

A Review of the Preparation of Regulatory Dossiers in CTD Format and ECTD Submissions

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ABSTRACT:

The information needed to prepare dossiers for multiple countries is discussed in this article, as well as the CTD format, which is projected to considerably decrease the time and resources needed by the industry to compile global registration applications and reports. The International Conference on Harmonization of the electronic common technical document (eCTD) aims to revolutionize the pharmaceutical submission procedure. In comparison to paper submissions volume, more than three-quarters of individuals with eCTD expertise were able to shorten their total time to approval, and more than 90% of this group was able to demonstrate cost savings.

KEYWORDS: Regulatory,CTD, eCTD, Dossier, ICH.

I. INTRODUCTION:

Regulatory Dossier

Dossier: In English, a dossier is a collection or file of materials about a specific subject, particularly one containing thorough information about a person or a topic. Any formulation is designed for human use, i.e., to alter or investigate physiological processes.^[1]

"Pharmaceutical" refers to the use of systems or pathological conditions for the benefit of the recipient. "A product for human consumption." Critiquing and evaluating pharmaceutical dossiers is a process. Administrative, chemistry, preclinical, and clinical data are all included in this product. Information and authorization issued by a country's regulatory agencies to "Marketing approval or Registration" is a term used to describe the process of supporting a product's marketing or approval in a country." Product License" or "Marketing Authorization" [2]

A dossier is a file document that is submitted for drug product approval in several regulatory jurisdictions based on their requirements. CTD is a harmonized format (template) for presenting data in the ICH regions, and it is submitted in many ways such as CTD, and e-CTD.

A dossier is a collection of documents that provide in-depth information about a specific person or subject. (Or) a collection of papers relating to a subject or a person. (Or) A dossier is a file document that contains detailed information about a drug product and is submitted to the regulatory authorities.^[3]

