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COMPREHENSIVE GUIDE TO CREATE ELECTRONIC COMMON TECHNICAL DOCUMENT: ALIGNING WITH UNITED STATES AND EUROPEAN GUIDELINES USING SPECIALIZED SOFTWARE

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ABSTRACT

This current review article underscores necessity of electronic Common Technical Document (eCTD) software as advanced tool for variety regulatory submissions. Electronic Common Technical Document can be considered as one of the most useful tool especially to create dossiers for several specified as well as Common Technical Document (CTD) format, which is expected to be used and reduce the amount of time and resources required by the sector to collect global reports and applications for registration. An Electronic Common Technical Document is composed of individual PDF documents arranged in accordance with the structure of the Common Technical Document in an organized manner. The present review article provides a guide for creating an Electronic Common Technical Document using the latest software, accompanied by detailed step-by-step instructions for utilizing the specified software. Furthermore, this current review article extends to include a concise comparison of the filling procedures for the Electronic Common Technical Document in accordance with both United States Food and Drug Administration and European guidelines.

Keywords: Common technical Documents, Dossier Submission, electronic Common Technical Documents, European guidelines, Portable Document Format, United States Food and Drug Administration

INTRODUCTION

Regulatory submissions comes in two types: CTD and eCTD. Electronic Common Technical eCTD software functions as a sophisticated tool facilitating diverse regulatory submissions. In contrast, CTD requires the electronic input of slip sheets and subsequent paper printing **[1]**. CTD, or Common Technical Document, comprises five modules, each serving a specific purpose: Module I covers Administrative and Regional Data, Module II provides a CTD Overview and Summaries, Module III focuses on Quality, Module IV addresses non-clinical aspects, and Module V incorporates safety and efficacy reports from clinical study reports **[2]**. eCTD is an electronic Common Technical Document which include submissions information. The submission's organizational framework is illustrated by an Extended Mark-up Language (XML) file at the central to eCTD. It includes file links additional metadata, Since XML plan is very demanding. No special character is allowed in eCTD, No space between title of eCTD, Use lower case hyphen, PDF Property: 1.4 version for eCTD-More than 10 pages bookmarks should be must to view PDF fast. Submit eCTD via CD/DVD format **[3]**. eCTD offers a range of benefits. It improved tracking and search capabilities, efficient resource usage, enhanced document accessibility across modules, improved industry communication, immediate FDA receipt via ESG, streamlined submission management, and increased reviewer efficiency **[3, 4]**. The dossier is a compendium of information about a certain topic, usually one that includes in-depth details about an individual or subject. A dossier is a file document that is filed accordance with the requirements by various regulatory authorities for the approval of a drug product. Data can be submitted in multiple formats, including CTD and e-CTD, and is presented in the ICH regions using the harmonized format (template) known as CTD **[4]**. The electronic submission of regulatory data, including reports, supplements, and applications, to the relevant Health Authorities (HAs) is known as eCTD. It offers a coordinated way to put the CTD into electronic form. An eCTD is unique PDF documents that are organized systematically in accordance with CTD structure. Additionally, it has an XML backbone that provides information about the submission and cross-links the necessary documents **[5]**.

This document file with detailed information of drug product and drug substance is submitted to regulatory authorities **[5]**. The "Regulatory Dossier" is elements of the documentation utilized to support regulatory submissions. Different countries have different regional version,

For USA it is 2.3 and Europe has 3.0.1 version. Submitting a dossier is a mandatory requirement for all regulatory agencies. Every application, including for marketing authorization (licensure), clinical trials, and patent approval alterations, necessitates that dossier submitted to the authorities. The Company and the Regulatory Agency both maintain records of every regulating contribution. The CTD contain five modules and eCTD contain electronic submission, requirements, Features and how to operate eCTD software **[5, 6]**.

1.0 DOSSIER SUBMISSION TYPES

There exist two submission types: 1.1). CTD submission and 1.2). eCTD submission.

