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Review

Regulatory Dossiers and GMP of INDIA and USA

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Abstract

The word "Dossier" has its English meaning as - a collection or file of documents on the same subject, especially a file containing detailed information about a person or a topic. Any preparation for human use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient is called as "pharmaceutical product for human use". Process of reviewing and assessing the dossier of a pharmaceutical product containing its detailed data (administrative, chemistry, pre-clinical and clinical) and the permission granted by the Regulatory Agencies of a country with a view to support its marketing / approval in a country is called as the "Marketing Approval or the "Registration" "Marketing Authorization" or the "Product Licensing". Good manufacturing practice (GMP) is a system for ensuring that products are consistently produced and controlled according to quality standards. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product.

Keywords: Dossier, GMP, Pharmaceutical Production, Registration, marketing authorization

INTRODUCTION

The word "Dossier" has its English meaning as - a collection or file of documents on the same subject, especially a file containing detailed information about a person or a topic. Any preparation for human use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient is called as "pharmaceutical product for human use". Process of reviewing and assessing the dossier of a pharmaceutical product containing its detailed data (administrative, chemistry, pre-clinical and clinical) and the permission granted by the Regulatory Agencies of a country with a view to support its marketing / approval in a country is called as the "Marketing Approval or the "Registration" "Marketing Authorization" or the "Product Licensing".

Dossier helps you create, assemble, update and publish a composite document(s) from various individual document sources and formats.

A compound document is resulting from a dynamic merge and assembly of elementary documents monitored by a structuring and publishing agent (the Dossier module). Elementary documents might be of heterogeneous types and formats. They should be managed as a whole. For instance, a training manual can be made up of Word documents, Powerpoint presentations, Excel spreadsheets and a video tape. It is published and made available to all users as a single document.

Does your business activity require that you merge various files created in different formats by several authors in a single and consistent dossier, with its own publishing rules, page numbering, headers, footers, table of contents, indices? Then Ennov5 Dossier is meant for you. Technical documents and marketing authorization submission dossiers call for tender, press and media kits: all these documents are managed as a single, consistent, structured and unified document. No more time wasted on assembling and maintaining a constantly moving document means immediate return on investment.

Each document or sub dossier follows its own lifecycle. Individual changes update in real time the whole dossier, up to the moment you decide to freeze and publish it. Several authors can work in parallel. Dossier allows various combinations of the same content in order to adapt to different contexts or targets: FDA approval, other regulatory approval, suppliers/customers needs, auditing purposes, etc.

Dossier offers both sophisticated and easy-to-use features

Thanks to its user friendly drag-and-drop interface it can manage documents stored in Ennov5 Doc as well as external documents. To structure a dossier, all you have to do is to specify what parts, chapters sections you want the dossier to be split into and then drag-and-drop. The dossier author describes layout elements rather than ask for publishing. This operation starts dossier version numbering. Publishing can be done in paper (PDF) or electronically. Dossier is eCTD compliant.[1]

Pharma Dossier Compiling / Writing

Pharmaceutical dossier is highly detailed and exhaustive document on the drugs which requires extensive datas on its various aspects. Dossier compilation requires skills of sourcing, interpreting and writing this document. This process of pharma dossier compilation needs a talented team of pharmacists, data analysts and research assistants. The entire procedure is highly time consuming and costly. For this pharma dossier compilation and writing please feel free to contact us.

Herbal Dossier Compiling / Writing

Herbal drugs are getting higher acceptance as an alternative medicine. Therefore some countries have started the registration for herbal drugs as well. Recently we are working on compiling and writing herbal dossiers too.

Pharma CTD / ACTD Dossier

Drug regulatory affairs in pharma industries has mandated two types of dossier namely CTD (Common Technical Dossier) and ACTD (Asian Common Technical Dossier). Regulated pharma markets (eg.USA, Europe) markets require submission of dossier in CTD format which has to provide clinical trial and bioequivalence studies. As against this, semi-regulated pharma markets (South East Asian and Gulf Countries) require ACTD format which does not require exhaustive details like CTD.