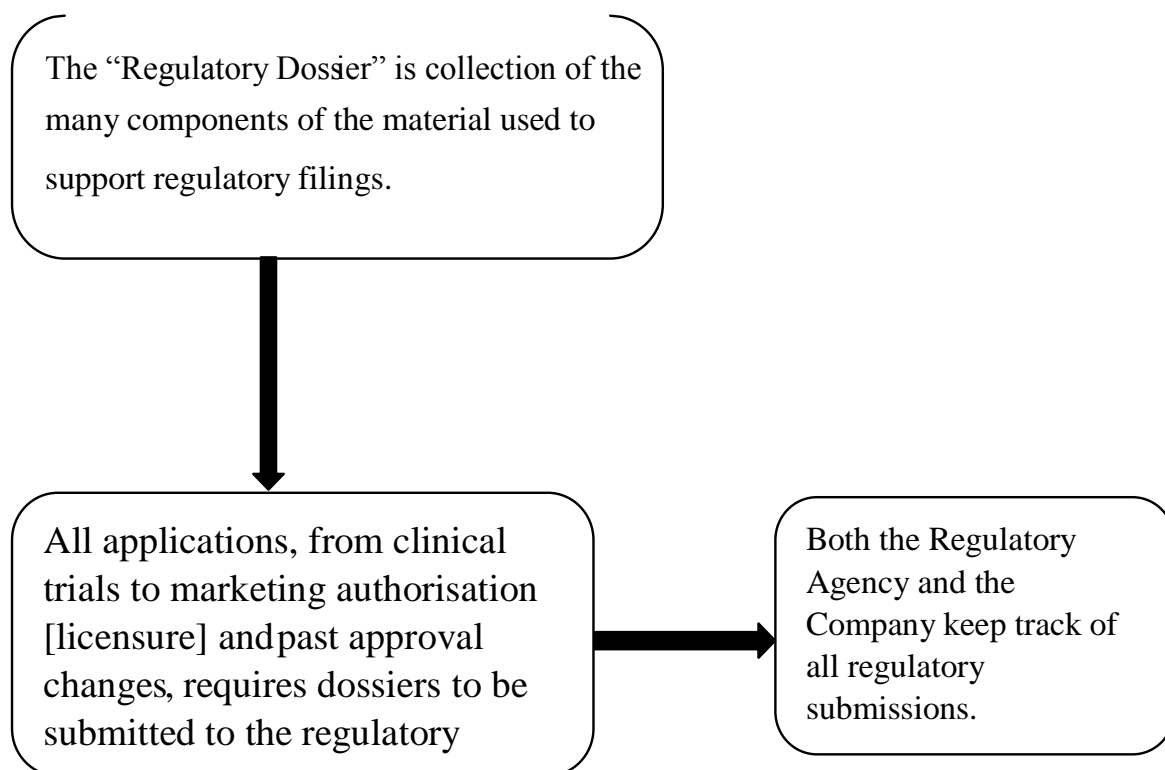


Figure 1: Regulatory Dossier Preparation.

COMMON TECHNICAL DOCUMENT (CTD):

A Common Technical Document (CTD) is a supporting list of leaflets that must be given to the regulatory body with pharmaceutical registration applications to obtain market authorization. CTD mostly describes the data format. It is customary for RA professionals to be aware of the documentation that must be provided when a medication product is approved. CTD, on the other hand, is primarily concerned with the orderly structure of information. CTD documents should be simple, straightforward, and transparent.^[4]

CTD is an ICH-defined format that has been agreed upon and accepted by regulatory agencies in Europe, Japan, and the United States. The FDA defines the CTD as an information package containing clinical, non-clinical, manufacturing, and technical data that would be

submitted for registration of novel pharmaceuticals in all three ICH regions, namely the United States, the European Union, and Japan^[8] Paper submission of ACTD and CTD format dossiers, as well as electronic submission of CD format dossiers, are used in semi-regulated markets such as ASEAN countries (Circle disk).^[6]

(See Fig. 2 for a diagram of the CTD triangle describing the various modules.) As a result, has it five modules^[4]

1. Administrative and prescribing information (Module 1).
2. Common Technical Document (Module 2) Summaries (Quality Overall summary)
3. Module 3: Data of High Quality
4. Non-clinical study reports (Module 4)
5. Clinical Study Reports (Module 5)^[13]

CTD STRUCTURE:

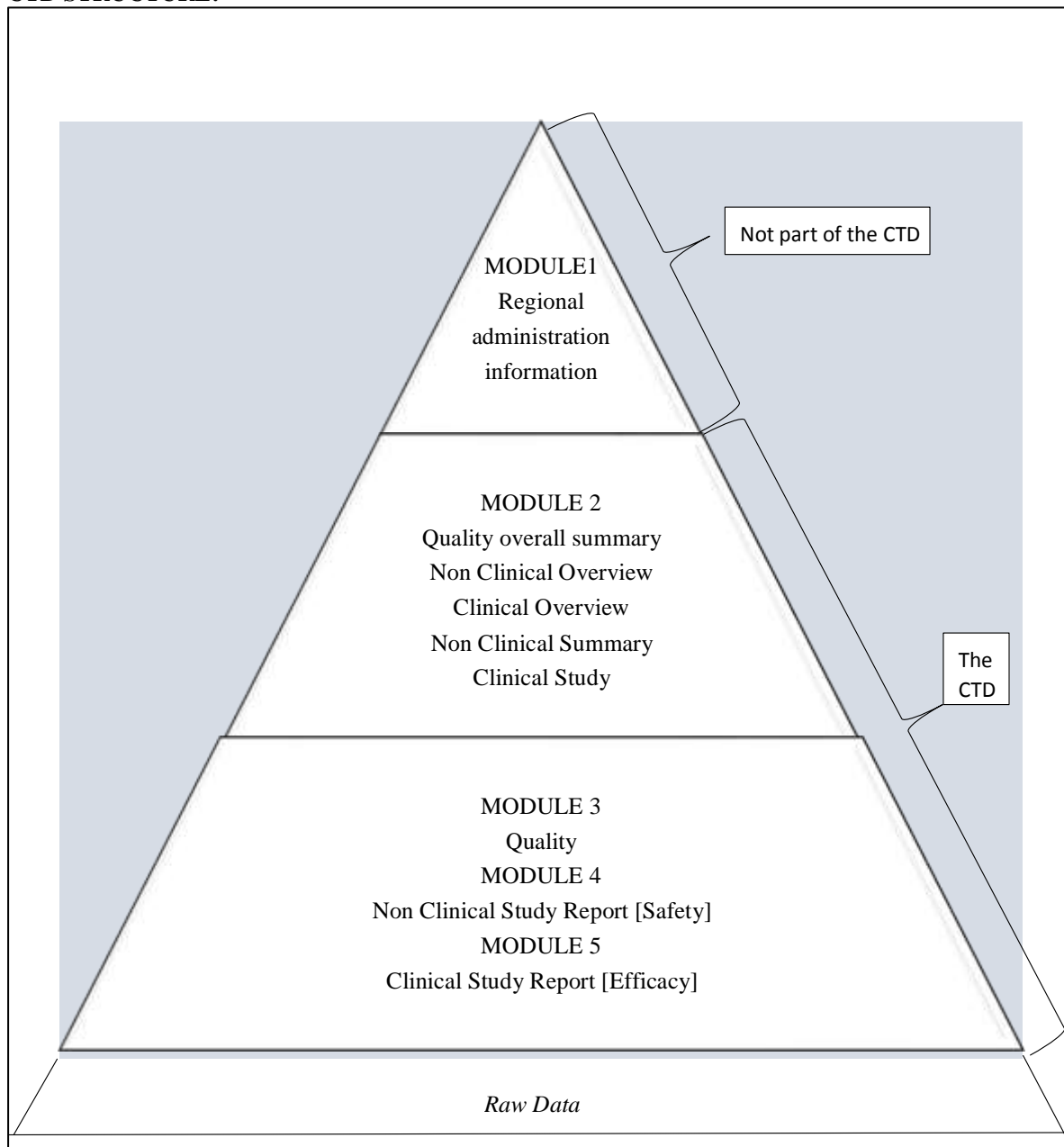


Figure 2: Triagonal Representation of Dossier Preparation

Modules are divided into two categories:

First Regional module

Only the content of the shared modules is defined by the CTD. Each of the ICH regions defines the contents of Regional module1. (USA, Europe, Japan).^[14]

ORGANISATION OF CTD:

The Common Technical Document is organized into five modules.

Module 1: Administrative Data.

Administrative information should include papers particular to each region, such as application forms or the proposed regional designation.^[5]

Module 2: Overall Quality Summary

CTD Synopsis Begin with a general overview of the drug (pharmacological class, mechanism of action, and intended clinical usage).

It begins with a general overview of the medicine, including its pharmacological class, mechanism of action, and potential clinical applications. Information (for example, pharmaceutical documentation), as well as the Non-Clinical and Clinical Overviews, NonClinical Written Summaries and Tabulated Summaries, and the Clinical Summary.^[7]

Module 2 is divided into seven sections, which should be kept in the following order:

- 2.1 Table of contents.
- 2.2 The Beginning

- 2.3 Overall Quality Summary. 2.4
- Overview of Non-Clinical Research

- 2.5 Overview of Clinical Practice. 2.6 Non-clinical Summaries (Written and Tabulated)

2.7

Clinical synopsis

Module 3: Quality Assurance

The M4Q's Quality component establishes a standardized structure and method for delivering CMC (Chemistry, Manufacturing, and Controls) data in a registration dossier. The following are the primary headings in this section (which must not be changed):^[5]

- 3.1 Module 3 Table of Contents
- 3.2 The data set
 - Drug Substance 3.2.S
 - Drug Product 3.2.P
- 3.3 Module 3 literature references^[11]