1.1). CTD submission

An International Council for Harmonisation of Technical (ICH) maintains standard Common Technical (CTD) format, which is widely recognized and well-organized with technical requirements for registration of medicines intended for human use **[6]**. The International Council for Harmonisation of Technical, Common Technical (ICH-CTD) is the result for collaboration between two US and European regulatory agencies. The CTD is one of the cross-disciplinary difficulties not fall under the categories of efficacy, safety, or effectiveness and a part of multidisciplinary guidelines **[7]**. Below, you'll find descriptions of the five modules, The CTD modules are shown in **Figure 1**.

1.1.1 Common Technical Document Modules

Module I: Administrative and Regional Data: This is not regarded as a part of the CTD. It contains geographical data, Application forms and other administrative paperwork are included, legal records, a suggested label and Raw data **[8, 9]**.

Module II: CTD Overview and Summaries: Module II comprises seven sections, each containing data pertaining to modules 3 through 5.

1 – Table of contents

2 – Introduction

3 – Quality overall summary

4 – Non-clinical overview

5 – Clinical overview

6 – Non-clinical written and tabulated summaries

7 – Clinical summary **[10]**.

Module III: Quality - It establishes a standardized structure and method of delivering Chemistry Manufacturing Control data in registration dossier. It includes information of drug substance, drug product and literature references **[11]**.

Module IV: Non-clinical- It includes information of pharmacology, pharmacokinetic and toxicological studies. The Nonclinical Overview must be limited to thirty pages and offer a comprehensive and a critical evaluation of the drug's toxicological, pharmacologic, and pharmacokinetic investigation. Non-

medical Composed Synopses (100–150 pages) are suggested for overviews and conversations about nonclinical pharmaceuticals, Information on pharmacokinetics and toxicology **[12]**.

Module V: It includes information of safety, efficacy reports of clinical study report **[12]**.

1.2). Electronic submission (eCTD)

An eCTD facilitates generation, review, lifecycle management, and sharing of regulatory data by acting as a channel between industry and government organizations. Every CTD and eCTD submissions include information. The submission's organizational framework is illustrated by an Extended Mark-up Language (XML) file at the central to eCTD. It includes file links in addition to additional metadata, like data checksums. Since XML plan is very demanding. Submission of CTD, all Subsequent application submissions should actually in the format of eCTD. The management of this contribution is streamlined with the use of eCTD, simplifying the process over its lifespan **[13]**.

The pharmaceutical sector and regulatory bodies can exchange regulatory information by eCTD organizations. A Standard Technical Document content in CTD format. The expert Working Group 2 of the Multidisciplinary Group. International Conference on Health (ICH M2 EWG) It is created by Harmonization (ICH) **[14, 15]**.

An eCTD function primarily as transport format that will enable updates electronically to be placed in an agency's evaluation setting. eCTD will function as data flow interface for regulations agency to business, and simultaneously creating the manufacturing, assessment, lifecycle supervision, and electronic entries are easier to archive **[14]**. No special character is allowed in eCTD, In Project name hyphen is allowed, no space between title of eCTD, use lower case hyphen, PDF Property: 1.4 version for eCTD, more than 10 pages bookmarks should be must, Fast way to view PDF – Bookmark **[15]**.

Submit eCTD in CD/DVD format or use an electronic gateway. eCTD highly recommended by USFDA for filing ANDA, INDA, NDA, BLAS, DMF etc. Beginning in year 2010, The European Union also demands the electronic submission of CTD for all individual processes **[15, 16]**. The Overview of eCTD submission is shown in **Figure 2**.