Regulatory Dossier

❖ Regulatory approach:

Parameters	US	Europe	Other markets	India
Stability data	1 batch	2 batches	2 or 3 batches	3 batches
Stability condition	Zone I & II condition	Zone I & II condition	Depends on the target market	Zone IV condition
Comparative dissolution study	3 media	3 media	Depends on the target market	1 to 3 media
Input materials	TSE/BSE, OVI statements	TSE/BSE	Depends on the target market	No such requirement
Packaging materials	Food grade certificate	Food grade certificate	Depends on the target market	No such requirement
Method validation data	As per ICH	ICH	ICH	No such guideline
Process validation data	Not required	Not required	Depends on the target market	Not required for submission
Bioequivalence study	US reference product under fast and fed condition	European reference product (generally under fasting condition)	Generally fasting bio study	Fasting bio study
Bioequivalence study	In USFDA approved CRO anywhere in the world	MHRA/EU approved CRO anywhere	Depends on the target market	Indian study required

Fig 1: Regulatory Dossier

Pharma Dossier Validation

For successful registration of medicines pharma dossiers validation is very vital. Several countries require some additional and specific drug information which needs to be incorporated in the standardize CTD and ACTD format. So verifying and assuring this match between the specific information required and the dossier prepared is known as pharma dossier validation. This is where we offer you our expert services at an affordable cost.

Pharma Regulatory & Registration Procedures

Being a highly regulated industry, pharmaceutical regulatory affairs have become very pivotal for all the companies. Pharmaceutical consulting for the registration procedures is indispensable and expensive. For these regulatory affairs pharmaceutical dossiers are key factors wherein we offer our pharma consulting services.

Registration of Medicines

Due to enormous number of medicines available worldwide, countries have enforce registration procedures for regulating quality. Company registration process is a preceding step for the registration process of medicines. With our contacts we can facilitate both company registration and registration of medicine.

Country List

ICPC provides pharmaceutical dossiers for almost all the countries of world.[2] Until recently, for each country or region, the information generated during drug development (i.e. study results, details of manufacture and legal/admin info) had to be documented in so-called regulatory dossier. This dossier was to be organized in accordance with country-specific national requirements and submitted for review by National Health Authorities. Fortunately, Health Authority representatives of the US, EU and Japan, together with representatives from the pharmaceutical trade associations form these regions founded the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, abbreviated ICH. This is a unique project that was established in 1990, with aims to produce a single set of technical requirements for the registration of new drug products, hence to streamlining the development process.

One of the major achievements of the ICH has been the development of the common technical document (CTD), a standard structure for the dossier used when applying for marketing approval of a pharmaceutical product in the EU, the US and Japan. More recently, further harmonization led to the development of exchange standards for an electronic CTD (eCTD).[3]

CTD - DOSSIERS

Common Technical Document (Product Dossier) is an integral Part of any registration application for Marketing Authorization. Dossier in CTD Format/ ACTD Format or local country format is submitted to Food & Drug Authority or Ministry of health or any other equivalent authority along with other required technical documents and legal manufacturing permissions. Perfect Pharmaceutical Consultants can help you prepare entire technical document for drug product registration in various countries all over the world. PPC Provides following consulting service in regards to Technical Document.

Regulatory Guidelines For Dossier Submission In Usa

Dossier is submitted in CTD format.

CTD format

Aim

To harmonize the structure and format of registration documentation.

Benefits

Complete, well-organized submissions

Facilitates electronic submissions

Easier analysis acrosss applications etc.

Regional Admin Information Module-1 Nonclinical overview Clinical overview Clinical Summary Quality overall summary Quality Module-3 Nonclinical Studies Reports Module-4 Clinical Study Reports Module-5 The CTD Module-2 Not Part of CTD

The CTD is organized into five modules

Module 1 is region specific.

Modules 2, 3, 4, and 5 are intended to be common for all regions.