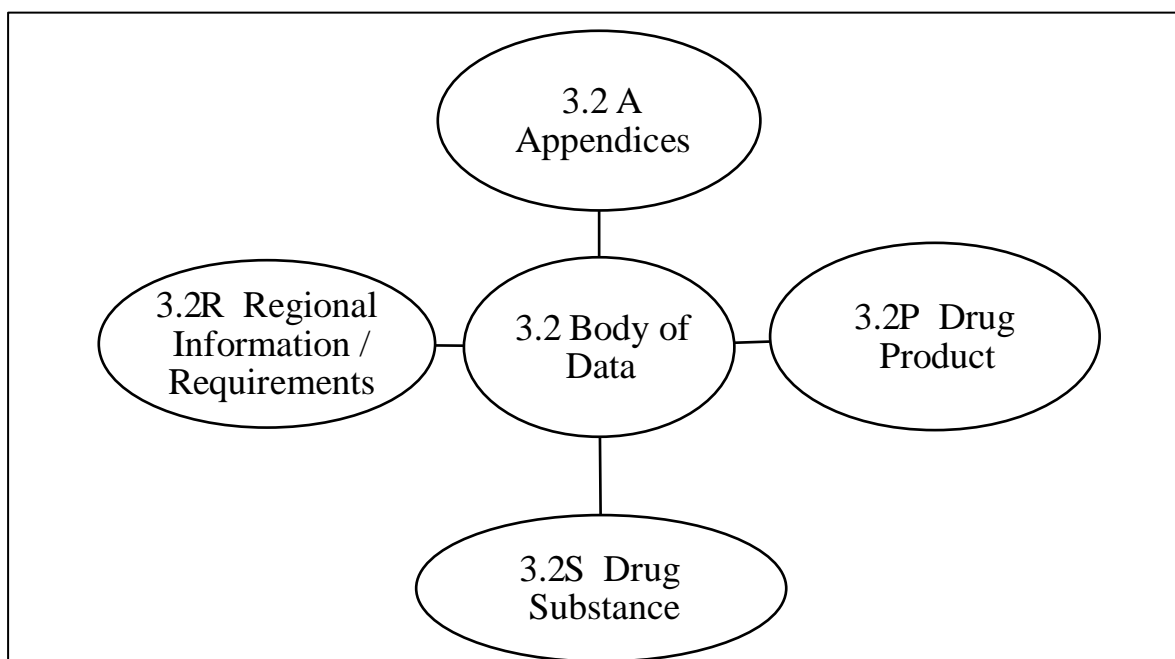


Figure 3: Dossier preparation in the CTD format.

Module 4: Reports on nonclinical and preclinical research

The CTD Safety (M4S) Guideline defines the nonclinical study's structure and format. Module 2 of the Common Technical Document summarises the information in Module 3 of the Common Technical Document and organizes Module 4 of the Nonclinical Study Reports.^[16] The Nonclinical Overview should be no more than 30 pages long and should provide an integrated and critical assessment of the pharmaceutical's

pharmacologic, pharmacokinetic, and toxicological examination. Nonclinical Written Summaries (100–150 pages) are indicated for more comprehensive summaries and discussions of nonclinical pharmacology, pharmacokinetics, and toxicological information.^[6]

- 3.1 Module 4 Table of Contents
- 4.2 Reports on research Pharmacology (section 4.2.1)^[11]

4.2.2 Pharmacokinetics is a term that refers to the study of how drug toxicology (section 4.2.3)

Module 4 uses 4.3 literature references^[5]

Module 5: Clinical Study Reports

The organization and format of clinical data in an application, including summaries and comprehensive study reports, is described by CTD-Efficacy (M4E). The Clinical Overview, a short document that gives a critical review of the clinical data, and the Clinical Summary, a larger document that focuses on data summary and integration, are both included in Module 2 of the CTD. Module 5 contains clinical study reports as well as raw data^[11]