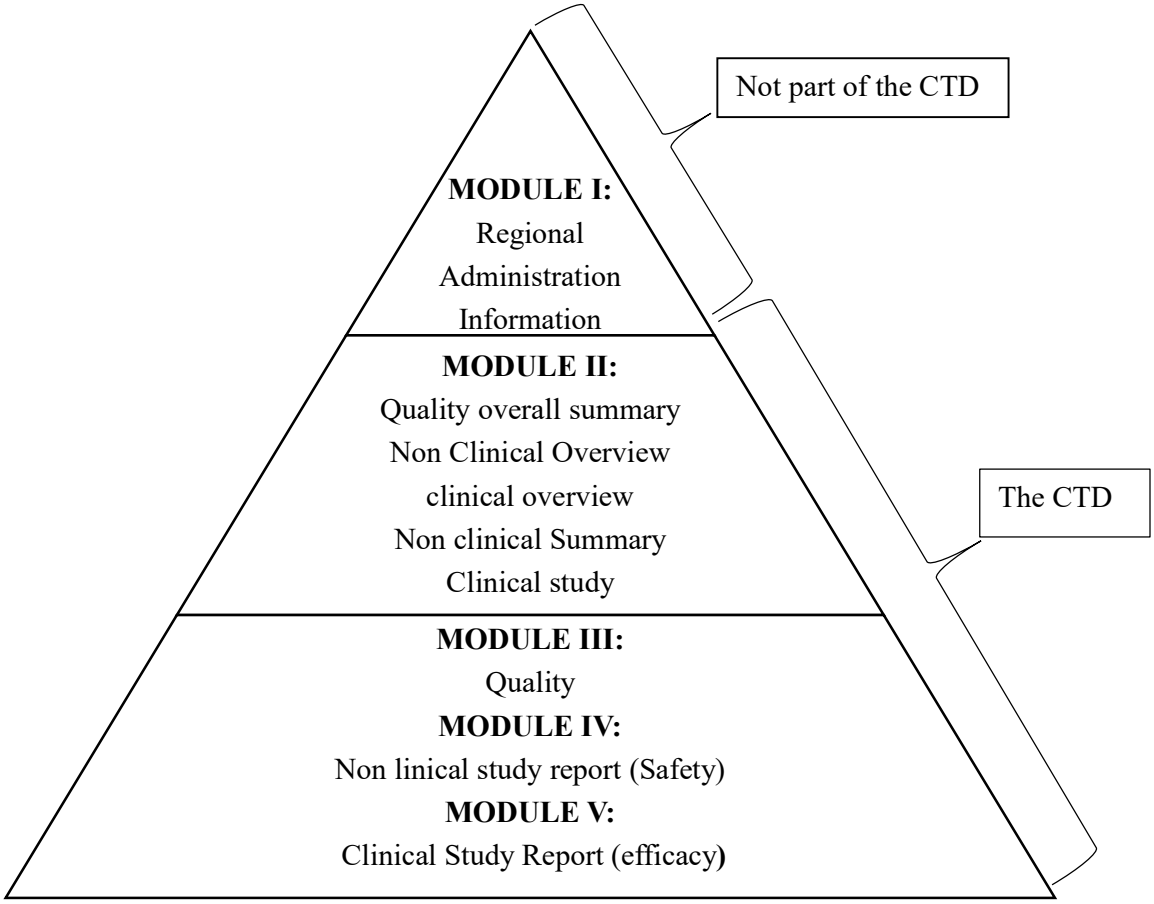

Figure 1: CTD Triangle

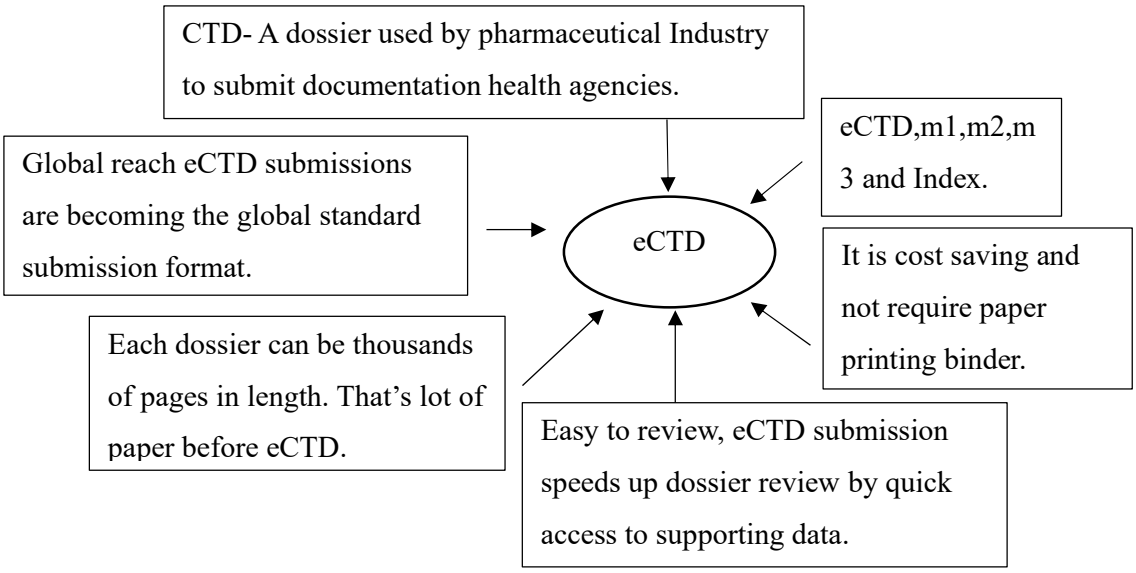

Figure 2: Overview of eCTD submission

1.2.1. eCTD Requirements

You must submit electronically utilizing the most recent version of eCTD that the FDA supports. The most recent supported version of eCTD is included in the Catalogue of Data Standards and additionally outlined in the document containing technical specifications beneath. CTD specification of ICH, Study tagging files ICH eCTD Backbone file specification. Software used in eCTD management **[16]**.

1.2.2. Software used in eCTD Submission

There are various software to use but some are mentioned below in **(Table 1)**.

Table 1: Software used in eCTD Submission

Sr. No.	Software
1	Take solution: www.PharmaReady.com.
2	Knowledge NET-Test Software - http://10.0.0.31:8000/KnowledgeNET-Test/Login_input.do
3	Amplexor, https://www.amplexorlifesciences.com/rim/submission-management-publishing/
4	Data farm, http://www.datafarminc.com.
5	Master Control submission Gateway™-Master Control, http://www.mastersolution.com.
6	ECTD X Press-Image solution-http://www.imagesolutions.com.
7	Lorenz Life Science: www.lorenz.com.

1.2.3. Key Considerations for eCTD Software Usage

Knowledge of eCTD, Software functions and system requirements, FDA Guidance submission format, Files are sent to Authorities by CD, Files are attached to e-mail, Files submitted through Eudralink or Gateway **[17]**.

2.0 COMPARISON OF CTD AND eCTD

The comparison between CTD and eCTD is mentioned below in **(Table 2)**.

Table 2: CTD and eCTD Statements in Comparison

Sr. No.	Paper CTD	eCTD
1	A4 size paper should be used.	A4 size or US letter size documents are acceptable.
2	TOCs and volume are used to navigate the CTD.	XML backbone for eCTD navigation.
3	The target CTD section number is included in the cross-reference.	The target linked to the cross-reference.
4	TOCs, page numbers, and caption Cross references are used to navigate the document manually	TOCs, bookmarks, and hyperlinks are used to navigate electronic documents.
5	Trucks delivered binders in boxes on pallets.	CD (or DVD) or email portal submissions are accepted.
6	Volumes, tabs, and slip sheets were entered electronically and printed on paper.	Electronically filed with e-documents in folders.

2.1. Comparison of USA and EU requirements for dossier submission

The comparison of USA and Europe Requirements for Dossier submission is mentioned below in **(Table 3) [18, 19]**.