Dossier Compilation and writing as per CTD Format – Common Technical Document

- **Module 1 – Administrative Information**
- **Module 2 - CT Overview**
- **Module 3 – Drug & Product Part /CMC**
- **Module 4 – Non Clinical**
- **Module 5 – Clinical**

CTD Format Dossier is widely used in semi regulated & regulated market like CIS Countries, Middle Eastern countries, European Union, USA , Australia , Canada, Japan, etc

- Dossier writing and compilation as per ACTD Format – Asian Common Technical Document
  - **Part I – Administrative Documents**
  - **Part II – Quality Documents**
  - **Part III – Non Clinical Documents**
  - **Part IV – Clinical Documents.**

ACTD Format is Asian harmonization for Common Technical Document used in Asian Countries like Vietnam, Thailand, Singapore, and Malaysia etc. We can help you compile and write entire technical document or specify modules as per your request, we also help companies establish their Document Management and technical writing system by guiding them with draft templates on BMR, COA, MOA, and other technical documents. We customize the same as per company requirement – Good for startup companies or scale up companies.[4]

Structure of dossier of medicinal products, information on the CTD format (1)

- A common format for the technical documentation:
  - significantly reduces the time and resources needed to compile applications for registration of human pharmaceuticals
  - eases the preparation of electronic submissions
  - Facilitates regulatory reviews and communication with the applicant by a standard document of common elements
    - Simplifies exchange of regulatory information between Regulatory Authorities

- This guideline is not intended to indicate what studies are required. It merely indicates an appropriate format for the data that have been acquired.

CTD format (2)

- Text and tables should be prepared using margins that allow the document to be printed on A4 paper.
- The left-hand margin should be sufficiently large that information is not obscured by the method of binding.
- Font sizes for text and tables should be easily legible, even after photocopying. Times New Roman, 12-point font, is recommended for narrative text.
- Every page should be numbered.
- Acronyms and abbreviations should be defined the first time they are used in each module.

References should be cited in accordance with the current edition of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, International Committee of Medical Journal Editors (ICMJE) 1.

CTD format (3)

- **The CTD is organized into five modules:**
  - Module 1 is region specific.
  - Modules 2, 3, 4, and 5 are intended to be common for all regions.
- **Module 1. Administrative Information and Prescribing Information**
  - Should contain documents specific to each region; e.g. application forms or the proposed label for use in the region. The content and format of this module can be specified by the relevant regulatory authorities.
- Module 1: Administrative Information and Prescribing Information
  - Table of Contents of the Submission Including Module 1

Documents Specific to Each Region (for example, application forms, prescribing information)

CTD format (4)

- **Module 2. Common Technical Document Summaries**

– Should begin with a general introduction to the pharmaceutical, including its pharmacological class, mode of action, and proposed clinical use. In general, the Introduction should not exceed one page.
– Should contain 7 sections in the following order :

- Common Technical Document Table of Contents (Modules 2-5)
- CTD Introduction
- Quality Overall Summary
- Non-clinical Overview
- Clinical Overview
- Non-clinical Written and Tabulated Summaries
  - Pharmacology
  - Pharmacokinetics
  - Toxicology
- Clinical Summary
  - Biopharmaceutical Studies and Associated Analytical Methods
  - Clinical Pharmacology Studies
  - Clinical Efficacy
  - Clinical Safety
  - Literature References

Synopses of Individual Studies

CTD format (5)

- **Module 3. Quality**

– Information on Quality should be presented in the structured format described in Guideline M4Q.

- Module 3: Quality

– Table of Contents of Module 3
– Body of Data

Literature References

- **Module 4. Non-clinical Study Reports**

– The non-clinical study reports should be presented in the order described in Guideline M4S.

- Module 4: Non-clinical Study Reports

– Table of Contents of Module 4
– Study Reports

CTD format (6)

- **Module 5. Clinical Study Reports**
  - The human study reports and related information should be presented in the order described in Guideline M4E.
- Module 5: Clinical Study Reports
  - Table of Contents of Module 5
  - Tabular Listing of All Clinical Studies
  - Clinical Study Reports

Literature References

eCTD AND REGULATORY PROCEDURES MANAGEMENT

RPN staff have wide experience in the preparation of eCTD and management of the regulatory procedures (e.g. Marketing Authorisation Applications, variations and renewals).