The following are the primary headings in this section (which must not be changed):

- 5.1 Module 5 Table of Contents
- 5.2 A list of all clinical studies in a tabular format
- 5.3 Reports on clinical trials
 - 5.3.1 Biopharmaceutical study reports
 - 5.3.2 Reports on experiments involving human biomaterials and pharmacokinetics.
 - 5.3.3 Human pharmacokinetic (PK) studies reports
 - 5.3.4 Human pharmacodynamics reports (PD) research
 - 5.3.5 Efficacy and safety study reports
 - 5.3.6 Post-marketing experience reports
 - 5.3.7 Individual patient listings and case report forms
- 5.4 Literature citations^[5]

ADVANTAGES OF CTD:

1. The main goal of implementing a common submission format is to make reviewing each application easier and to avoid other critical data or analysis missions. Omissions of this information can cause approvals to be delayed unnecessarily.
2. A common format for technical documentation will significantly reduce the time and resources required to compile applications for human pharmaceutical registration, as well as make electronic submission preparation easier^[6]
3. A standard document with common elements will be used to facilitate regulatory reviews and communication with the applicant.
4. The implementation of CTD is expected to significantly reduce the amount of time and resources required by the industry to compile global registration applications^[10]

CTD'S SILENT BENEFITS:

1. Global application harmonisation.
2. Establishes guidelines for preparing submission-ready documents during the IND stages.

3. Standardization makes project management and data management easier.
4. Makes life cycle management easier.
5. Aids in the planning of drug development^[10]

ELECTRONIC SUBMISSIONS (eCTD):

The electronic submission equivalent of the CTD is the eCTD. The eCTD serves as a conduit between industry and government agencies for the exchange of regulatory data, facilitating the development, review, lifecycle management, and archiving of electronic submissions. All CTD information is included in the eCTD submissions. The structure of the submission is represented by an XML file (Extensible Mark-up Language) at the heart of eCTD. It contains links to files as well as other metadata such as checksum data. The XML scheme is extremely rigorous. CTD submission, all subsequent submissions for the application should be in eCTD format. The submission's lifecycle management is simplified using eCTD^[7]

The electronic Common Technical Document (eCTD) is a regulatory information transfer link between the pharmaceutical industry and regulatory agencies. The Common Technical Document (CTD) format is used for the main content. The Multidisciplinary Group 2 Expert Working Group (ICH M2 EWG) of the International Conference on Harmonisation (ICH) produced it^[15] Essentially, the electronic Common Technical Document (eCTD) will be a transport format that will allow electronic submissions to be moved into an agency's review environment. The eCTD will act as an interface for the flow of regulatory information from industry to agencies, while also making the production, evaluation, lifecycle management, and archiving of electronic submissions easier.^[17]

An eCTD application is a CTD application, but then electronically.

Electronically means for eCTD:

I complete the dossier in electronic format I XML files (XML backbone)

I Specifications followed for the Granularity, folder- & filename convention of the dossier Navigation through the dossier using hyperlinks and bookmarks.^[9]