Table 3: Comparing US and EU Requirements for Dossier Submission

Module	USA	EU
Module 1:	**a. Information about patent and exclusivity, plans for risk assessment and administrative details.**	**a. Details on clinical trials, orphan drug market exclusivity, prerequisites of particular applications, such as generic summaries, hybrid applications, and bibliographic applications, as well as pharmacovigilance and environmental risk assessment.**
Module 2:	**b. Summary of module 3,4,5**	**b. Summary of module 3,4,5**
Module 3: Drug Substance	**a. 3.2.S- The manufacturer drug substance may have directly supplied FDA Substance with DMF data, which could be cited in the dossier.** **b. 3.2.S.7- Stability: Labels must specify the necessary storage conditions in accordance with FDA regulations.**	**a. 3.2.S- Drug substance information can be provided through a two-part DMF in the EU or by referencing a Certificate of Suitability from the European Pharmacopoeia.** **b. 3.2.S.7- Stability: The storage needs must be addressed in compliance with CHMP guidelines.**
Module 3: Drug Product	**a. 3.2.P-The FDA received DMF data directly from manufacturers of excipients and containers/closures, which could be mentioned in the dossier.** **b. 3.2.P.1- The Colours specified in the FDA's approved list for colour schemes must be used, and when a monograph is available, excipients should be indicated as compliant with USP/NF standards.** **c. 3.2.P.4- Excipients should align with USP/NF standards when specified in a monograph.** **d. 3.2.P.5- For drug product control, assay values must not exceed a 10% limit, and there may be a single regulatory specification related to shelf life.** **e. 3.2.P.7- The manufacturer's name(s) for the container closure system is necessary.** **f. 3.2.P.8- It is obligatory to follow the FDA's language guidelines for storage in context of stability.**	**a. 3.2.P.1-Description and Composition: Colours listed in European Union's approved colour registry. It is necessary to specify that excipients conform to the European Pharmacopoeia where a monograph is available.** **b. 3.2.P.4- Excipients should comply with the European Pharmacopoeia or relevant European national pharmacopoeia standards when indicated in monograph.** **c. 3.2.P.5- Drug Product Control: Assay values shouldn't be higher than 5%. Goods that follow the monograph of the European Pharmacopoeia.** **d. 3.2.P.7- The manufacturer's name(s) for the container closure system is not necessary.** **e. 3.2.P.8-Stability: It should adhere to the guidelines established by CHMP (Committee for Medicinal Products for Human Use).**
Module 4:	**a. It contains nonclinical study reports. It also includes table of content, study reports and related information, literature references.**	**a. It contains nonclinical study reports. It also includes table of content, study reports and related information, literature references.**
Module 5:	**b. 5.3.5.3- In addition to Clinical Overview and Clinical Summary in sections 2.5 and 2.7, FDA Integrated Summaries of Safety and Efficacy (ISS/ISE) are typically a mandatory requirement, must be included in reports of analyses from multiple studies.**	**b. In bioequivalence studies, the reference product should utilize a European batch.**

3.0 STEP BY STEP GUIDE TO USED WELL-KNOWN eCTD SOFTWARE [20]

1) These steps outline the process for operating eCTD software in a step-by-step manner.
2) Upon opening the software, the initial action involves configuring the default page setting to the most recent page. "Add client name"
3) After incorporating the client's name, the subsequent step involves initiating the project creation process.
4) After successfully creating the project, the next step entails populating all the details specified in the software. Subsequently, by clicking on 'Create the Project', A new page will open.
5) The project is established, Exemplified by its designation such as 'USA-PCM-500'.
6) Sequentially incorporate files into modules.
7) To upload files into modules, simply click on the 'Add File' option.
8) In this instance files are uploaded for Module 1, Module 2, Module 3, Module 4, Module 5.
9) Following the completion of file uploads, the next stage involves the submission process. Ensure accurate details are filled, then proceed to submit the information.
10) Upon submission, All details are successfully saved and recorded.