RPN services are:

- Support for the preparation of registration dossiers including critical sections (e.g. Pharmacovigilance System Master File, Risk Management Plan, Environmental Risk Assessment)
- Advise on different national requirements for the submission of Marketing Authorisation Applications
- Assistance in writing response documents to authority deficiency letters/list of questions
- Assistance in preparing and attending oral hearings with the authority during procedures
- Assistance in updating dossier sections in response to authority deficiency letters during Marketing Authorisation procedures
- Preparation of CTDs
- Preparation of eCTD or non-eCTD electronic submission (NeeS)
- Management of e-submissions, whether eCTD or (NeeS)
- Assessment of eCTD or NeeS applications for compliance prior to submission
- Preparation, submission and management of variation, renewal and Marketing Authorisation Holder Transfer applications
- Preparation, submission and management (through local agent) of application procedures in the USA: IND, NDA, ANDA or DMF
- Proxy service with national authorities

Facilitation of local concerns via a network of partners in EU countries and USA

Consolidated network of partners in EU countries and a local Agent in the USA allow us to support our clients facing specific local issues.[5]

REGISTRATION DOSSIER OF PHARMACEUTICALS

A regulatory process, by which a person/organization/sponsor/innovator gets authorization to launch a drug in the market, is known as drug approval process. In general, a drug approval process comprises of various stages: application to conduct clinical trials, conducting clinical trials, filing of Registration Dossier/ New Drug Application (NDA) and post-marketing studies. 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 the drugs. The single regulatory approach for marketing authorization of a new drug product applicable to various countries (on the basis of single dossier) is utmost difficult. Therefore, the knowledge of exact and detailed regulatory requirements for Registration Dossier of each country should be known to establish a suitable regulatory strategy.

Drug registration implements one of the legal requirements for marketing of drugs in a country. Drug registration guidelines provide guidance to applicants who may wish to market their pharmaceutical products in the market. They intend to assist applicants in the preparation of acceptable application documents. It is therefore essential that every person who intends to market a medicinal product in country reads the whole of these guidelines carefully and follows strictly the instructions prescribed herein. Submission of applications, which do not comply with the prescribed requirements, may result in delays, queries or rejection of registration.

REGULATORY DOSSIER SUBMISSION IN ICH COUNTRIES

The complete name of ICH is the "International Conference on harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use". ICH is a joint initiative involving both regulators and research-based industry representatives of the European Union, Japan and the USA in scientific and technical discussions of the testing procedures required to assess and ensure the safety, quality and efficacy of medicines. The

goal of ICH is to promote international harmonization by bringing together representatives from the three ICH regions (EU, Japan and USA) to discuss and establish common guidelines.

For example, since year 2003, the authorities in the United States, the European Union (EU) and Japan ask for the Common Technical Document (CTD) format set out by the 2003 International Conference on Harmonization (ICH) which was agreed by the Regulatory Agencies of Europe, Japan and the US and the Research-based Industry and more recently, its electronic version - the electronic Common Technical Document (eCTD). CTD provides a common format for the submission of information to the Regulatory Agencies for the registration of the pharmaceutical product.

The CTD is organized into five modules as shown in Figure I. Module 1 is region specific and Modules 2, 3, 4 and 5 are intended to be common for all regions. The agreement to assemble all the Quality, Safety and Efficacy information in the CTD format has revolutionized the regulatory review processes, led to harmonized electronic submission that, in turn, enabled implementation of good review practices.