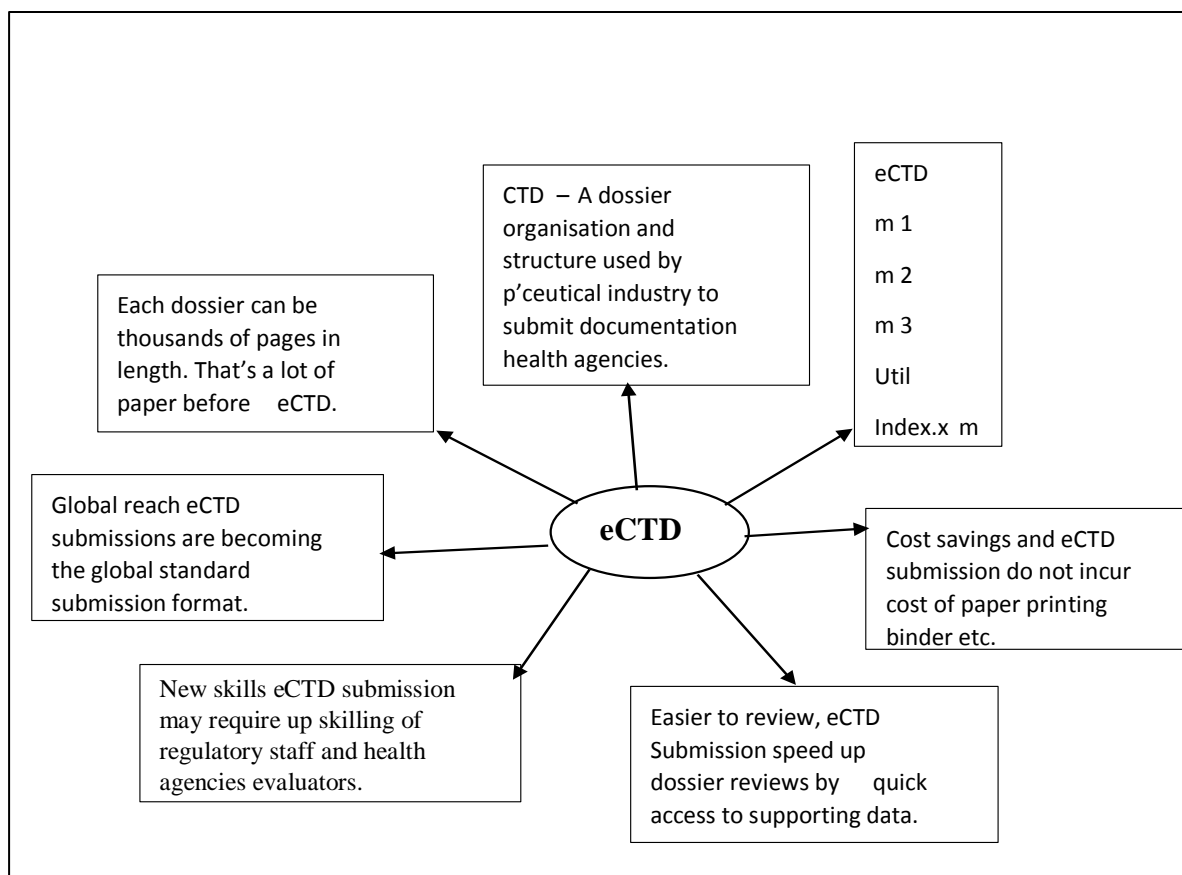


Figure 4: Overview of eCTD Submission.

eCTD Submission Checklist:

- eCTD Software
- Software training and support from the supplier
- Compiling and eCTD

eCTD hyperlinking

QC of eCTD

Submit eCTD on CD/DVD or Use an electronic gateway^[2]

eCTD STRUCTURE:
 eCTD is highly recommended by USFDA for NDAS, BLAS, DMFS, and INDs filing. From the year 2010 European Union also make compulsory for electronic CTD submission to all procedures.^[2]

