clinical trials should typically adhere to FDA regulatory guidance where these exist.
	EU
	Ø Clinical trials should typically follow CHMP Efficacy recommendations where these are available.
	Ø Where necessary, a European batch of the reference product must be used in BE studies for generic medications.
	Ø Both placebo studies and clinical trials comparing new pharmaceutical goods to approved «gold standard treatments» in Europe are crucial.

Conclusion

For the governing agencies to approve the drug for sale, a dossier including comprehensive details on the drug and the results of the studies conducted during its development phase is required. CTD is crucial for dossier submissions. A high-quality dossier is required for any export market and can be created through the methodical production of formulas. A consistent dossier and responses to regulatory authorities' questions could benefit from careful planning and formulation production. It is challenging for pharmaceutical companies to design therapeutic formulations that can be concurrently submitted for approval in many countries because the regulatory standards of various nations differ from one another. Therefore, there are ongoing procedures of harmonization around the world. As a result, the clear regulatory strategy should be carefully understood and established through an examination of the target regions, the various terms and conditions of the patent and its extension, the various implementation options, the data needs, and the potential schedule for marketing launches in the various regions. As a result, less testing is required, drug approvals are launched more quickly, and the overall cost of manufacture is reduced.

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Conflict of Interest

The author(s) declared no potential conflict of interest concerning this article's research, authorship, and/ or publication.

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