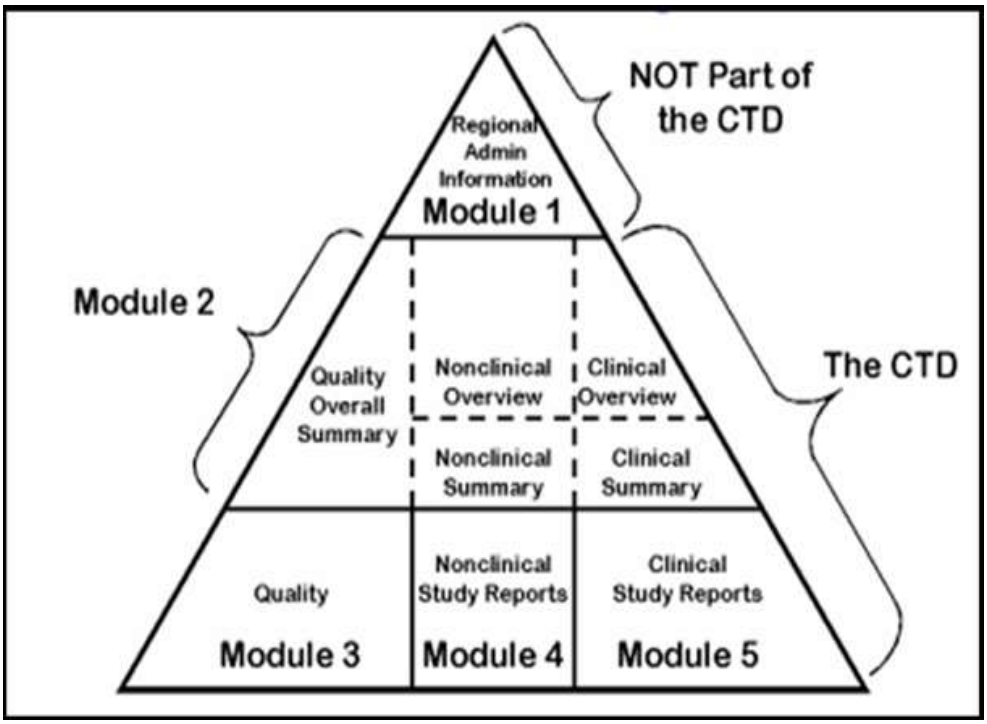

Fig 2: CTD Triangle

Module 1: Administrative Information and Prescribing Information
- Table of Contents of the Submission Including Module 1.
- Documents Specific to Each Region e.g. the application forms, labeling etc

Module 2: CTD Summaries
This module should begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action, and proposed clinical use, not exceeding one page.
Module 2 should contain 7 sections in the following order:

· CTD table of contents
· CTD introduction
· Quality overall summary
· Nonclinical overview
· Clinical overview
· Nonclinical written and tabulated summaries
· Clinical summary

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INDIAN REGULATORY DOSSIR PREPARATION

Things to remember while preparing your regulatory dossier

Below are some of the key points to remember while preparing your regulatory dossier for Medical Device submission in India. This is ensure seamless document submission. Ensure that you receive the latest updated version of the checklist from your Authorized Indian Agent.

Power of Attorney and Forms

The name of the manufacturer has to be same as in Free Sale Certificate (FSC), Form 40, Power of Attorney (POA) and Schedule D(I). The name of the Indian agent has to be same as in Wholesale Drug License, Form 40, POA and Schedule D(I). The Power of Attorney only needs an Apostil if the manufacturer is part of a Hague convention countries viz. USA, Europe, Canada, Australia, Japan etc. The apostilled Power of Attorney should have the word "Apostil" in it to differentiate it from notarization. The article number and the pack sizes of the medical devices mentioned in Form 40, POA and Schedule D(I) should be the same as in the Free Sales Certificate from the country of origin. Add a listing of the various sizes of the product in the appendix of the forms.

Regulatory and Quality Certificates

The notarized Regulatory Certificates FSC from country of origin and FSC from GHTF countries namely USA, Canada, Australia and Japan must mention the product(s) for which the application is filed. The notarized Quality Certificates (ISO 13485, CE Full Quality Assurance, CE Design and Declaration of Conformity) have to be within 6 months of validity at the time of submission. If the ISO 13485 mentions a warehouse site along with a manufacturing site then an application for two sites (USD 1500 each) has to be filed. As per the European Medical Device Committee is no CE Design Certificate for Class I and II products. Each product/medical device has a separate Declaration of Conformity (DOC). The DOC has to mention risk class. The same need to be printed on the manufacturer's letter head and signed by the authorized person(s).

CONCLUSION

Significantly reduces the time and resources. Needed to compile applications for registration of human pharmaceuticals. Eases the preparation of electronic submissions .Facilitates regulatory reviews and Communication with the applicant by a standard .Document of common elements Simplifies exchange of regulatory information Between Regulatory Authorities**.**

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