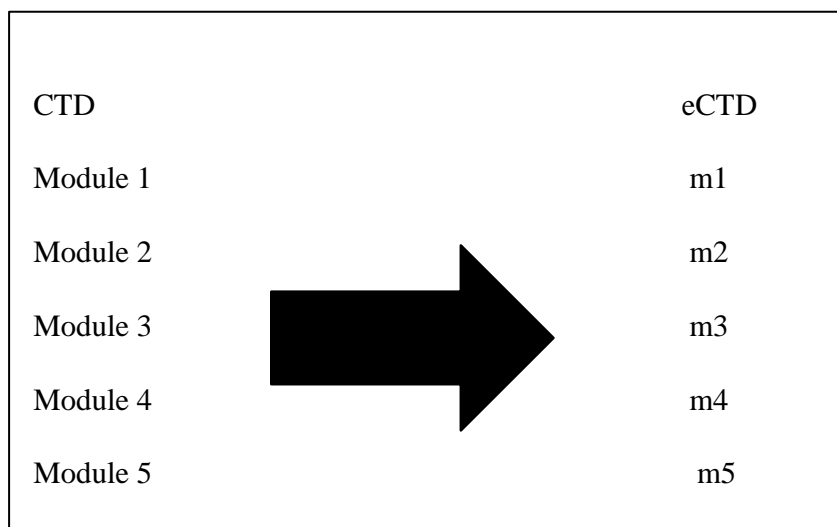


Figure 5: Electronic Submission to all Procedures.

eCTD ADVANTAGES:

The eCTD dossier becomes the single authoritative regulatory archive, thus reducing the use and costs associated with producing and storing paper dossiers. Enhanced ability to organize, prepare, and manage submission content.

Opportunity for streamlined interactions with agency reviewers, decreased response times to agency requests, and ultimately, a faster approval timeline.

Facilitates collaboration between teams of document authors, reviewers, publishers, and external partners.^[6]

There are five modules in eCTD as mentioned here:

1. Region-specific information.
2. Summary documents.
3. Information related to quality.
4. Non-clinical study reports.
5. Clinical study reports (CSRs).

Comparison OF CTD and eCTD:

Sr. No.	Paper CTD [Common Technical Document]	eCTD [Electronic Common Technical Document]
1.	Volumes, tabs, and slip sheets were entered electronically and then printed on paper.	Electronically filed with e-documents in folders.
2.	A4 paper must be used.	A4 or US letter size documents are acceptable.
3.	TOCs and volume are used to navigate the CTD.	XML backbone for eCTD navigation.

4.	The target CTD section number is included in the cross-reference.	The target is linked to the cross-reference.
5.	TOCs, page numbers, and caption crossreferences are used to navigate the document manually.	TOCs, bookmarks, and hyperlinks are used to navigate electronic documents.
6.	Trucks delivered binders in boxes on pallets.	CD (or DVD) or email portal submissions are accepted.

Table 1.CTD and eCTD Statements in Comparison.

eCTD submissions are accepted for the following applications:

1. Investigational New Drugs (INDs).
2. New Drug Applications (NDAs).
3. Abbreviated New Drug Applications (ANDAs).
4. Biologics License Applications (BLAs).
5. All the applications following submission of the above-stated applications.
6. All the Master Files (MFs) are part of any above-mentioned applications.