2.2. Comparison of eCTD software for USA and EUROPE

Comparison of eCTD Software for USA and Europe is mentioned below in **(Table 4)**.

Table 4: Comparison of eCTD Software for USA and Europe [20]

Sr. No.	Requirements	USA	Europe
01	Home Page	Recent pg. project, Default project i.e.- set project.	Recent pg. project, Default project i.e.- set project.
02	Masters	Department: Regulatory, Client: e.g.- Company.	Department: Regulatory, Client: e.g.- Company.
03	Project	Creation of project, Upload of file, Approving file, Submission Details, Publication.	Creation of project, Upload of file, Approving file, Submission Details, Publication.
	a. Creation of project	a. Project Name – short name-hyphen-API name (only for system) b. Template Name – US-v2.3. c. Region – US d. Department – Regulatory e. Client – Company name f. Project Type – eCTD	a. Project Name – eu-pcm-600 (only lower-case characters, no space, Hyphen used) b. Template - EU-v3.0.1, i.e., centralized, decentralized. c. Region – EU d. Department – Regulatory e. Client – Company name f. Project Type – eCTD
	b. Upload file	1) Drag method 2) Browsing method Note: - Parent node cannot be changed, so repeat the note and change. Repeat node	a. Select EU-eCTD-v3.0.1, 5 modules will see. b. Select module 1 (m1) m1-eu m1-0- ⟶

		only when two different files for same point. **Lock node: upload file.**	**cover → specific (edqm)** **c. Add a leaf note in specific (edqm cover.pdf) select the country then repeat and close.**
	c. STF/CEP	**Study Tagging File (STF):** **a. STF is only used for US, STF should be in 1.4 Version.** **b. STF Node name is important** **c. STF document- Study title and node title should be same as per version study ID**	**a. European Pharmacopoeia and certificates of suitability (CEP) File: EDQM** **b. Initial sequence for Europe- Tetra sequence i.e. 0000** **c. -**
04	**Submission**	**a. Click on Submission → Click on eCTD → Click on submission details.** **b. Country - USA** **c. Regional Version – 2.3** **d. Agency Name- USFDA** **e. Application Number – 6-digit no.** **f. Application Id- 9 times** **g. (If we don't have dense no. then write 999999999)** **h. Submission Id- 4 digit.** **i. -**	**a. Click on submission and go on submission detail, Fill detail required.** **b. Country - Europe** **c. Regional Version – 3.0.1** **d. Agency Name - EMA** **e. -** **f. -** **g. -** **h. -** **i. UUID- Permanent no. of entire product.**
05	**Publication**	**a. No hyperlink before uploading.** **b. All work should be on path i.e.- Add link, broken link, hyperlink, etc.**	**a. No hyperlink before uploading.**

CONCLUSION

A well-prepared dossier for any market export can be generated, the proper planning and execution development will facilitate the creation of superior dossiers and the reaction to governmental bodies inquiries. The CTD and the eCTD format was created, an individual PDF documents that are organized in a sequential manner in accordance with the CTD structure make up eCTD. Additionally, It contains XML backbone that offers information about the submission and cross-links the necessary documents. This review states that procedure for submitting the dosage, As per the CTD and eCTD formats for Module I - contains Administrative Regional Information, Module II- contains the Overview and summaries, and Module III- contains the Quality Information, Module IV- contains preclinical data, while Module V- contains clinical data. So, there are method that how to operate eCTD software. Different countries have different regional version, For USA it is 2.3 and Europe has 3.0.1 version. Submitting a dossier is a mandatory requirement for all regulatory agencies. The provided explanation proves highly valuable when preparing regulatory dossier submissions. It also offers a comprehensive guide that outlines the fundamental steps for utilizing the software to file an e-CTD dossier reduce the burden of reviewers and simplifies the process of submission as all the Regulatory authorities use it as standard format.

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