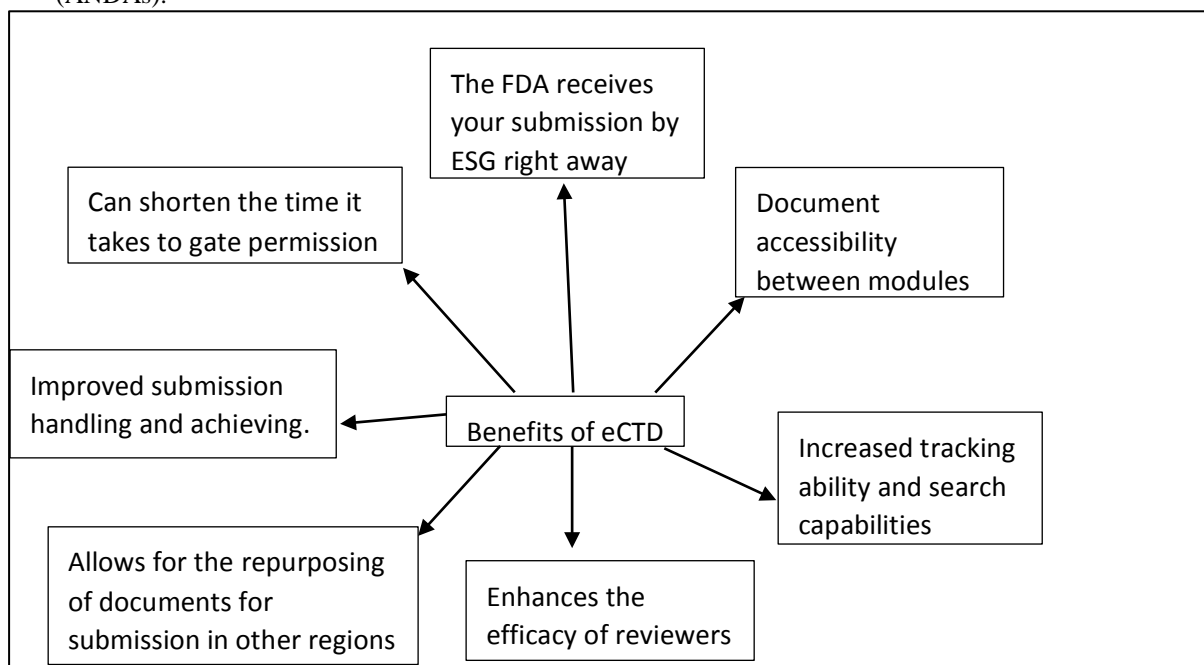


Figure 5: Overview of Benefits of eCTD

Content specification– as defined by ICH specified below-

1. Technical specification- Electronic software
2. CTD -TOC [pdf] [paper]
3. eCTD- XML Backbone

The eCTD is an electronic document similar to the CTD. Is an eCTD backbone describing the Structure of the submission, the XML file (Extensible Mark-up Language) includes links

to files and other metadata such as checksum information.

1. The schema for the XML is very rigid.
2. Easy to distribute and review.
3. More efficient use of resources with less cost and stress to the organization.
4. Self-validating.

The eCTD Requirements:

You must submit electronic submission using the FDA’s current supported version of eCTD.

The current version of eCTD, that is supported is listed in the Data standards Catalog and further explained in the technical specification document below.

Electronic Common Technical Document Specification of the International Council for Harmonisation (ICH). Study tagging files ICH eCTD Backbone file specification. ^[15] **Software used in eCTD management:**^[9]

Sr. No	Software
1.	ECTDXPress-Image solution-http://www.imagesolutions.com.
2.	ECTDXPress-Image solution-http://www.imagesolutions.com.
3.	Data farm, http://www.datafarminc.com.
4.	Take solution: www.PharmaReady.com.
5.	MasterControlsubmissionGateway™-MasterControl, http://www.mastersolution.com.
6.	Lorenz Life Science: www.lorenz.com.

Table 2. Software used in eCTD Submission.

Things to know before using eCTD software

- eCTD knowledge
- General eCTD tool knowledge
- Document format types and editing
- Software functions and system requirements
- FDA ESG submission requirements
- FDA Guidance Submission format delivery

How to send it to Authorities?

- Files on a CD or DVD
- Files attached to an e-mail
- Files submitted via Eudralink
- Files submitted via CESP 1 File submitted via a Gateway. ^[2]

II. CONCLUSION:

Any export market requires a high-quality dossier, which may be created via a methodical

Formulation Development process. The right planning and execution of Formulation development will aid in the production of high-quality dossiers and the response to regulatory bodies’ questions. It is critical to assemble documentation in a format that is acceptable internationally for both regulated and non-regulated markets when registering pharmaceutical products in any of the exporting countries. Due to significant discrepancies in the requirements for dossier registration for pharmaceutical products, the CTD and eCTD formats were developed. This aids in the compilation of documents in the above-mentioned format as per the registering requirements.

According to the thesis, the way of submitting a Dossier, according to CTD and eCTD format, Module 1- contains Administrative Information, Module 2- contains the Overall summary, and Module 3- contains the Quality Information. In

summary, Module 4 contains preclinical data, while Module 5 contains clinical data.

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